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[Intervention Review]

Combined oestrogen and progesterone for preventing miscarriage

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ABSTRACT

Background

Historically, oestrogen and progesterone were each commonly used to save threatened pregnancies. In the 1940s it was postulated that their combined use would be synergistic and thereby led to the rationale of combined therapy for women who risked miscarriage.

Objectives

To determine the efficacy and safety of combined oestrogen and progesterone therapy to prevent miscarriage.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (23 June 2013) CENTRAL (OVID) (*The Cochrane Library* 2013, Issue 6 of 12), MEDLINE (OVID) (1946 to June Week 2 2013), OLDMEDLINE (1946 to 1965), Embase (1974 to Week 25 2013), Embase Classic (1947 to 1973), CINAHL (1994 to 23 June 2013) and reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials that assessed the effectiveness of combined oestrogen and progesterone for preventing miscarriage. We included one stratified randomised trial and one quasi-randomised trials. Cluster-randomised trials were eligible for inclusion but none were identified. We excluded studies published only as abstracts.

We included studies that compared oestrogen and progesterone versus placebo or no intervention.

Data collection and analysis

Two review authors independently assessed trials for inclusion and assessed trial quality. Two review authors extracted data. Data were checked for accuracy.

Main results

Two trials (281 pregnancies and 282 fetuses) met our inclusion criteria. However, the two trials had significant clinical and methodological heterogeneity such that a meta-analysis combining trial data was considered inappropriate.

One trial (involving 161 pregnancies) was based on women with a history of diabetes. It showed no statistically significant difference between using combined oestrogen and progestogen and using placebo for all our proposed primary outcomes, namely, miscarriage (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.32 to 2.80), perinatal death (RR 0.94, 95% CI 0.53 to 1.69) and preterm birth (less than 34 weeks of gestation) (RR 0.91, 95% CI 0.80 to 1.04). In terms of this review's secondary outcomes, use of combined oestrogen and progestogen was

associated with an increased risk of maternal cancer in the reproductive system (RR 6.65, 95% CI 1.56 to 28.29). However, for the outcome of cancer other than that of the reproductive system in mothers, there was no difference between groups. Similarly, there were no differences between the combined oestrogen and progestogen group versus placebo for other secondary outcomes reported: low birthweight of less than 2500 g, genital abnormalities in the offspring, abnormalities other than genital tract in the offspring, cancer in the reproductive system in the offspring, or cancer other than of the reproductive system in the offspring.

The second study was based on pregnant women who had undergone in-vitro fertilisation (IVF). This study showed no difference in the rate of miscarriage between the combined oestrogen and progesterone group and the no treatment group (RR 0.66, 95% CI 0.23 to 1.85). The study did not report on this review's other primary outcomes (perinatal death or rates of preterm birth), nor on any of our proposed secondary outcomes.

Authors' conclusions

There is an insufficient evidence from randomised controlled trials to assess the use of combined oestrogen and progesterone for preventing miscarriages. We strongly recommend further research in this area.

PLAIN LANGUAGE SUMMARY

Combined use of oestrogen and progesterone for preventing miscarriage

The hormones oestrogen and progesterone have established physiological roles in maintaining pregnancy. It has been suggested that supplementation of these hormones could help prevent miscarriage before 24 weeks of pregnancy, particularly in women who have low levels of the hormones, in assisted reproductive technology programs, or who have a history of repeated miscarriages. In our review of randomised controlled trials published in major scientific databases, we only identified two trials that met our inclusion criteria. The two trials involved small numbers of women. One involved 161 women with diabetes who took oral placebo or oral diethylstilboestrol and ethisterone in increasing doses from before the end of the 16th week until birth. The other trial involved 120 women with pregnancy assisted by in vitro fertilisation and embryo transfer who continued treatment until the completed 12th week of gestation.

From the little evidence available, the two trials found no evidence that combined oestrogen and progestogen can prevent miscarriage (progestogen is a major class of hormones which includes progesterone) when compared with placebo or usual care. The first of the two studies indicated an increased risk for the mothers who used hormonal therapy during pregnancy of developing cancer later in life. Diethylstilboestrol is no longer in use and poses serious adverse effects while ethisterone contains androgenic properties thought to be responsible for genital abnormalities and has been replaced by progesterone.

Overall, we acknowledge the lack of trials, especially large-scale trials, and therefore suggest further research is needed in this area before supporting or disproving the use of combined oestrogen and progesterone for the prevention of miscarriages.

BACKGROUND

Description of the condition

Definitions

Miscarriage, or 'spontaneous abortion', is defined as the loss of pregnancy under 24 weeks of gestation (RCOG 2006). 'Recurrent miscarriage' is defined as having three or more consecutive spontaneous miscarriages (RCOG 2003). Pregnant women may undergo 'threatened miscarriage', which presents as vaginal bleeding, with or without pain, within the first 20 weeks of pregnancy (Cunningham 2010). A closed cervix helps keep the fetus viable inside the uterine cavity. Once cervical dilatation occurs, a miscarriage is deemed as 'inevitable' (Cunningham 2010).

Incidence

Miscarriage is common and occurs in 10% to 15% of all clinically recognised pregnancies (Everett 1997; Liu 1991; Regan 1989; Stirrat 1990; Warburton 1964). Furthermore, an even higher miscarriage rate of 31% has been reported when undetected pregnancies are considered (Wilcox 1988). Threatened miscarriage has been reported to be present in 20% to 25% of pregnant women (Cunningham 2010; Everett 1997). Around 1% of all women suffer from recurrent miscarriage and, given that this incidence rate is higher than that expected by chance, a proportion of women with recurrent miscarriage will have particular aetiologies underlying their miscarriages (RCOG 2003).

Impact

The miscarriage process may be a traumatic event for women both physically and psychologically. Physical impact may involve sudden, considerable pain, blood loss, rapid hospitalisation and operation (Lee 1996). Furthermore, the operative process such as dilatation and curettage is known to be associated with - other than surgical risks - stress and emotional responses (Lee 1996). After miscarrying, the psychological impact may also include depressive symptoms, anxiety and development of obsessive-compulsive disorder. Such decline in mental health can last up to six months or more after miscarrying (Janssen 1996).

Pathophysiology

The process of miscarriage initiates within a few weeks after the death of the embryo. Haemorrhage in the decidua basalis, which is the endometrial area that forms the base of the implanted site, together with adjacent tissue necrosis and inflammation, lead to detachment of the gestational sac and implanted ovum. The detachment stimulates uterine contractions and cervical dilation, subsequently resulting in expulsion (Porter 2008).

Aetiology

Spontaneous miscarriage

Despite numerous theories, there remains a large number of miscarriage cases in which an exact cause cannot be identified. Ultrasonography and histological investigations from cases of spontaneous miscarriages show that 70% is related to a defective ovum or fetus, the most common cause being chromosomal abnormalities (Oats 2010). In fact, chromosomal abnormalities have been reported to account for more than 50% of all miscarriages (Burgoyne 1991; Goddijin 2000; Simpson 2007). Other causes which are less common include defective implantation, systemic maternal disease (such as poorly-controlled insulin-dependent diabetes) (Mills 1988), uterine abnormalities and possibly psychosomatic causes, although the latter have been difficult to evaluate in studies (Oats 2010). Maternal infections are an uncommon cause (Cunningham 2010). There are many risk factors which are associated with a higher incidence of miscarriage: maternal age of greater than 35 years, previous history of miscarriage (Garcia-Enguidanos 2002; Walch 2008), smoking, alcohol use, high caffeine use and exposure to certain environmental toxins (Cunningham 2010).

Recurrent miscarriage

The known aetiologies are similar to the causes described for spontaneous miscarriage; however there is some difference in terms of their occurrence. For instance, chromosomal abnormalities become a less likely cause for recurrent miscarriage, while uterine malformations, particularly cervical incompetence, are more likely (Oats 2010). Other aetiologies include predisposing conditions to thrombosis (such as antiphospholipid syndrome and thrombophilia), endocrinological factors (such as polycystic ovaries, thyroid dysfunction) and immunological factors (such as systemic lupus erythematosus) (Carrington 2005; Li 2002; Toth 2010). Despite all this, around 50% of recurrent miscarriages remain unexplained (Habayeb 2004; Tulppala 1993).

Description of the intervention

Progesterone and oestrogen are both female sex hormones which are essential in the maintenance of pregnancy. Progesterone is produced from the ovary by the corpus luteum after ovulation. While the corpus luteum continues progesterone synthesis up to the 10th week of gestation (Speroff 2005), the placenta concurrently begins to synthesise progesterone and by the 12th week, enough progesterone is produced to replace the corpus luteum source (Genuth 2006). Progesterone is responsible for multiple functions in the pregnancy - *see* How the intervention might work - and the insufficiency of progesterone during the luteal phase of the menstrual cycle and during early pregnancy are thought to be one of the many causes of miscarriage (Haas 2008). For this reason, women who have low progesterone levels of 10 ng/mL or less during early pregnancy may be supplemented with 100 mg progesterone daily until the 10th week (Speroff 2005). Women who use assisted reproductive technology may also require progesterone use before pregnancy, during the luteal phase of their menstrual cycle as a means of preparing the endometrium for successful implantation (Balasch 1987).

Similarly, progestogen has also been used in cases of assisted reproductive technology (Abu-Musa 1998; Daya 2009) and in prevention of miscarriages (Hemminki 1999; Johnson 1979), including threatened cases (Duan 2010; Thierstein 1959). One of the main concerns about maternal progestogen use has been the adverse effect of genital tract abnormalities presenting in newborns who were exposed in utero (Silver 1999; Wilkins 1960), but the association with malformations may be weak (Kullander 1976).

The second element of the intervention is oestrogen, another hormone produced from the ovaries. Historically, it was proposed that diethylstilboestrol, a synthetic oestrogen which enhanced both oestrogen and progesterone secretion, could combat the problem of hormonal deficiency in pregnancy, thereby acting as a

therapeutic agent for preventing miscarriages, and perhaps hinder or lessen the impact of adverse pregnancy outcomes, such as eclampsia and preterm delivery (Smith 1948).

However, from the 1970s onwards, some adverse effects were identified in offspring who were exposed to diethylstilboestrol in utero, leading to the declaration of its contraindicated use in pregnancy by the US Food and Drug Administration in 1971 (FDA 1971). Adverse effects included premature birth and genital tract abnormalities in both male and female offspring (Bibbo 1977; Herbst 1971; Palmer 2005). For female offspring, established and documented effects include cervical adenocarcinoma (Herbst 1981), vaginal adenocarcinoma (Herbst 1971) and vaginal adenosis (Bibbo 1977; Herbst 1971). Amongst the lesser known adverse effects, one 1977 follow-up study of prenatally exposed offspring from the early 1950s reported abnormalities, namely, irregular menstrual cycle and lower incidence of pregnancy in female offspring; and in male offspring, increased cases of pathologic semen (Bibbo 1977). Other sources describe poorer pregnancy outcomes for females exposed in utero; specifically higher rates of ectopic pregnancies, miscarriages and preterm births (Barnes 1980; Berger 1980; Goldberg 1999). Increased risk of infertility in female offspring (Palmer 2005) and slightly increased risk in males (Perez 2005) have also been postulated, while other authors have dismissed an increased risk of infertility when exposed to oestrogen or progestins (Hemminki 1999).

In recent decades, scientific literature has typically described the combined use of oestrogen and progesterone in the context of assisted reproductive technologies, in particular in-vitro fertilisation (IVF), by which if the woman achieves pregnancy, hormonal supplementation would be continued throughout the early pregnancy period, or until the placenta has assumed the role of hormonal production (Davar 2007; Devroey 1998; Lelaidier 1992; Muasher 1991; Navot 1986; Queenan 1997; Schindler 2005). Despite the varying results over which drug protocol is best for luteal support, this review will only include trials which compare combined oestrogen and progesterone versus placebo or no intervention, where the comparison is undertaken during, but not limited to, the time of pregnancy. We also aim to clarify the effect of such therapy on preterm birth since there are both therapeutic claims and claims of preterm birth as an adverse effect from therapy.

How the intervention might work

The established roles of oestrogen and progesterone have been known to be beneficial towards maintenance of pregnancy. First, progesterone can stimulate secretory changes in the endometrial layer of the uterus, in order to create a stabilised surface for the fertilised egg to implant upon (Duan 2010; Potdar 2005). Second, progesterone keeps the myometrial layer of the uterus quiescent; that is, suppresses the uterus from contracting, which again is important for stable implantation, and important for preventing preterm labour later on in pregnancy (Duan 2010; Rao 1998). Third, progesterone is a potent modulator working in the maternal immune system to prevent the rejection of the fetus as foreign tissue (Genuth 2006; Schorge 2008; Walch 2008). By these various physiological functions, progesterone supplementation and its effects are assumed to be beneficial for pregnancy.

Oestrogen induces proliferation of the endometrial layer, which also helps to prepare for successful implantation (Genuth 2006). In addition, oestrogen stimulates continuous growth of uterine muscles (Bengtsson 1973) and influences blood flow to the uterus (Genuth 2006), all of which aim to accommodate for pregnancy. Another feature of oestrogen is the ability to increase synthesis of oestrogen receptors and progesterone receptors. This enables oestrogen to amplify its own effects on uterine growth as well as enhancing the effects of progesterone (Genuth 2006).

Why it is important to do this review

Related reviews and protocols evaluating the efficacy of hormone administration for miscarriage prevention are already available in *The Cochrane Library.*

- Oestrogen supplementation, mainly diethylstilbestrol, for preventing miscarriages and other adverse pregnancy outcomes (Bamigboye 2003)
- Progestogen for preventing miscarriage (Haas 2008)
- Progestogen for treating threatened miscarriage (Wahabi 2011)

The above Cochrane reviews have only addressed the evidence of these two hormones separately, and not in combination. In all three reviews, any combination therapy used in a randomised controlled trial (RCT) resulted in the exclusion of that RCT from their analyses. However, given that for decades, both oestrogen and progesterone have been viewed as essential hormones supportive of pregnancy and given that the added presence of oestrogen can amplify the effects of progesterone (Genuth 2006), it would therefore be important to formally examine the evidence to support the efficacy of such combined use.

OBJECTIVES

To determine the efficacy and safety of combined oestrogen and progesterone as preventative therapy against miscarriage.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials that assessed the effectiveness of combined oestrogen and progesterone for preventing miscarriage. We included one stratified randomised trial and one quasi-randomised trial. Cluster-randomised trials were eligible for inclusion but none were identified. We excluded studies published only as abstracts.

Types of participants

We included all pregnant women, but in order for results to be meaningful in terms of clinical applicability, we categorised participants according to particular clinical conditions or particular risk factors in the subgroup analysis - *see* Subgroup analysis and investigation of heterogeneity.

Types of interventions

We compared oestrogen and progesterone versus placebo or no intervention. We also included studies which used a progestogen different to progesterone, due to its historic relevance and use in assisted reproductive technology - *see* Description of the intervention. However, because of differences in chemistry, we had to view other progestogens as a separate intervention

from progesterone. Hence, we presented data on the first two comparisons.

- Combined oestrogen and progestogen (other than progesterone) versus placebo
- Combined oestrogen and progesterone versus no hormonal treatment
- Combined oestrogen and any progestogen versus placebo or no hormonal treatment

We do not exclude the possibilities of other comparisons arising from future updates of this review.

Studies that compare therapy with no treatment rather than with placebo have more potential for bias. This potential for bias has been addressed in the review by analysing the placebo-based trial and no-treatment-based trial both separately and in conjunction.

Types of outcome measures

We included the following outcomes.

Primary outcomes

1. Miscarriage
2. Perinatal death
3. Preterm birth (less than 34 weeks of gestation)

Secondary outcomes

Offspring

1. Low birthweight of less than 2500 g
2. Genital tract abnormalities
3. Abnormalities other than of the genital tract
4. Cancer in the reproductive system
5. Cancer other than of the reproductive system

Mother

1. Cancer in the reproductive system
2. Cancer other than of the reproductive system

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (23 June 2013).

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

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

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

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched CENTRAL (OVID) (*The Cochrane Library* 2013, Issue 6 of 12), MEDLINE (OVID) (1946 to June Week 2 2013), OLDMEDLINE (1946 to 1965), Embase (1974 to Week 25 2013), Embase Classic (1947 to 1973) and CINAHL (1994 to 23 June 2013). *See* Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; and Appendix 6 for search strategies.

Searching other resources

We also scanned through studies referenced in three related Cochrane reviews (Bamigboye 2003; Haas 2008; Wahabi 2011) and other retrieved studies.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all potential studies identified as a result of the search strategy. We resolved any disagreement through discussion. We did not require any consultation with a third party, although if in the future, during the process of updating this review, there is disagreement that is unable to be resolved between the two review authors, we will maintain the strategy of consulting a third party.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We did not require any consultation with a third party, but shall maintain this strategy if required when conducting future updates. We entered data into Review Manager software (RevMan 2012) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. We did not require consultation with a third party, but shall maintain this strategy if required when conducting future updates.

(1) Sequence generation (checking for possible selection bias)

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

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

- low risk of bias (where less than 20% of the randomised population was excluded);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting bias

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

We assessed the methods as:

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

(6) Other sources of bias

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

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

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

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

No continuous data were used. However, for the purpose of future updates, we maintain the strategy of using the mean difference if outcomes are measured in the same way between trials. If appropriate in future updates of this review, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were included in this version of the review. However, in future updates of the review, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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

Cross-over trials

We excluded cross-over trials due to concerns over order effects and carry-over effects related to our proposed outcomes of interest.

In one study (MRC 1955), a minority of the randomised population proved to be cross-over participants. We intended to collect individual participant data as far as possible, to utilise the results from the first period of the cross-over only. However, the individual data in this minority group were unavailable, and hence we reported 'unclear risk' under the category 'other potential sources of bias'.

Other unit of analysis issues

Multiple pregnancies

For trials involving multiple pregnancies, we undertook methods described in *Cochrane Pregnancy and Childbirth Group Methodological Guidelines* accordingly (Gates 2009). One trial involved one set of twins in their data, which was not substantial within the randomised population, but nonetheless we analysed the fetuses as if independent and used the number of fetuses as the denominator according to *Cochrane Pregnancy and Childbirth Group Methodological Guidelines* accordingly (Gates 2009) and to our protocol. For the purpose of future updates, we will maintain the same strategy if it is not possible to make adjustments for the multiple pregnancies due to unavailable information.

Dealing with missing data

For included studies, we noted the levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

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

We excluded from the analyses data from trials or outcomes that were at high risk of bias, e.g. those with high levels of missing data or a large number of participants analysed in the wrong group.

Assessment of heterogeneity

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

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

In future updates of this review, we will carry out statistical analyses using the Review Manager software (RevMan 2012). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

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

Subgroup analysis and investigation of heterogeneity

We did not carry out subgroup analyses given the substantial heterogeneity between the two included studies. For the purpose of future updates, we will maintain the strategy of carrying out formal subgroup analysis for the following subsets, if required.

1. Women with threatened miscarriage versus women without threatened miscarriage.
2. Women with recurrent miscarriage versus women without recurrent miscarriage.
3. Women using IVF versus women without IVF treatment.

We will analyse each subgroup in relation to each of the primary outcomes - *see* Primary outcomes.

We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the χ2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will conduct sensitivity analyses to investigate the following effects on primary outcomes.

1. Inclusion/exclusion of trials with 'no intervention' as the control group.
2. Inclusion/exclusion of trials at high risk of bias, as determined the risk of allocation concealment.
3. Variations in the analysis of trial types stated in Unit of analysis issues.
4. Inclusion/exclusion of trials with high levels of missing data.
5. Fixed-effect/random-effects analyses for outcomes with statistical heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We retrieved four reports of two studies from the search of the Pregnancy and Childbirth Group's Trials Register, three reports for MRC 1955 and one from Prietl 1992). These two studies were included in our analysis.

The total number of 'hits' from searching databases was 960; nine from CENTRAL; 365 from MEDLINE; 31 from OLDMEDLINE; 470 from Embase; 20 from Embase Classic; and 65 from CINAHL. Of the 960 hits, 906 were immediately excluded due to duplicated hits of the exact same study or due to irrelevance to our research topic. We could not obtain the full texts or translations of 54 results despite our access to 12 international library systems. We postulate that this is due to the fact that the articles were published some time ago and the lack of access to non-English titles, evident by the fact that 52 of 54 were non-English language papers. Therefore, our list of potentially relevant studies was five.

Of the five studies, four studies were assessed and classified as excluded studies - *see* Excluded studies - and the remaining study was assessed and classified as an included study. In addition, we scanned the references of significant reports, which resulted in one extra study. This extra study produced two reports, one report for its original study and another report for its follow-up results of the same cohort. Hence in total, two studies were classified as included studies - *see* Included studies.

Included studies

Two trials were included, involving 281 pregnancies and 282 fetuses. One trial, MRC 1955, subsequently had two follow-up studies performed 27 years after, on mothers and offspring respectively. The follow-up studies involved 156 mothers and 136 children.

The MRC 1955 study was conducted across nine centres. One-hundred and sixty-one pregnancies from 156 women were randomised by simple stratification, however 147 were included in their analysis - *see* Incomplete outcome data (attrition bias). Of the 147 pregnancies, one set of twins was included hence there were 148 fetuses. All analysed participants were pregnant women under 16 weeks' gestation with a background of diabetes mellitus (duration of diabetes averaged around eight years in both groups). Participants were allocated to either oral placebo or oral diethylstilboestrol and ethisterone. Diethylstilboestrol and ethisterone were started at 50 mg/day and 25 mg/day before the end of the 16th week then the dosage increased every three weeks until birth, by which time dosage was 200 mg/day and 250 mg/day respectively -see Characteristics of included studies for detailed dose regimen. For the offspring, the outcomes of interest included were miscarriage, stillbirth, neonatal death, time of delivery and birthweight. For the mother, the outcomes included maternal death and pre-eclampsia.

The same 156 women were followed up in the MRC 1955 study, however 151 were included in their analysis - *see* Incomplete outcome data (attrition bias). The mothers were not contacted directly. Instead, data were collected from their general practitioners, from hospital and diabetic clinics, and from Office of Population Censuses and Surveys. General practitioners were asked to complete questionnaires, which included questions about the occurrence of cancer. Outcomes of interest included death, cancer in the reproductive sites and cancers in other sites.

Twelve miscarriages occurred in the 148 fetuses in the MRC 1955 study, thus 136 offspring were included in the follow-up study. This group included data from stillbirths and neonatal deaths. Five were excluded. Children were not contacted directly and all methodology was identical to that described for the follow-up study of the mothers. Outcomes of interest included death under and over the age of one, urogenital abnormalities, other abnormalities, cancers, number of those who consulted for infertility, number of those married with history of miscarriage, and number of those married with at least one child. However, data for the latter three outcomes were not used in our analyses and we explain why - *see* Incomplete outcome data (attrition bias).

The second included trial, Prietl 1992, was a quasi-randomised trial involving 120 pregnancies assisted by in vitro fertilisation and embryo transfer (IVF-ET). Two participants were excluded. Women were ensured of normal endocrine profiles before IVF treatment. Despite different IVF protocols used before pregnancy, a balanced baseline in protocol types was achieved between the intervention and control group. After confirmation of pregnancy, participants were randomised, according to their odd or even year of birth, to either intramuscular injection of 500 mg 17α-hydroxyprogesterone caproate and 10 mg oestradiol valerate in an oily vehicle (Gravibinon) twice a week, or, to no hormonal treatment. Treatment continued until the completed 12th week of gestation. The only outcome of interest was miscarriage.

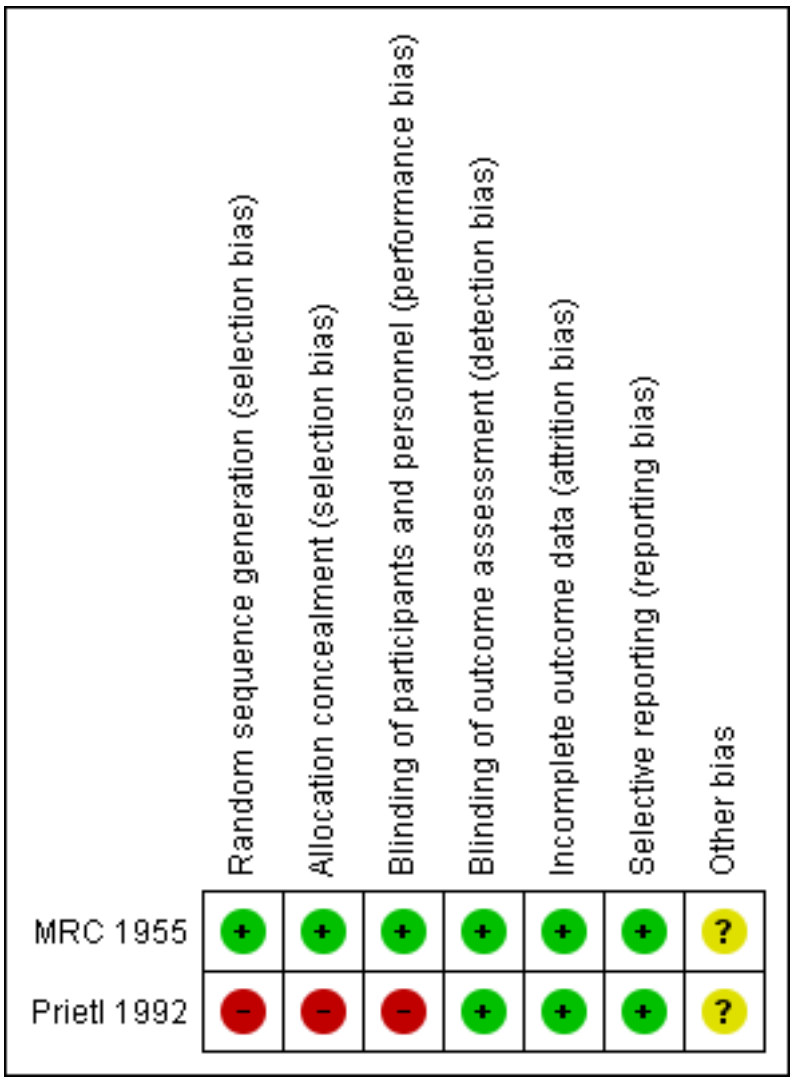
Excluded studies

We excluded four studies (Berle 1977; Crowder 1950; Lightman 1999; Sathanandan 1991). An explanation for exclusion of each study is provided - *see* Characteristics of excluded studies.

Risk of bias in included studies

See: Figure 1 for a summary of risk of bias assessed in our included studies. For detailed descriptions of each risk of bias, see Characteristics of included studies.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation and allocation concealment was adequate in one study (MRC 1955) and inadequate in the other (Prietl 1992).

Blinding

In MRC 1955, blinding of both patients and personnel was adequate. Blinding continued throughout follow-up period. In the other study, Prietl 1992, there was no placebo use and the sequence was known to personnel, thus blinding was deemed inadequate.

Incomplete outcome data

The MRC 1955 study performed randomisation before assessment for eligibility. After assessment for eligibility, there were 14 exclusions (10 control, four treated) of which eight were reasonably excluded, due to non-pregnancies and miscarriage prior to intervention use. Of the remaining six, two had advanced beyond the age of 16 weeks, which still meets our review criteria, but not the criteria set by the original study and hence excluded in the original study. Finally, four were avoidable exclusions quoted to have "lacked cooperation or some other complication supervened" (MRC 1955). Given this, the latter six would have been ideally included in our analyses on the basis of intention-to-treat, however the intervention to which these six participants were allocated to was unknown. Despite this, attrition bias remains low because 14 exclusions out of 161 participants is only 8.7%.

Only two exclusions eventuated from Prietl 1992 due to ectopic pregnancy (one control, one treated). These are unavoidable exclusions, which remain excluded in our analyses.

The overall low levels of missing data in both studies deem low risk in attrition bias. For further details - *see* Risk of bias in included studies.

Selective reporting

In both studies, all pre-specified outcomes were reported, hence we assessed both studies as being free from selective reporting bias.

Other potential sources of bias

Cross-over participants

One study, MRC 1955, was inadequate for this risk of bias due to five cross-over participants accounting for 10 pregnancies. This is not without concern of order effects and carry-over effects, and ideally, only data from the first period of the cross-over would be used in our analyses, however due to unavailable individual data, we cannot achieve this. Despite everything, we are reminded that the inclusion of five pregnancies from a second period cross-over represents only 3.12% of the randomised population. We proceeded to include these data, but assessed the trial as 'unclear' under 'other bias'.

Effects of interventions

Justification of why meta-analysis was not performed

Two trials met our inclusion criteria (MRC 1955; Prietl 1992). We extracted data from MRC 1955 for all three of our primary outcomes and seven of secondary outcomes. From Prietl 1992, only one primary outcome was measured. This single common primary outcome was miscarriage. We decided that the pooling of results from both trials for this common outcome was inappropriate as there is obvious clinical and methodological heterogeneity between the two trials.

1. One trial was on women with long histories of diabetes (MRC 1955), the other was conducted in the context of pregnant women who had undergone IVF treatment on various protocols (Prietl 1992).
2. Average age of the women differed approximately 10 years.
3. Intervention used differed in type, dosage, mode of administration, timing of use in pregnancy, and the type of control was different.
4. Definition of miscarriage was different.
5. Trial design was different.
6. The way trials were conducted differed in terms of allocation concealment and blinding.

Comparison 1 - Combined oestrogen and progestogen (other than progesterone) versus placebo (in women with history of diabetes)

Primary outcomes

In one trial of 148 women (MRC 1955), miscarriage was not significantly different between the combined hormonal and placebo groups (risk ratio (RR) of 0.95, 95% confidence interval (CI) 0.32 to 2.80) - Analysis 1.1. Other primary outcomes had similar results: perinatal death (RR 0.94, 95% CI 0.53 to 1.69 - Analysis 1.2) and preterm birth less than 34 weeks (RR 0.91, 95% CI 0.80 to 1.04 - Analysis 1.3).

Secondary outcomes

For the offspring

Secondary outcomes for the offspring revealed no statistical significance between groups: low birthweight of less than 2500 g (RR 0.87, 95% CI 0.43 to 1.77 - Analysis 1.4); genital tract abnormalities (RR 1.57, 95% CI 0.60 to 4.08 - Analysis 1.5); abnormalities other than of the genital tract (RR 0.42, 95% CI 0.14 to 1.30 - Analysis 1.6); cancer in the reproductive system of offspring (RR 2.83, 95% CI 0.12 to 68.29 - Analysis 1.7) and cancer other than of the reproductive system (RR 2.83, 95% CI 0.12 to 68.29 - Analysis 1.8). All of these long-term secondary outcomes were recorded 27 years after the original study.

Maternal outcomes

Amongst the outcomes for the mother, the rate of cancer in the reproductive system was statistically significant (RR 6.65, 95% CI 1.56 to 28.29 - Analysis 1.9). In other words, our findings suggest that maternal hormone use is associated with an increased risk of having cancer in a reproductive site 27 years later by 565%. Cancer other than of the reproductive system in mothers was not statistically significant (RR 1.90, 95% CI 0.36 to 10.07 - Analysis 1.10).

Comparison 2 - Combined oestrogen and progesterone versus no hormonal treatment (in pregnant women having undergone IVF treatment)

Primary outcomes

For a single trial of 118 women (Prietl 1992), the only available outcome reported was miscarriage (RR 0.66, 95% CI 0.23 to 1.85) and there was no statistical difference between groups - Analysis 2.1.

Secondary outcomes

None of our pre-specified secondary outcomes were reported in the Prietl 1992 trial.

DISCUSSION

Summary of main results

Two trials were included in our systematic review on the maternal use of combined oestrogen and progesterone. Both trials were regarded separately due to clinical and methodological heterogeneity.

One trial MRC 1955 compared combined oestrogen and progestogen versus placebo in mothers with a history of diabetes. There was no statistical difference for the following outcomes: miscarriage, perinatal death, preterm birth and low birthweight. In the follow-up study, which was conducted 27 years later, there was no statistical difference for the following outcomes: genital abnormalities in offspring, abnormalities other than of the genital tract in offspring, cancer of the reproductive system in offspring, cancer other than of the reproductive system in offspring, cancer other than of the reproductive system in mothers. There was however, a statistical difference in cancer of the reproductive system of mothers 27 years later by 565% (RR 6.65, 95% CI 1.56 to 28.29 - Analysis 1.9).

The other trial Prietl 1992 compared combined oestrogen and progesterone versus no hormonal treatment in pregnant women who had undergone IVF treatment. There was no statistical

difference for the outcome of miscarriage. Other outcomes were not measured in this trial.

Overall completeness and applicability of evidence

To the best of our knowledge, this is the only systematic review on the maternal use of combined oestrogen and progesterone for preventing miscarriage. Very little on this topic was identified, with only two trials meeting our inclusion criteria. Both trials recruited small numbers of women, the pooling of which was deemed inappropriate. Therefore, there is insufficient evidence overall.

In terms of outcomes, most of our data for the pre-specified outcomes derived from one of the two studies, MRC 1955, whereas the other study, Prietl 1992, only addressed one of our outcomes. Therefore, more evidence is needed in order to address other outcomes.

We question the clinical applicability of the MRC 1955 due to its interventions diethylstilboestrol and ethisterone. Diethylstilboestrol is no longer in use and poses serious adverse effects (Bamigboye 2003) while ethisterone contains androgenic properties thought to be responsible for genital abnormalities, hence has been commonly substituted by progesterone in modern times (Abu-Musa 1998; Sullivan 1986).

Quality of the evidence

One of the two included studies, Prietl 1992, is at high risk of bias - *see* Figure 1 - with its alternation sequence generation thus inadequacy in allocation concealment and lack of placebo, thus performance bias.

Potential biases in the review process

We could not obtain the full texts or translations of 55 results despite our access to 12 international library systems. We postulate that this is due to the age of the articles and the lack of access to non-English titles, evident by the fact that 53 of 55 were non-English language papers.

There are no other potential biases.

Agreements and disagreements with other studies or reviews

The authors of MRC 1955 and Prietl 1992 could not support the benefit of hormone treatment for the prevention of miscarriages (as defined by their own definition), however Prietl 1992 claimed that the significantly higher rate of preclinical pregnancies in their control group, which towards the end resulted in significantly lower ongoing pregnancy rate reflected the ability of hormone treatment in salvaging early pregnancies. This claim however, lacks support from other IVF studies of the non-randomised type. These studies involved comparison of natural cycle IVF and programmed hormone cycle IVF, and the latter intervention always implied continuous hormone support throughout early pregnancy. Three such studies were identified, of which two had dealt with very small numbers (de Ziegler 1990; Schmidt 1989) and the third, a large retrospective study (Queenan 1994) showed almost identical rates in pregnancies, clinical pregnancy losses and ongoing pregnancies. Studies not dealing with IVF similarly refuted the hypothesis of better salvage rates with hormonal therapy (Crowder 1950; Nesbitt 1965).

In our analyses, the only outcome that showed statistical significance was the higher rate of cancer in reproductive sites of treated mothers. Our data for this outcome derived from the follow-up study of MRC 1955, and the authors of MRC 1955 investigated for a possible dose-response relationship between the total amount of diethylstilboestrol taken during pregnancy and the occurrence of such cancers (there was no explanation of why the authors called it 'diethylstilboestrol dose-response' when presumably combined diethylstilbostrol and ethisterone were given). Nonetheless, a convincing dose-response relationship was not established. A 25-year follow-up study focusing on mothers who were exposed to diethylstilboestrol only (Bibbo 1978) followed up a much larger population but its original trial involved lower amounts of diethylstilboestrol exposure than MRC 1955. When we interpreted the data from Bibbo 1978 we found that, in contrast to our findings, there was no significant difference in reproductive site cancers between exposed and unexposed mothers. Hence, the relationship between hormonal exposure during pregnancy and rate of cancer in reproductive sites remains a gap in research.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to assess the effectiveness and safety of the maternal use of combined oestrogen and progesterone for the prevention of miscarriage. One small study suggests that combined hormonal use was associated with increased risk of reproductive cancer for the mother, however, this increased risk could not be supported by evidence in other scientific trials. We conclude that more research is needed prior to establishing any implications for practice.

Implications for research

There is an insufficient number of trials to support or refute the use of combined oestrogen and progesterone in preventing miscarriages. Ideally, trials should recruit a large number of participants, use randomised allocation, use placebo, remain blinded, minimise drop-out rates and report the results of all pre-specified outcomes. For information of some of the secondary outcomes, we recommend that a follow-up study of original participants and their offspring be conducted in the long term.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

MRC 1955

Methods	Simple, stratified randomisation in a multicentre trial. Stratified by age and parity. Timing of randomisation: occurred before assessment for eligibility. Baseline characteristics in each intervention group were established and made comparable.
Participants	From across 9 centres, 161 pregnancies of women with diabetes in their 16th week of gestation or less were randomised. 14 were excluded (8 not pregnant prior to intervention use, 2 whose gestational age surpassed their '16 weeks or less' criteria, 4 "lacked cooperation or some other complication supervened"). Remaining 147 were analysed (71 control, 76 intervention).

MRC 1955 *(Continued)*

	Age: all participants were aged 40 or below. Treatment group mean age was 22.4. Control group mean age was 20.4. Country: UK. Date of study: July 1950 to January 1953.
Interventions	Control: placebo tablets identical to intervention. Intervention: oral diethylstilboestrol (Stilbestrol) and ethisterone in increasing doses. Dosage and duration: (in mg/day) • Before the end of 16th week - end of 19th week: 50 diethylstilboestrol, 25 ethisterone. • 20th - 23rd weeks inclusive: 100 diethylstilboestrol, 50 ethisterone. • 24th - 27th weeks inclusive: 100 diethylstilboestrol, 75 ethisterone. • 28th - 31st weeks inclusive: 150 diethylstilboestrol, 125 ethisterone. • 32nd week - delivery: 200 diethylstilboestrol, 250 ethisterone.
Outcomes	Miscarriage (defined as fetal death before 28 weeks of gestation). Stillbirth (defined as expulsion after 28 weeks' gestation without breath or showing any signs of life). Neonatal death (defined as death after showing signs of life). Living children (defined as children surviving for at least 1 month. This group was followed up for at least 6 months). Maternal death. Preterm birth (not defined, but delivery times were tabulated by week of delivery). Birthweight (not defined, but weights were tabulated by whole pounds). Congenital abnormalities (not defined). Pregnancy complications: oedema, albuminuria, toxaemia and hydramnios. **Outcomes from follow-up study on mothers** Death in later life. Cancer in the reproductive system. Cancer other than of the reproductive system. **Outcomes from follow-up study on offspring** Death in later life. Cancer in the reproductive system. Cancer other than of the reproductive system.
Notes	UK's Medical Research Council appointed a conference committee to conduct study. Report was prepared by DD Reid.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by age and parity, and simple with an 1:1 allocation ratio. Baseline characteristics in both groups were similar.

MRC 1955 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sequence was controlled by a central office. Participants given a series number which was attached to their clinical record sheet and bottle of tablets. Treatment tablets, placebo tablets and packaging were made identical such that both participant and personnel would not know which intervention was received.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment tablets, placebo tablets and packaging were made identical such that both participant and personnel would not know which intervention was received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detection bias is low risk since the outcome is miscarriage. The outcome measurement is not likely to be influenced by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 exclusions (10 control, 4 treated) from entire analysis were explained: 5 miscarried before commencing intervention, 3 were non-pregnancies, 2 had advanced beyond the 16 weeks age criteria, 4 "lacked cooperation or some other complication supervened". For the outcomes of miscarriage, there were no further exclusions. For the outcome of preterm birth, 1 set of twins was excluded (2 control group). For the outcome of low birth weight, 1 stillbirth was excluded (treated group) due to unstated reason. **Exclusions in follow-up study of mothers** A total of 136 women were included. For outcomes of death, genital tract cancer and non-genital tract cancer, 5 exclusions were due to emigration (1 control), untraceable medical records/GP reluctant to fill out questionnaire /'not traced' (3 controls, 1 treated). **Exclusions in follow-up study of offspring** A total of 136 offspring, including stillbirths, were included. For outcomes of genital tract abnormalities and non-genital tract abnormalities, none were excluded. At long-term follow-up, 5 were excluded due to emigration (1 control, 1 treated) and adoption (1 control, 2 treated). For outcomes of genital tract cancer and non-genital tract cancer, 12 were excluded (same 5 exclusions lost to follow-up, 8 probably due to incomplete questionnaires from GP). Of the 8, 4 were control, 4 were treated.
Selective reporting (reporting bias)	Low risk	Protocol not available but all pre-specified outcomes were reported.
Other bias	Unclear risk	It is probable that 5 women were cross-over participants whom each had 2 pregnancies during the original trial. In all 5 cases, their second pregnancy was allocated to the opposite intervention to that of the first pregnancy. This is not without concerns of order effects and carry-over effects, but individual data on the 5 participants were not available.

Prietl 1992

Methods	Quasi-randomised trial. TIming of randomisation: once pregnancy was confirmed by rising HCG levels from day 13 to day 15 since oocyte retrieval in IVF. Baseline characteristics in each intervention group were established and deemed comparable.
Participants	120 women having undergone IVF-ET were allocated once pregnancy was confirmed (65 control, 55 intervention). Age: treatment group mean age was 31.7 +/- 0.7; age range was 25 to 39. Control group mean age was 32.8 +/- 0.7; age range was 26 to 40. Country: Germany. Date of study: September 1989, but end time not stated.
Interventions	Control group: no hormonal treatment during pregnancy. No placebo was given. Intervention group: intramuscular injection of 500 mg 17α-hydroxyprogesterone caproate and 10 mg oestradiol valerate in an oily vehicle (Gravibinon) twice a week. Duration: from confirmation of pregnancy until the end of the 12th week of gestation.
Outcomes	Miscarriage (defined as loss between 7th and 12th week of gestation, confirmed by ultrasound and decrease in HCG).
Notes	Sources of funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation sequence was by year of birth. However, baseline characteristics in each intervention group were established and deemed comparable.
Allocation concealment (selection bias)	High risk	Sequence known to personnel.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was given.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detection bias is low risk since the outcome is miscarriage. The outcome measurement is not likely to be influenced by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants (1 control, 1 treated) were excluded due to ectopic pregnancies.
Selective reporting (reporting bias)	Low risk	Protocol not available but all pre-specified outcomes were reported.
Other bias	Unclear risk	Sources of funding not stated.

HCG: human chorionic gonadotropin
IVF-ET: in-vitro fertilisation and embryo transfer

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

Study	Reason for exclusion
Berle 1977	This study was about treating established threatened miscarriage, rather than the prevention of miscarriage.
Crowder 1950	This study was about treating established threatened miscarriage, rather than the prevention of miscarriage. This study randomised before accurate eligibility assessment, leading to the exclusion of over 20% of randomised participants. This study compared oestrogen and standard treatment versus standard treatment only. Although some in the oestrogen group also received progesterone, the criteria of selection for such added progesterone was not mentioned. Progesterone dosage was low (30 mg/day) and duration was short (hospitalisation period) whereas oestrogen use continued until the 28th week, hence the authors considered the progesterone component negligible.
Lightman 1999	This study introduced intervention prior to established pregnancy. This study did not have a placebo/no treatment group. This study compared intramuscular progesterone and oestrogen versus vaginal progesterone and oestrogen.
Sathanandan 1991	This study introduced intervention prior to established pregnancy. This study was semi-randomised and did not assess any of our specified outcomes.

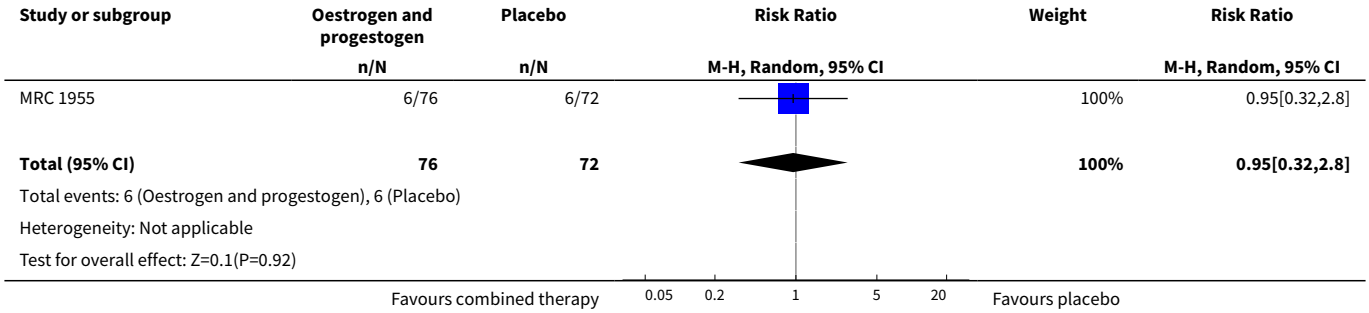
DATA AND ANALYSES

Comparison 1. Combined oestrogen and progestogen (other than progesterone) versus placebo

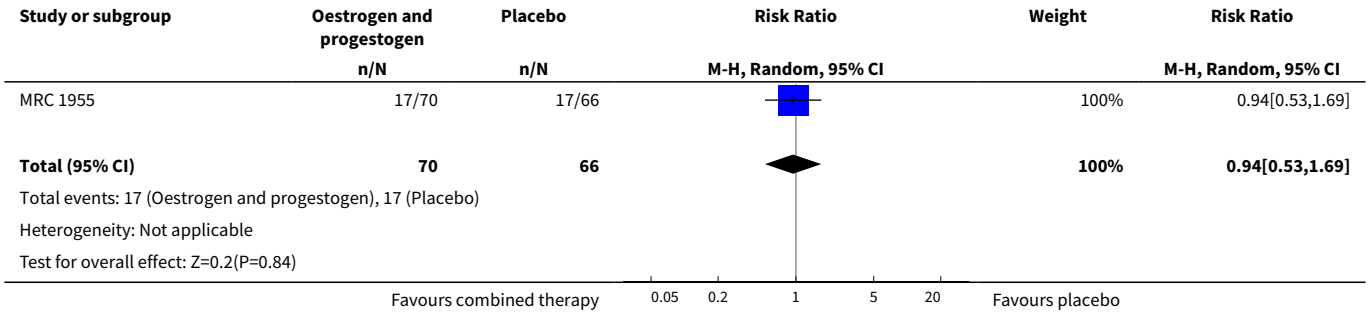
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Miscarriage	1	148	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.32, 2.80]
2 Perinatal death	1	136	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.53, 1.69]
3 Preterm birth (less than 34 weeks of gestation)	1	134	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.04]
4 Low birthweight of less than 2500 g	1	136	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.43, 1.77]
5 Genital abnormalities in offspring	1	136	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.60, 4.08]
6 Abnormalities other than of the genital tract in offspring	1	136	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.14, 1.30]
7 Cancer in the reproductive system in offspring	1	136	Risk Ratio (M-H, Random, 95% CI)	2.83 [0.12, 68.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Cancer other than of the reproductive system in offspring	1	136	Risk Ratio (M-H, Random, 95% CI)	2.83 [0.12, 68.29]
9 Cancer in the reproductive system in mothers	1	156	Risk Ratio (M-H, Random, 95% CI)	6.65 [1.56, 28.29]
10 Cancer other than of the reproductive system in mothers	1	156	Risk Ratio (M-H, Random, 95% CI)	1.9 [0.36, 10.07]

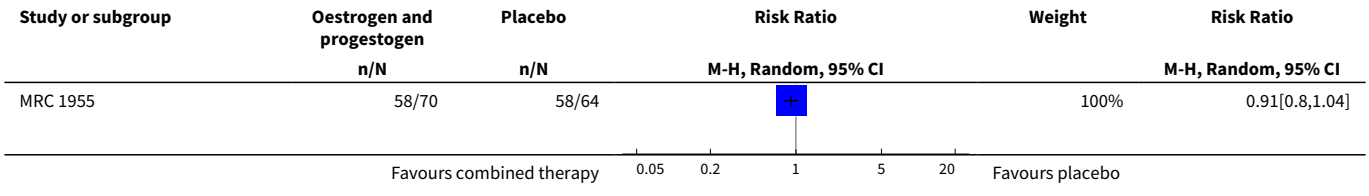
Analysis 1.1. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 1 Miscarriage.

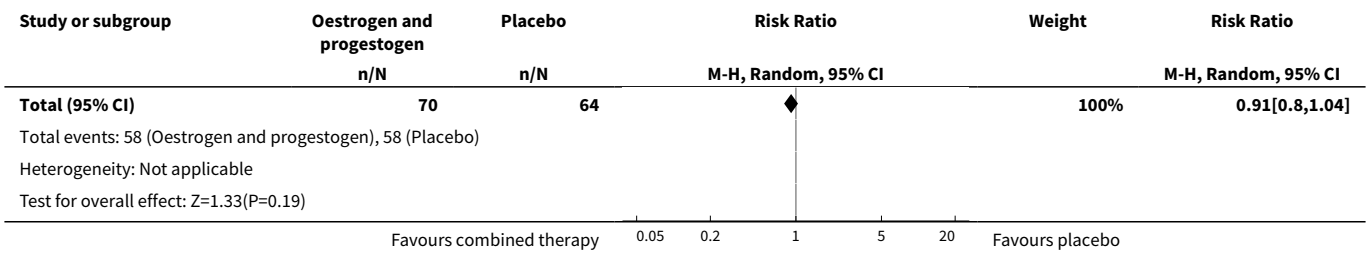


Analysis 1.2. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 2 Perinatal death.

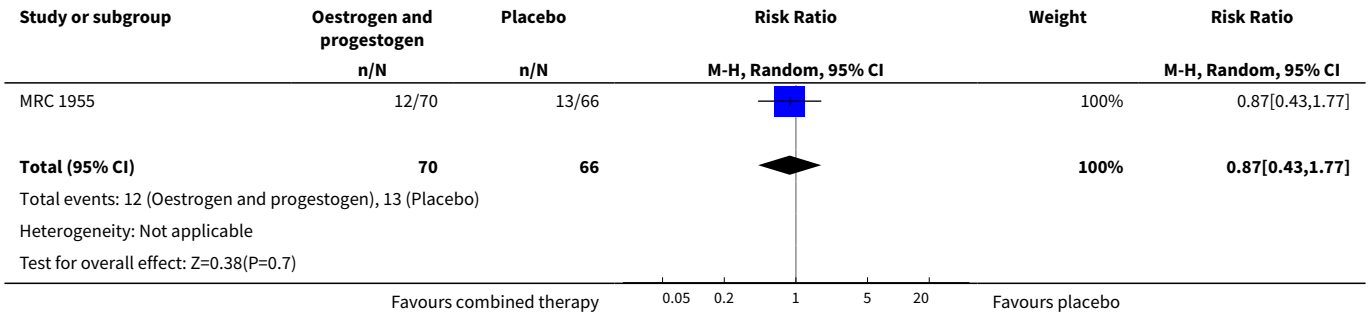


Analysis 1.3. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 3 Preterm birth (less than 34 weeks of gestation).

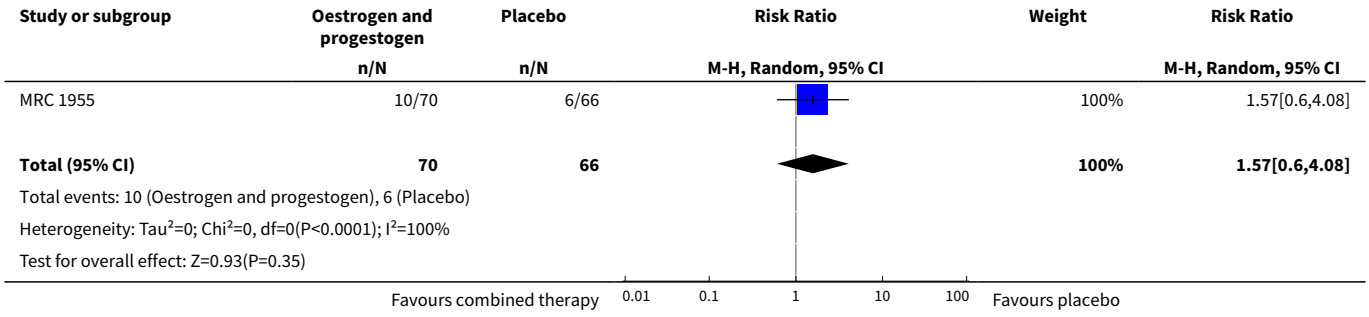




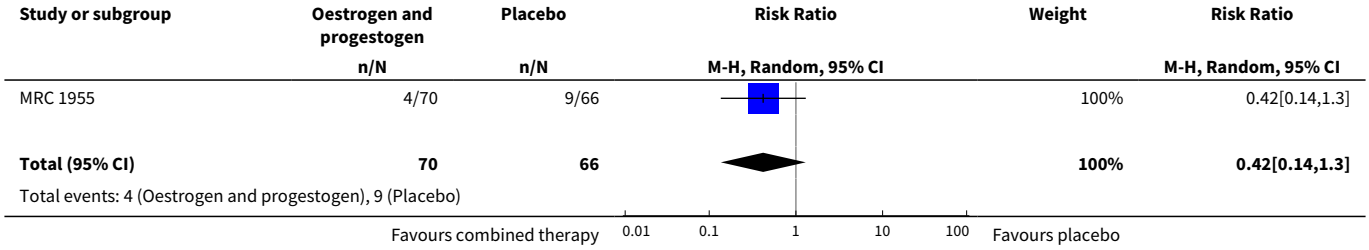
Analysis 1.4. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 4 Low birthweight of less than 2500 g.

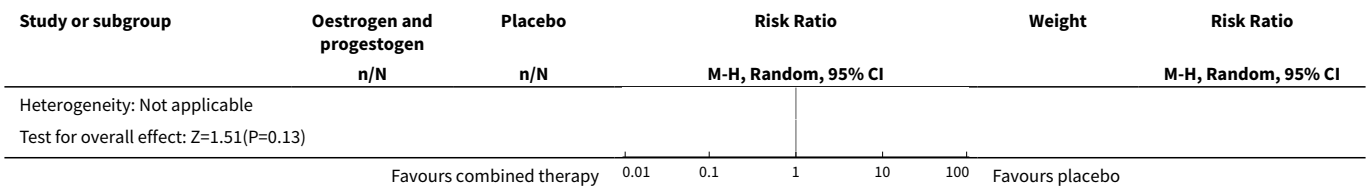


Analysis 1.5. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 5 Genital abnormalities in offspring.

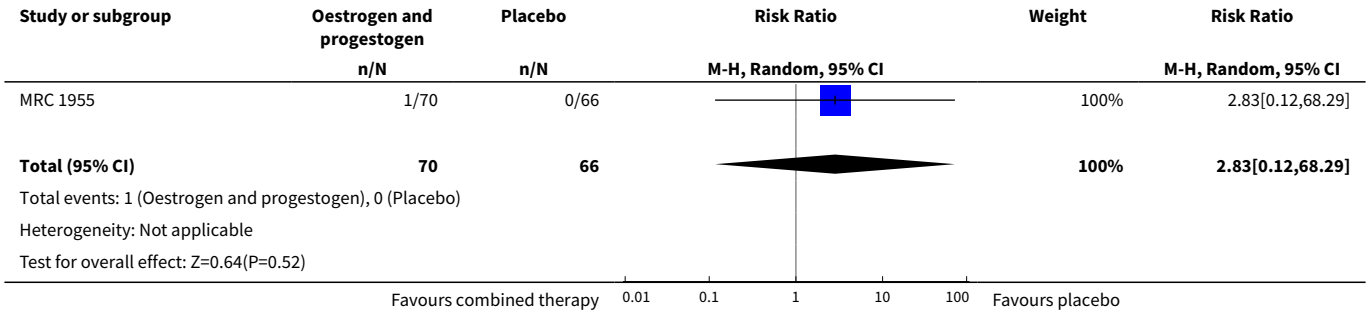


Analysis 1.6. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 6 Abnormalities other than of the genital tract in offspring.

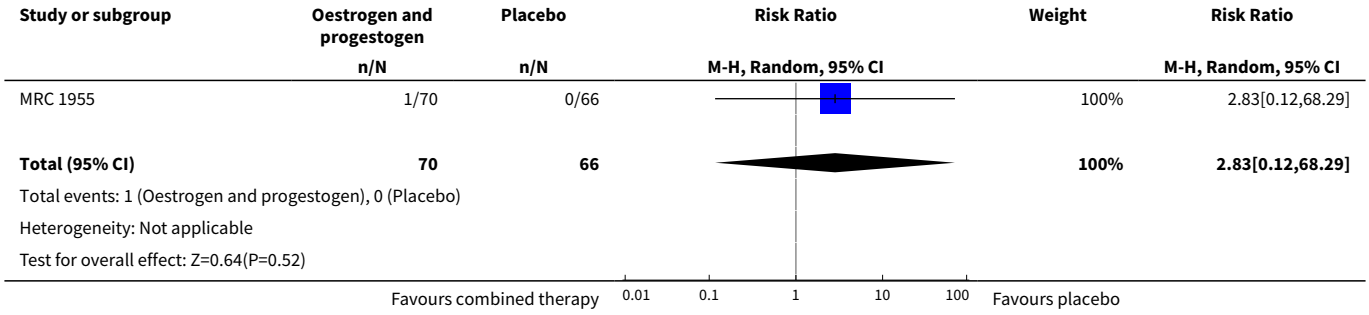




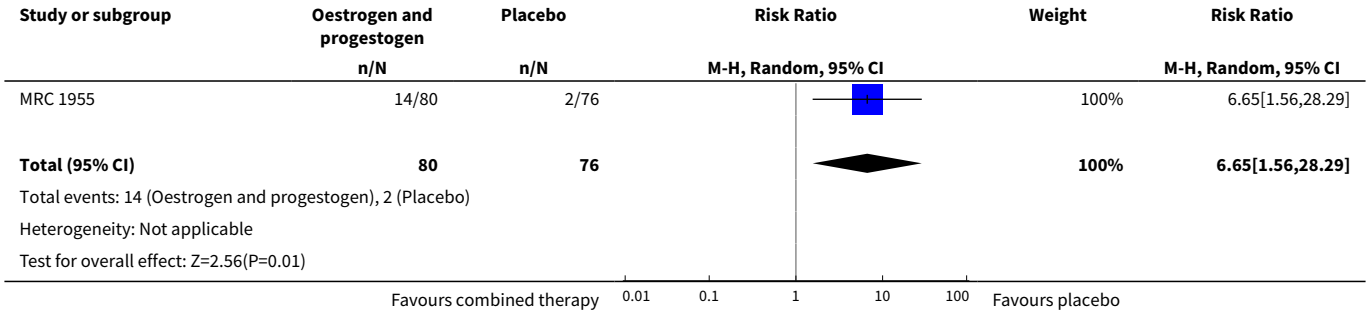
Analysis 1.7. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 7 Cancer in the reproductive system in offspring.



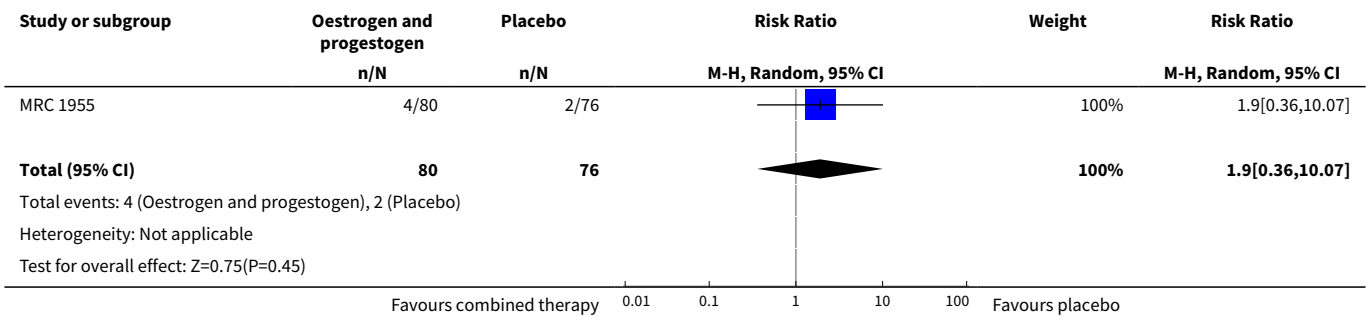
Analysis 1.8. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 8 Cancer other than of the reproductive system in offspring.



Analysis 1.9. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 9 Cancer in the reproductive system in mothers.



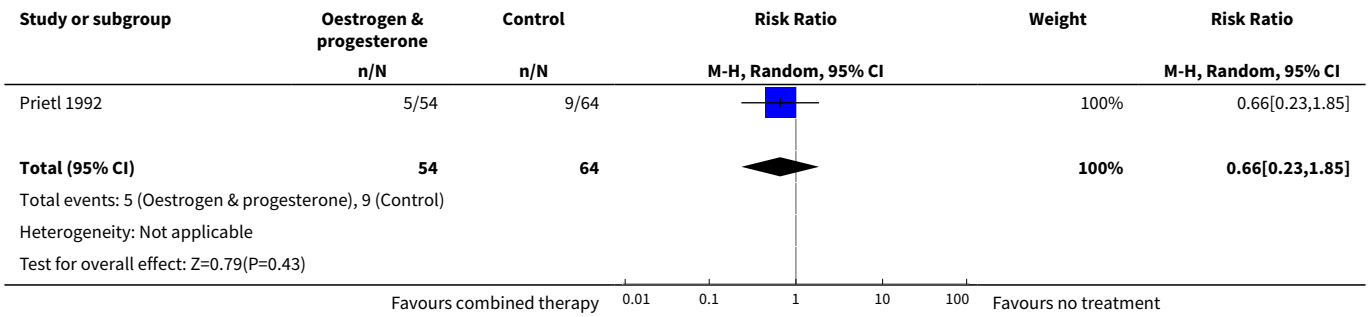
Analysis 1.10. Comparison 1 Combined oestrogen and progestogen (other than progesterone) versus placebo, Outcome 10 Cancer other than of the reproductive system in mothers.



Comparison 2. Combined oestrogen and progesterone versus no hormonal treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Miscarriage	1	118	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.23, 1.85]

Analysis 2.1. Comparison 2 Combined oestrogen and progesterone versus no hormonal treatment, Outcome 1 Miscarriage.



APPENDICES

Appendix 1. CENTRAL Search Strategy

1. MeSH descriptor Abortion, Spontaneous explode all trees
2. miscarriag* in Clinical Trials
3. spontaneous abortion in Clinical Trials
4. spontaneous pregnancy loss in Clinical Trials
5. f?etal death in Clinical Trials
6. recurrent ADJ abortion in Clinical Trials
7. recurrent ADJ pregnancy loss in Clinical Trials
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

9. MeSH descriptor Progestins explode all trees
10. progesteron* in Clinical Trials
11. progestin* in Clinical Trials
12. progest?gen* in Clinical Trials
13. MeSH descriptor Estrogens explode all trees
14. ?estrogen* in Clinical Trials
15. ?estr?diol* in Clinical Trials
16. (#9 OR #10 OR #11 OR #12)
17. (#13 OR #14 OR #15)
18. (#8 AND #16 AND #17)

Appendix 2. CINAHL Search Strategy

Limiters/Expanders: All terms were expanded. Search mode: Boolean/Phrase

1. (MM "Abortion, Spontaneous+") OR (MH "Abortion, Habitual")
2. miscarriag*
3. abortion*
4. pregnan* N3 los*
5. (f?etal or f?etus*) and (death* or die* or dead or decease*)
6. recurrent N2 abort*
7. S1 or S2 or S3 or S4 or S5 or S6
8. (MM "Progesterone+")
9. progesteron*
10. (MM "Progestational Hormones+")
11. progest?gen*
12. S8 or S9 or S10 or S11
13. (MH "Estrogens+") OR (MM "Phytoestrogens+")
14. ?estrogen*
15. ?estr?di?l*
16. S13 or S14 or S15
17. (MH "Clinical Trials") OR (MH "Preventive Trials") OR (MH "Intervention Trials") OR (MH "Random Assignment")
18. PT clinical trial*
19. AB randomi?ed control* trial*
20. AB control* clinical trial*
21. AB randomi?ed
22. AB placebo*
23. AB randomly
24. TI trial
25. random* N2 allocat*
26. (MH "Quantitative Studies") OR (MH "Experimental Studies") OR (MH "Comparative Studies") OR (MH "Double-Blind Studies") OR (MH "Triple-Blind Studies")
27. S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
28. (MM "Animals") OR (MM "Animals, Laboratory") OR (MM "Animal Studies")
29. S27 not S28
30. S7 and S12 and S16 and S29

Appendix 3. Embase Search Strategy

1. exp SECOND TRIMESTER ABORTION/ or exp SPONTANEOUS ABORTION/ or exp IMMINENT ABORTION/ or exp RECURRENT ABORTION/
2. miscarriag$.tw.
3. miscarriage/
4. abortion$.tw.
5. (pregnan$ adj3 los$).tw.
6. ((f?etal or f?etus$) adj3 (death$ or die$ or dead or decease$)).tw.

7. (recurrent adj miscarriag$).tw.
8. (recurrent adj abort$).tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp PROGESTERONE/ or exp ESTRADIOL BENZOATE PLUS PROGESTERONE/ or exp PROGESTERONE DERIVATIVE/
11. progesteron$.tw.
12. progestin$.tw.
13. progest?gen$.tw.
14. 10 or 11 or 12 or 13
15. exp ESTROGENS/
16. ?estrogen$.tw.
17. ?estr?di?l$.tw.
18. 15 or 16 or 17
19. exp controlled clinical trial/
20. randomi?ed control$ trial$.mp.
21. randomi?ed.ti,ab,sh.
22. randomly.ti,ab,sh.
23. placebo$.ti,ab,sh.
24. trial.ti.
25. (random$ adj allocat$).ti,ab,sh.
26. clinical trials as topic/
27. control$ clinical trial$.mp.
28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. animals/ not (humans/ and animals/)
30. 28 not 29
31. 9 and 14 and 28 and 30

Appendix 4. Embase Classic (1947 to 1973) Search Strategy

1. exp RECURRENT ABORTION/ or exp SECOND TRIMESTER ABORTION/ or exp IMMINENT ABORTION/ or exp ABORTION/ or exp SPONTANEOUS ABORTION/
2. miscarriag$.tw
3. miscarriage/
4. abortion$.tw.
5. (pregnan$ adj3 los$).tw.
6. (f?etal adj3 (death$ or die$ or dead or decease$)).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp PROGESTERONE/ or exp ESTRADIOL BENZOATE PLUS PROGESTERONE/
9. progesteron$.tw.
10. progestin$.tw.
11. progest?gen$.tw.
12. 8 or 9 or 10 or 11
13. exp CONJUGATED ESTROGEN/ or exp CATECHOL ESTROGEN/ or exp ESTROGEN/ or exp ESTROGEN THERAPY/
14. ?estrogen$.tw.
15. ?estr?di?l$.af.
16. 13 or 14 or 15
17. controlled study/
18. exp controlled clinical trial/
19. exp PROSPECTIVE STUDY/ or exp QUANTITATIVE STUDY/ or exp REPLICATION STUDY/ or exp COMPARATIVE STUDY/ or exp EXPERIMENTAL STUDY/ or exp CLINICAL STUDY/ or exp IN VIVO STUDY/ or exp PREVENTION STUDY/ or exp INTERVENTION STUDY/
20. 17 or 18 or 19
21. animal/ not (human/ and animal/)
22. 20 not 21
23. 7 and 12 and 16 and 22

Appendix 5. MEDLINE Search Strategy

1. exp Abortion, Habitual/ or exp Abortion, Spontaneous/
2. miscarriag$.tw.
3. miscarriage/
4. abortion$.tw.
5. (pregnan$ adj3 los$).tw.
6. ((f?etal or f?etus*) adj3 (death$ or die$ or dead or decease$)).tw.
7. (recurrent adj abort$).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Progesterone Congeners/ or exp Progesterone/
10. exp Progestins/
11. progesteron$.tw.
12. progestin$.tw.
13. progest?gen$.tw.
14. 9 or 10 or 11 or 12 or 13
15. exp "Estrogens, Conjugated (USP)"/ or exp "Estrogens, Esterified (USP)"/ or exp Estrogens/ or exp Estrogens, Catechol/ or exp Estrogens, Non-Steroidal/
16. ?estrogen$.tw.
17. exp Ethinyl Estradiol/ or exp Estradiol/ or exp Estradiol Congeners/ or exp Ethinyl Estradiol-Norgestrel Combination/
18. ?estr?di?l$.tw.
19. 15 or 16 or 17 or 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp animals/ not humans.sh
30. 28 not 29
31. 8 and 14 and 19 and 28

Appendix 6. OLDMEDLINE (1946 to 1965) Search Strategy

1. exp Abortion, Spontaneous/ or exp Abortion, Threatened/ or exp Abortion, Habitual/
2. miscarriag*.tw.
3. miscarriage/
4. abortion$.tw.
5. (pregnan$ adj3 los$).tw.
6. ((f?etal or f?etus*) adj3 (death$ or die$ or dead or decease$)).tw.
7. (recurrent adj abort$).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Progesterone/
10. exp Progestins/
11. progesteron*.tw.
12. progestin*.tw.
13. progest?gen$.tw.
14. 9 or 10 or 11 or 12 or 13
15. exp "Estrogens, Conjugated (USP)"/ or exp Estrogens/
16. exp Estradiol Congeners/ or exp Estradiol/ or exp Ethinyl Estradiol/
17. ?estrogen$.tw.

18.?estr?di?l$.tw.
19.15 or 16 or 17 or 18
20.8 and 14 and 19

CONTRIBUTIONS OF AUTHORS

Danforn Lim (DL) is guarantor for the review and developed the concept of topic. The topic was conceived by LC and FW. DL and KH completed the independent assessment of studies for inclusion, assessment of trial quality and data extraction. DL, LC, and KH were involved in developing the protocol and final review. All authors reviewed the final version. LC provided a methodological and statistical perspective and FW provided a clinical perspective.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Two changes were made from the protocol. In this review, we changed the criteria for included studies so that quasi-randomised trials were included, but in keeping with the protocol, any quasi-randomised trial included was labelled as high risk of bias in its sequence generation. The second change from our original protocol was that search strategies in OLDMEDLINE, MEDLINE, Embase Classic and Embase were based upon results that started from an earlier year of publication. This change reflected the newly default ranges of publication dates set within the mentioned databases. Nonetheless, since earlier dates were used in our searches we can only be more confident that more literature was reviewed rather than less.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [*prevention & control]; Diethylstilbestrol [administration & dosage]; Drug Combinations; Estrogens [*administration & dosage]; Ethisterone [administration & dosage]; Fertilization in Vitro; Progesterone [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy