ClinicalEvidence

Recurrent miscarriage

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ABSTRACT

INTRODUCTION: Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester, and affects 1% to 2% of women, half of whom have no identifiable cause. Overall, 75% of affected women will have a successful subsequent pregnancy, but this rate falls for older mothers and with increasing number of miscarriages. Antiphospholipid syndrome, with anticardiolipin or lupus anticoagulant antibodies, is present in 15% of women with recurrent first and second trimester miscarriage. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for unexplained recurrent miscarriage? What are the effects of treatments for recurrent miscarriage caused by antiphospholipid syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 14 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: aspirin (low dose), bed rest, corticosteroids, early scanning in subsequent pregnancies, heparin plus low-dose aspirin, human chorionic gonadotrophin, intravenous immunoglobulin treatment, lifestyle adaptation, oestrogen, paternal white cell immunisation, progesterone, trophoblastic membrane infusion, and vitamin supplementation.

QUESTIONS

INTERVENTIONS

Key points

- Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester; it affects 1% to 2% of women, in half of whom there is no identifiable cause.

  Overall, 75% of affected women will have a successful subsequent pregnancy, but this rate falls for older mothers and with increasing number of miscarriages.

  Antiphospholipid syndrome, with anticardiolipin or lupus anticoagulant antibodies, is present in 15% of women with recurrent first- and second-trimester miscarriage.

- We don't know whether bed rest, early scanning, lifestyle adaptation (to stop smoking, reduce alcohol consumption, and lose weight), low-dose aspirin, human chorionic gonadotrophin, trophoblastic membrane infusion, or vitamin supplementation increase the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

- We also don't know whether oestrogen supplementation increases the live birth rate in women with unexplained recurrent miscarriage, but it may increase the miscarriage rate and cause abnormalities in the fetus.

  We don't know whether progesterone supplementation or corticosteroids reduce miscarriage rates compared with placebo in women with unexplained recurrent miscarriage.
- Paternal white cell immunisation and intravenous immunoglobulin treatment do not seem likely to improve live birth rates compared with placebo in women with unexplained recurrent miscarriage.
- We don't know whether low-dose aspirin, alone or combined with heparin, can increase the live birth rate compared with placebo in women with antiphospholipid syndrome.

  Prednisolone plus aspirin does not seem to increase live birth rates, compared with placebo or aspirin alone, in women with antiphospholipid syndrome, and it increases the risk of adverse effects including hypertension, preterm birth, low birth weight, and admission to neonatal intensive care.

DEFINITION

Recurrent miscarriage is usually defined as three or more consecutive, spontaneous miscarriages occurring in the first trimester, with the same biological father. [1] They may or may not follow a successful birth. About half of recurrent miscarriages are unexplained. [2] **Antiphospholipid syndrome (APS)** is one of the known causes of first- and second-trimester recurrent miscarriage. APS is defined as the presence of anticardiolipin antibodies or lupus anticoagulant antibodies, in association with either three or more consecutive fetal losses before week 10 of gestation, one or more unexplained intrauterine deaths beyond 10 weeks of gestation, or one or more premature births before 34 weeks due to severe pre-eclampsia or impaired fetal growth. [3] This review covers unexplained recurrent miscarriages and both first- and second-trimester recurrent miscarriages in women with APS.

INCIDENCE/ PREVALENCE

In Western populations, recurrent miscarriage affects 1% to 2% of women of childbearing age, and about half of these are unexplained. [1] [2] Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. [4]

AETIOLOGY/ RISK FACTORS

Increasing maternal age and number of previous miscarriages increase the risk of further miscarriages. [5] No separate risk factors for APS are known.

PROGNOSIS

On average, the live birth rate for women with unexplained recurrent miscarriage is 75% in a subsequent pregnancy, with a miscarriage rate of 20% up to 9 weeks, and a 5% miscarriage rate after this period. [5] However, prognosis varies depending on maternal age and number of previous miscarriages. The chance of a successful subsequent pregnancy after three previous unexplained miscarriages varies from about 54% in a 45-year-old woman to about 90% in a 20-year-old woman. [5] A 30-year-old woman with two previous unexplained miscarriages has about an 84% chance of a successful subsequent pregnancy, whereas for a woman of the same age with 5 previous unexplained miscarriages, the success rate drops to about 71%. Prospective studies of low-risk pregnancies have found that the presence of anticardiolipin antibodies carried a three to 9 times greater risk of fetal loss. [6] Women with a history of at least three prior miscarriages and no abnormality other than the presence of antiphospholipid antibodies are highly likely to have a future miscarriage. [6]

AIMS OF INTERVENTION

To prevent miscarriage and achieve live birth, with minimal adverse effects of treatment.

OUTCOMES

Live birth rates, **miscarriage rates**, **adverse effects** of treatment in both mother and infant, including perinatal mortality.

METHODS

Clinical Evidence search and appraisal January 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2010, Embase 1980 to January 2010, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to contain 20 or more individuals of whom more than 80% were followed up. We included blinded and open-label RCTs. The minimum length of follow-up required to include RCTs was 1 year or until the end of pregnancy if the woman conceived. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we did an observational search for harms — searching for cohort studies (prospective or retrospective, with or

without a control group, minimum 20 people), case-control studies (minimum 20 people), and case series (minimum 100 people). We also use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. We have included trials that described their population as women with unexplained recurrent miscarriage, which is usually defined as three or more consecutive, spontaneous miscarriages occurring in the first trimester, with the same biological father. Most trials were not explicit about the gestational age at miscarriage, which can be difficult to determine clinically, or whether recurrent miscarriages occurred with the same biological father. Where it was clear that a trial had used a definition that varies from the usual definition of unexplained recurrent miscarriage, we have reported this. We have also included trials that described their population as women with recurrent miscarriage caused by antiphospholipid syndrome. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 22). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for unexplained recurrent miscarriage?

OPTION BED REST IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about bed rest in women with unexplained recurrent miscarriage.

Benefits and harms

Bed rest:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION EARLY SCANNING IN SUBSEQUENT PREGNANCIES OF WOMEN WITH UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about early scanning in subsequent pregnancies in women with unexplained recurrent miscarriage.

Benefits and harms

Early scanning in subsequent pregnancies:

We found no systematic review or RCTs.

Further information on studies

Comment: Early scanning in subsequent pregnancies may reduce anxiety in women with recurrent miscarriage. It has been hypothesised that reducing anxiety may reduce immunological factors that may be detrimental in early intrauterine development.

OPTION HUMAN CHORIONIC GONADOTROPHIN IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether human chorionic gonadotrophin increases the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

Benefits and harms

Human chorionic gonadotrophin versus placebo:

We found one systematic review (search date 1998, 4 RCTs, 180 women; see comment below). [7]

Miscarriage rates

Compared with placebo Human chorionic gonadotrophin may be more effective at reducing miscarriages in women with unexplained recurrent miscarriage (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[7] Systematic review	180 women with unexplained recurrent miscarriage 4 RCTs in this analysis	**Proportion of women who had a miscarriage** 13/95 (14%) with human chorionic gonadotrophin 34/85 (40%) with placebo	RR 0.35 95% CI 0.20 to 0.63 Results may be unreliable owing to methodological weaknesses of the included RCTs; see further information on studies	●●○	human chorionic gonadotrophin

Live birth rates

No data from the following reference on this outcome. [7]

Adverse effects

No data from the following reference on this outcome. [7]

Further information on studies

[7] The review included studies in women with two or more consecutive unexplained miscarriages. Three of the 4 included RCTs did not provide any data on randomisation or allocation methods, one study had missing data, and another had several exclusions after randomisation. The authors of the review state that the reduction in miscarriage should be interpreted with caution because it is largely reliant on two older and methodologically weaker studies. This review was withdrawn by The Cochrane Library because it is out of date; a protocol for an updated version of the review has been registered in The Cochrane Library.

Comment: None.

OPTION INTRAVENOUS IMMUNOGLOBULIN IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- Intravenous immunoglobulin treatment does not seem likely to improve live birth rates compared with placebo in women with unexplained recurrent miscarriage.

Benefits and harms

Intravenous immunoglobulin versus placebo/no treatment:

We found one systematic review (search date 2005, 8 RCTs). [8] We found one non-systematic review that reported adverse effects. [9]

Live birth rates

Compared with placebo/no treatment Intravenous immunoglobulin treatment is no more effective at increasing live birth rates in women with unexplained recurrent miscarriage (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[8] Systematic review	303 women with unexplained recurrent miscarriage 8 RCTs in this analysis	**Proportion of women having a live birth** 92/159 (58%) with intravenous immunoglobulin 85/144 (59%) with placebo/no treatment	RR 0.99 95% CI 0.83 to 1.19	⟷	Not significant

Miscarriage rates

No data from the following reference on this outcome. [8]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[9] Non-systematic review	Number of people not reported	**Adverse effects** with intravenous immunoglobulin Absolute numbers not reported The review reported that mild adverse events such as fever, headache, nausea, blood pressure changes, and mild tachycardia occur in between 1% and 15% of people receiving intravenous immunoglobulin treatment; see further information on studies	Significance not assessed		

No data from the following reference on this outcome. [8]

Further information on studies

[9] Rare severe adverse effects include anaphylactic reactions, haemolytic anaemia, viral infection (due to contamination of immunoglobulin), renal failure, and thrombotic events. Most severe adverse reactions tended to occur in people with anti-IgA antibodies.

Comment: None.

OPTION LIFESTYLE ADAPTATION (SMOKING CESSATION, REDUCING ALCOHOL CONSUMPTION, LOSING WEIGHT) IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about lifestyle adaptation (smoking cessation, reduced alcohol consumption, losing weight) in women with unexplained recurrent miscarriage.

Benefits and harms

Lifestyle adaptation:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION ASPIRIN (LOW DOSE) IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether low-dose aspirin increases the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

Benefits and harms

Low-dose aspirin versus placebo:

We found one systematic review (search date 2008), which identified one RCT. [10] We found one systematic review of RCTs of aspirin (search date 2000) in any pregnant women, not specifically those with unexplained recurrent miscarriage, which reported on adverse effects. [11]

Live birth rates

Compared with placebo We don't know whether low-dose aspirin is more effective at increasing live birth rates in women with unexplained recurrent miscarriage (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[10] Systematic review	54 women with recurrent miscarriage without antiphospholipid syndrome Data from 1 RCT	**Proportion of women who had a live birth** 22/27 (81%) with low-dose aspirin (50 mg/day) 22/27 (81%) with placebo	RR 1.00 95% CI 0.78 to 1.29	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT had a small sample size, important methodological limitations, and questionable external validity			

Miscarriage rates

No data from the following reference on this outcome. [10]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Perinatal mortality					
[11] Systematic review	28,208 pregnant women, not specifically those with unexplained recurrent miscarriage 20 RCTs in this analysis	**Perinatal mortality** 2.9% with aspirin 20 mg to 150 mg daily 3.1% with placebo Absolute numbers not reported	RR 0.92 95% CI 0.81 to 1.05	⟷	Not significant
[11] Systematic review	Pregnant women (number not reported), not specifically those with unexplained recurrent miscarriage 13 RCTs in this analysis	**Perinatal mortality** with aspirin up to 75 mg daily with placebo Absolute numbers not reported	RR 0.92 95% CI 0.78 to 1.09	⟷	Not significant
Neonatal bleeding					
[11] Systematic review	26,058 pregnant women, not specifically those with unexplained recurrent miscarriage 12 RCTs in this analysis	**Neonatal bleeding** 1.8% with aspirin (any dose) 1.8% with placebo Absolute numbers not reported	RR 1.03 95% CI 0.86 to 1.25	⟷	Not significant

No data from the following reference on this outcome. [10]

Low-dose aspirin plus corticosteroids versus either drug alone:
We found no systematic review or RCTs.

Low-dose aspirin plus heparin versus aspirin alone:
We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION OESTROGEN IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about oestrogen supplementation in women with unexplained recurrent miscarriage.
- Exposure to diethylstilbestrol in utero may increase primary infertility and vaginal adenosis or cervical polyps among female offspring, and may increase testicular abnormalities in male offspring.

Benefits and harms

Oestrogen supplementation:

We found no systematic review or RCTs of oestrogen supplementation in women with unexplained recurrent miscarriage. We found one systematic review (search date 2002, 7 RCTs) [12] comparing oestrogen (mainly diethylstilbestrol) versus placebo for the prevention of miscarriage, not specifically in women with unexplained recurrent miscarriage, which reported on adverse effects.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	2379 pregnant women, not specifically those with unexplained recurrent miscarriage 5 RCTs in this analysis	**Proportion of women having a miscarriage** 117/1220 (10%) with oestrogen 69/1159 (6%) with placebo	RR 1.37 95% CI 1.08 to 1.74	●○○	placebo
[12] Systematic review	1966 pregnant women, not specifically those with unexplained recurrent miscarriage 2 RCTs in this analysis	**Proportion of women delivering a baby weighing <2500 g** 94/988 (10%) with oestrogen 64/978 (7%) with placebo	RR 1.48 95% CI 1.09 to 2.00	●○○	placebo
[12] Systematic review	2173 pregnant women, not specifically those with unexplained recurrent miscarriage 3 RCTs in this analysis	**Proportion of women delivering a baby before 38 weeks** 161/1100 (15%) with oestrogen 100/1073 (9%) with placebo	RR 1.61 95% CI 1.28 to 2.02	●○○	placebo
[12] Systematic review	365 pregnant women, not specifically those with unexplained recurrent miscarriage Data from 1 RCT	**Proportion of female offspring with vaginal adenosis or cervical polyps** 153/229 (67%) with oestrogen 5/136 (4%) with placebo	RR 18.17 95% CI 7.65 to 43.17	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] Systematic review	796 pregnant women, not specifically those with unexplained recurrent miscarriage Data from 1 RCT	**Proportion of female offspring with primary infertility** 69/408 (17%) with oestrogen 28/388 (7%) with placebo	RR 2.34 95% CI 1.55 to 3.55	●●○	placebo
[12] Systematic review	1361 pregnant women, not specifically those with unexplained recurrent miscarriage Data from 1 RCT	**Proportion of female offspring with cancer of the genital tract** 14/693 (2.0%) with oestrogen 9/668 (1.3%) with placebo	RR 1.50 95% CI 0.65 to 3.44	⟷	Not significant
[12] Systematic review	879 pregnant women, not specifically those with unexplained recurrent miscarriage 2 RCTs in this analysis	**Proportion of male offspring with testicular abnormalities (not further defined)** 119/434 (27%) with oestrogen 53/445 (12%) with placebo	RR 2.32 95% CI 1.71 to 3.13	●●○	placebo

Further information on studies

[12] The review compared oestrogen (mainly diethylstilbestrol) versus placebo for the prevention of miscarriage.

Comment: None.

OPTION PATERNAL WHITE CELL IMMUNISATION IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- Paternal white cell immunisation does not seem likely to improve live birth rates compared with placebo in women with unexplained recurrent miscarriage.
- White cell immunisation may be associated with allergic reactions such as soreness and redness at the injection site, fever, maternal platelet alloimmunisation, blood group sensitisation, and cutaneous graft-versus-host reaction.

Benefits and harms

Paternal white cell immunisation versus placebo:

We found one systematic review (search date 2005, 12 RCTs, 641 women). [8]

Live birth rates

Compared with placebo Paternal white cell immunisation is no more effective at improving live birth rates in women with unexplained recurrent miscarriage (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[8] Systematic review	641 women with unexplained recurrent miscarriage 12 RCTs in this analysis	**Proportion of women having a live birth** 205/316 (65%) with immunisation 195/325 (60%) with placebo	RR 1.08 95% CI 0.96 to 1.22	⟷	Not significant

Miscarriage rates

No data from the following reference on this outcome. [8]

Adverse effects

No data from the following reference on this outcome. [8]

Further information on studies

Comment: Immunisation with blood products, such as mononuclear cells, carries risk of transmitting infections such as hepatitis B and HIV. Non-systematic reviews have suggested that white cell immunisation may be associated with allergic reactions such as soreness and redness at the injection site, fever, maternal platelet alloimmunisation, blood group sensitisation, and cutaneous graft-versus-host reaction. [13] [14]

OPTION PROGESTERONE IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether progesterone supplementation reduces miscarriage rates compared with placebo in women with unexplained recurrent miscarriage.

Benefits and harms

Progesterone versus placebo:

We found one systematic review (search date 2008). [15] We also found one retrospective observational study in women who had received infertility treatment, which reported on adverse effects. [16]

Miscarriage rates

Compared with placebo/no treatment Progesterone may be more effective at reducing miscarriage in women with unexplained recurrent miscarriage. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[15] Systematic review	223 women, 93 with 3 or more consecutive miscarriages 4 RCTs in this analysis	**Proportion of women who had a miscarriage** 23/130 (18%) with progesterone 35/93 (38%) with placebo	Peto OR 0.38 95% CI 0.20 to 0.70 P = 0.002 See further information on studies for details of methodological weaknesses of included RCTs	●●○	progesterone

Live birth rates

No data from the following reference on this outcome. [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	300 pregnant women 4 RCTs in this analysis	**Neonatal death risk** 4/173 (2%) with progesterone 1/127 (1%) with placebo	RR 2.27 95% CI 0.36 to 14.23 See further information on studies for details of methodological weaknesses of included RCTs This analysis was underpowered to detect a clinically important difference between groups	⟷	Not significant
[15] Systematic review	228 pregnant women 4 RCTs in this analysis	**Genital tract abnormalities** 1/135 (0.7%) with progesterone 0/93 (0%) with placebo	RR 7.64 95% CI 0.15 to 385.21 See further information on studies for details of methodological weaknesses of included RCTs This analysis was underpowered to detect a clinically important difference between groups	⟷	Not significant
[16] Cohort study	913 women (1016 pregnancies) who had received infertility treatment Retrospective study	**Incidence of infant congenital abnormalities** 4.1% with medroxyprogesterone acetate 3.5% with control Absolute numbers not reported	P value not reported Reported as not significant	⟷	Not significant

Further information on studies

[15] The RCTs in women with unexplained recurrent miscarriage included in the review had methodological weaknesses. They either did not provide details of randomisation, or they used quasi-randomisation methods. Allocation concealment was inadequate or unclear. One RCT excluded a large number of people after randomisation (26/56 [46%] women) and the other RCTs did not describe withdrawal. The review did not report on harms specifically in women with unexplained recurrent miscarriage.

Comment: **Clinical guide**
There is no evidence to support routine use of progestogen to prevent miscarriage in early to mid-pregnancy. There seems to be evidence of benefit in women with a history of recurrent miscarriages. More trials are needed, particularly trials that measure potential adverse effects on the fetus.

OPTION CORTICOSTEROIDS IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about corticosteroids (either alone or combined with heparin or low-dose aspirin) in women with unexplained recurrent miscarriage.

Benefits and harms

Corticosteroids:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION TROPHOBLASTIC MEMBRANE INFUSION IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether trophoblastic membrane infusion increases the likelihood of a successful pregnancy in women with unexplained recurrent miscarriage.

Benefits and harms

Trophoblastic membrane infusion versus placebo:

We found one systematic review (search date 2005), which identified one small RCT. [8]

Live birth rates

Compared with placebo Trophoblastic membrane infusion seems no more effective at increasing live birth rates in women with recurrent miscarriage (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[8] Systematic review	37 women with recurrent miscarriage Data from 1 RCT	**Proportion of women who had a live birth** 8/17 (47%) with trophoblastic membrane infusion 14/20 (70%) with placebo	RR 0.67 95% CI 0.38 to 1.20 The review may have lacked power to detect differences between groups	⟷	Not significant

Miscarriage rates

No data from the following reference on this outcome. [8]

Adverse effects

No data from the following reference on this outcome. [8]

Further information on studies

Comment: None.

OPTION VITAMIN SUPPLEMENTATION IN UNEXPLAINED RECURRENT MISCARRIAGE

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about vitamin supplementation in women with unexplained recurrent miscarriage.

Benefits and harms

Vitamin supplementation:

We found no systematic review or RCTs.

Further information on studies

Comment: We found one systematic review (search date 2004) that addressed vitamin supplementation before 20 weeks' gestation in pregnant women, but not specifically in women with recurrent miscarriage or at particular risk for miscarriage. [17] There was no significant difference in total fetal loss or early or late miscarriage between vitamin supplementation compared with no vitamins or minimal vitamins (total fetal loss: 10 RCTs, 31,167 women; RR 1.05, 95% CI 0.95 to 1.15; early or late miscarriage: 7 RCTs, 8490 women; RR 1.08, 95% CI 0.95 to 1.24). Most RCTs included in the review did not clearly present data about previous miscarriages, and meaningful subgroup analyses could therefore not be performed in such groups. It is not clear whether the findings of this review are generalisable to women with unexplained recurrent miscarriage.

QUESTION What are the effects of treatments for recurrent miscarriage caused by antiphospholipid syndrome?

OPTION ASPIRIN (LOW DOSE) IN ANTIPHOSPHOLIPID SYNDROME

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether low-dose aspirin, alone or combined with heparin, can increase the live birth rate compared with placebo in women with antiphospholipid syndrome.

Benefits and harms

Low-dose aspirin versus placebo or usual care:

We found one systematic review (search date 2004). [6]

Miscarriage rates

Compared with placebo/usual care Low-dose aspirin seems no more effective at reducing pregnancy loss (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[6] Systematic review	71 women 3 RCTs in this analysis	**Proportion of women who had a miscarriage** 10/37 (27%) with low-dose aspirin (50–81 mg/day)	RR 1.05 95% CI 0.66 to 1.68	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		8/34 (24%) with control			

Live birth rates

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	40 women Data from 1 RCT	**Proportion of women who had a premature birth** 2/20 (10%) with low-dose aspirin (50–81 mg/day) 0/20 (0%) with control	RR 5.0 95% CI 0.3 to 98.0 This analysis was likely to have been underpowered to detect differences between groups	⟷	Not significant
[6] Systematic review	125 women 3 RCTs in this analysis	**Proportion of women who had fetal growth restriction** 4/64 (6%) with low-dose aspirin (50–81 mg/day) 8/61 (13%) with control	RR 0.6 95% CI 0.2 to 1.7 This analysis was likely to have been underpowered to detect differences between groups	⟷	Not significant

Low-dose aspirin alone versus low-dose aspirin plus unfractionated heparin:
We found one systematic review [6] and one subsequent small RCT. [18]

Miscarriage rates

Compared with low-dose aspirin plus unfractionated heparin Low-dose aspirin alone may be less effective at reducing pregnancy loss (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[6] Systematic review	140 women 2 RCTs in this analysis	**Proportion of women who had a miscarriage** 40/70 (57%) with low-dose aspirin alone (75–81 mg/day) 18/70 (26%) with low-dose aspirin plus unfractionated heparin (5000 U twice daily)	RR 2.17 95% CI 1.41 to 3.45	●●○	low-dose aspirin plus unfractionated heparin

No data from the following reference on this outcome. [18]

Live birth rates

Compared with low-dose aspirin plus unfractionated heparin Low-dose aspirin alone seems less effective at increasing live birth rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Live birth rates					
[18] RCT	72 women	**Proportion of women who had a live birth** 24/39 (62%) with low-dose aspirin alone (80 mg/day) 28/33 (85%) with low-dose aspirin plus unfractionated heparin (5000 U twice daily)	P = 0.04 The trial reported that it was randomised, but the method of randomisation was not described. The level of blinding was not reported	○○○	low-dose aspirin plus unfractionated heparin

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	140 women 2 RCTs in this analysis	**Proportion of women who had a premature birth** 5/70 (7%) with low-dose aspirin alone (75–81 mg/day) 11/70 (16%) with low-dose aspirin plus unfractionated heparin (5000 U twice daily)	RR 0.5 95% CI 0.2 to 1.3 This analysis was likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant
[6] Systematic review	140 women 2 RCTs in this analysis	**Proportion of women who had fetal growth restriction** 2/70 (3%) with low-dose aspirin alone (75–81 mg/day) 6/70 (9%) with low-dose aspirin plus unfractionated heparin (5000 U twice daily)	RR 0.3 95% CI 0.1 to 1.6 This analysis was likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant
[18] RCT	72 women	**Adverse effects** with low-dose aspirin alone (80 mg/day) with low-dose aspirin plus unfractionated heparin (5000 U twice daily) Absolute numbers not reported The RCT reported minor epistaxis in 3 women with aspirin plus unfractionated heparin, and occasional bruising at the injection site in women given subcutaneous heparin (no further details reported)	Significance not assessed The trial reported that it was randomised, but the method of randomisation was not described. The level of blinding was not reported		

Low-dose aspirin alone versus low-dose aspirin plus low molecular weight heparin:
We found one systematic review. [6]

Miscarriage rates

Compared with low-dose aspirin plus low molecular weight heparin We don't know whether low-dose aspirin alone is more effective at reducing pregnancy loss (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[6] Systematic review	98 women Data from 1 RCT	**Proportion of women who had a miscarriage** 13/47 (28%) with low-dose aspirin (75 mg/day) 11/51 (22%) with low-dose aspirin plus low molecular weight heparin	RR 1.28 95% CI 0.64 to 2.56	⟷	Not significant

Live birth rates

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	98 women Data from 1 RCT	**Proportion of women who had a premature delivery** 4/47 (9%) with low-dose aspirin (75 mg/day) 2/51 (4%) with low-dose aspirin plus low molecular weight heparin	RR 2.2 95% CI 0.4 to 11.1 This analysis was likely to have been underpowered to detect differences between groups	⟷	Not significant

Low-dose aspirin alone versus corticosteroids plus low-dose aspirin:

See option on corticosteroids, p 17 . For adverse effects see option on corticosteroids, p 17 .

Further information on studies

[6] One of the RCTs included in the review (90 women) found that unfractionated heparin plus aspirin reduced maternal lumbar spine bone mineral density (median change –5.4%, range –8.6% to +1.7%), but there were no vertebral fractures (figures not reported for aspirin-alone group; see comment below). [19] This decrease is similar to that normally seen with 6 months of lactation.

Comment: Higher doses of aspirin (such as 300–600 mg every 6–8 hours) are associated with bronchospasm, gastrointestinal haemorrhage, and hypersensitive skin reactions. However, the adverse profile of lower-dose aspirin may differ. See also option on low-dose aspirin in treatment of women with unexplained recurrent miscarriage, p 6 .

The RCTs included in the review comparing low-dose aspirin versus low-dose aspirin plus low molecular weight heparin (LMWH) may have underestimated fetal loss rate because women were enrolled up until week 12 of gestation (mean 6.7 weeks, range 4.0 weeks to 12.0 weeks), by which time some antiphospholipid-related pregnancy losses would already have taken place. [6] Further RCTs are needed to explore the potential differences between unfractionated heparin and LMWH. The reduction in bone mineral density seen with unfractionated heparin may be reversible to some extent once heparin is discontinued, and may be less marked with LMWH. [20]

OPTION ASPIRIN (LOW DOSE) PLUS HEPARIN

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We don't know whether low-dose aspirin combined with heparin can increase the live birth rate compared with placebo in women with antiphospholipid syndrome.

Benefits and harms

Low-dose aspirin plus unfractionated or low molecular weight heparin versus placebo:

We found one systematic review (search date 2004), which found no RCTs. [6] We found no subsequent RCTs.

Low-dose aspirin plus unfractionated heparin versus low-dose aspirin alone:

See option on low-dose aspirin, p 13 .

Low-dose aspirin plus low molecular weight heparin versus low-dose aspirin alone:

See option on low-dose aspirin, p 13 .

Further information on studies

Comment:

Adverse effects One case series (150 pregnant women with antiphospholipid syndrome) found that heparin plus low-dose aspirin was associated with a median reduction in lumbar spine bone mineral density of +3.4% (range –11.7% to +9.0%). [21] One cohort study (123 pregnant women with antiphospholipid syndrome receiving low-dose aspirin plus heparin) found no significant difference in bone mineral density loss between women receiving unfractionated heparin and those receiving low molecular weight heparin (LMWH) (lumbar spine loss: 0.044 g/cm^2 with LMWH *v* 0.049 g/cm^2 with unfractionated heparin; P = 0.6). [22] See also comment on low-dose aspirin, p 13 and harms of low-dose aspirin, p 13 .

OPTION CORTICOSTEROIDS IN ANTIPHOSPHOLIPID SYNDROME

- For GRADE evaluation of interventions for Recurrent miscarriage, see table, p 22 .
- We found no direct information from RCTs about corticosteroids alone in women with recurrent miscarriage caused by antiphospholipid syndrome.
- Prednisolone plus low-dose aspirin does not seem to increase live birth rates, compared with placebo or aspirin alone, in women with antiphospholipid syndrome.
- Prednisolone plus low-dose aspirin increases the risk of hypertension, preterm birth, low birth weight, and admission to neonatal intensive care.

Benefits and harms

Corticosteroids alone:

We found one systematic review (search date 2004), which found no RCT. [6]

Corticosteroids plus low-dose aspirin versus placebo:

We found one systematic review, [6] which identified one RCT. [23]

Miscarriage rates

Compared with placebo Corticosteroids plus low-dose aspirin seem no more effective at reducing pregnancy loss (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[6] Systematic review	88 women Data from 1 RCT	**Proportion of women who had a miscarriage** 17/42 (40%) with prednisolone plus low-dose aspirin (100 mg/day) 22/46 (48%) with placebo	RR 0.85 95% CI 0.53 to 1.36	⟷	Not significant

Live birth rates

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	88 women Data from 1 RCT	**Proportion of women with hypertension** 13% with prednisolone plus low-dose aspirin (100 mg/day) 5% with placebo Absolute numbers not reported	P = 0.05	⟷	Not significant
[6] Systematic review	202 women, including 88 women with antiphospholipid syndrome Data from 1 RCT	**Proportion of women with gestational diabetes** 15/101 (15%) with prednisolone plus low-dose aspirin (100 mg/day) 5/101 (5%) with placebo	RR 3.0 95% CI 1.1 to 7.9	●●○	placebo
[6] Systematic review	202 women, including 88 women with antiphospholipid syndrome Data from 1 RCT	**Proportion of women who had a preterm birth** 41/101 (41%) with prednisolone plus low-dose aspirin (100 mg/day) 7/101 (7%) with placebo	RR 5.9 95% CI 2.8 to 12.4	●●●	placebo
[6] Systematic review	202 women, including 88 women with antiphospholipid syndrome Data from 1 RCT	**Proportion of babies admitted to neonatal ICU** 18/101 (18%) with prednisolone plus low-dose aspirin (100 mg/day) 2/101 (2%) with placebo	RR 9.0 95% CI 2.1 to 37.8	●●●	placebo

Corticosteroids plus low-dose aspirin versus low-dose aspirin alone:

We found one systematic review, which identified one small RCT. [6]

Miscarriage rates

Compared with low-dose aspirin alone Corticosteroids plus low-dose aspirin may be no more effective at reducing miscarriages (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Miscarriage rates					
[6] Systematic review	39 women randomised Data from 1 RCT	**Proportion of women who had a miscarriage** 0/12 with prednisolone plus low-dose aspirin 0/22 with aspirin alone Analysis not by intention to treat	Significance not assessed		

Live birth rates

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	39 women randomised Data from 1 RCT	**Proportion of women who had a preterm birth** 8/12 (67%) with prednisolone plus low-dose aspirin 3/22 (14%) with aspirin alone Analysis not by intention to treat	RR 4.9 95% CI 1.6 to 15.1	●●○	aspirin alone
[6] Systematic review	39 women randomised Data from 1 RCT	**Mean birth weight** 2800 g with prednisolone plus low-dose aspirin 3352 g with aspirin alone No infants in either group were growth retarded (below 10th percentile) at birth. There were no perinatal deaths and no mother or neonate had significant haemorrhage Analysis not by intention to treat	Mean difference in birth weight 552 g 95% CI 1064 g to 39 g	●●○	aspirin alone

Further information on studies

Comment: The review [6] identified one RCT comparing prednisolone plus low-dose aspirin versus heparin plus low-dose aspirin. [24] Although the review reported that the RCT included 45 women, the original paper reported that only 20 of these women had been randomised to their treatment group,

with only 8 women randomised to prednisolone plus aspirin. [24] This RCT therefore did not meet *Clinical Evidence* inclusion criteria, which, because of the need for adequate power to detect clinically important differences between groups, requires at least 10 randomised people in each treatment group.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Progesterone in unexplained recurrent miscarriage Updated version of already included review added; no new evidence found. Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge effects of this intervention.

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GRADE **Evaluation of interventions for Recurrent miscarriage.**

Important outcomes				Live birth rates, Miscarriage rates					
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for unexplained recurrent miscarriage?									
4 (180) [7]	Miscarriage rates	Human chorionic gonadotrophin versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, uncertainty about randomisation, and for allocation and methodological weaknesses. Directness point deducted for inclusion of women with 2 or more consecutive miscarriages
8 (303) [8]	Live birth rates	Intravenous immunoglobulin versus placebo/no treatment	4	0	0	0	0	High	
1 (54) [10]	Live birth rates	Low-dose aspirin versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and for methodological weaknesses
12 (641) [8]	Live birth rates	Paternal white cell immunisation versus placebo	4	0	0	0	0	High	
4 (223) [15]	Miscarriage rates	Progesterone versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, uncertainty about randomisation, allocation concealments, and methodological weaknesses
1 (37) [8]	Live birth rates	Trophoblastic membrane infusion versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments for recurrent miscarriage caused by antiphospholipid syndrome?									
3 (71) [6]	Miscarriage rates	Low-dose aspirin versus placebo or usual care	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (140) [6]	Miscarriage rates	Low-dose aspirin alone versus low-dose aspirin plus unfractionated heparin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (72) [18]	Live birth rates	Low-dose aspirin alone versus low-dose aspirin plus unfractionated heparin	4	–2	0	0	0	Low	Quality points deducted for sparse data, and uncertainty about blinding and method of randomisation
1 (98) [6]	Miscarriage rates	Low-dose aspirin alone versus low-dose aspirin plus low molecular weight heparin	4	–2	0	0	0	Low	Quality points deducted for sparse data and for enrolling women up to later gestation periods
1 (88) [6]	Miscarriage rates	Corticosteroids plus low-dose aspirin versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (39) [6]	Miscarriage rates	Corticosteroids plus low-dose aspirin versus low-dose aspirin alone	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no intention-to-treat analysis

Important outcomes			Live birth rates, Miscarriage rates						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									