Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome (Review)

Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S
Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Stef Kaandorp1, Marcello Di Nisio2, Mariette Goddijn3, Saskia Middeldorp4

1Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, Netherlands. 2Department of Vascular Medicine, F4-138, Academic Medical Center, Amsterdam, Netherlands. 3Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center (F4-205), Amsterdam, Netherlands. 4Department of Clinical Epidemiology, Department of General Internal Medicine, Leiden University Medical Center (LUMC), Leiden, Netherlands

Contact address: Stef Kaandorp, Obstetrics and Gynaecology, Academic Medical Center, Meibergdreef 9, P.O. Box 22660, Amsterdam, 1100 DD, Netherlands. s.p.kaandorp@amc.uva.nl.

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ABSTRACT

Background

Since hypercoagulability might result in recurrent miscarriage, anticoagulant agents could potentially increase the live-birth rate in subsequent pregnancies in women with either inherited thrombophilia or unexplained recurrent miscarriage.

Objectives

To evaluate the efficacy and safety of anticoagulant agents, such as aspirin and heparin, in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group’s Trials Register (April 2008), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 1), MEDLINE (January 1966 to March 2007), and EMBASE (1980 to March 2007). We scanned bibliographies of all located articles for any unidentified articles.

Selection criteria

Randomised and quasi-randomised controlled trials that assessed the effect of anticoagulant treatment on the live-birth rate in women with a history of at least two miscarriages (up to 20 weeks of amenorrhoea) without apparent causes other than inherited thrombophilia were eligible. Interventions included aspirin, unfractionated heparin, and low molecular weight heparin for the prevention of miscarriage. One treatment could be compared with another or with placebo.

Data collection and analysis

Two authors assessed the trials for inclusion in the review and extracted the data. We double checked the data.
Main results

Two studies (189 participants) were included in the review. In one study, 54 pregnant women with recurrent miscarriage (RM) but no detectable anticardiolipin antibodies were randomised to low-dose aspirin or placebo. RM was defined as three or more consecutive miscarriages (occurring before 22 weeks' gestational age (based on last menstrual period)). Similar live-birth rates were observed with aspirin and placebo, both 81% (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.78 to 1.29). In the other study, 107 women with consecutive recurrent miscarriage without any apparent cause and no hereditary thrombophilia were randomised between enoxaparin and aspirin. Here RM was stated as three or more consecutive first trimester miscarriages or at least two consecutive second trimester miscarriages. Similar live birth rates were observed with enoxaparin and aspirin, respectively 82% and 84% (RR 0.97, 95% CI 0.81 to 1.16).

Authors' conclusions

There is a paucity in studies on the efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. The two reviewed trials studied different treatments and only one study was placebo-controlled. Neither of the studies showed a benefit of one treatment over the other. Therefore, the use of anticoagulants in this setting is not recommended. However, large randomised placebo-controlled trials are still urgently needed.

PLAIN LANGUAGE SUMMARY

Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Two studies (189 women) were included in the review. There is Insufficient evidence to say if anticoagulants help women with recurrent miscarriage without antiphospholipid syndrome.

Recurrent miscarriage (RM) is associated with inherited blood clotting disorders that could interfere with the placental blood circulation. Anticoagulant drugs for women with RM and such an underlying blood clotting problem may help, although these drugs may also cause excessive bleeding. Judgement if anticoagulants help women with RM in the absence of antiphospholipid syndrome is not possible because of the lack of sufficient evidence from the reviewed trials on this subject.

BACKGROUND

Recurrent miscarriage (RM) is devastating for women and their families, while up to 15% of all clinically recognised pregnancies end in miscarriage (miscarriage before the 20th week of gestational age) (Everett 1997; Huisjes 1984). Approximately 5% of women experience two or more miscarriages, whereas RM, defined as three or more first trimester miscarriages, may affect as many as 1% to 2% of women of reproductive age (Clifford 1994; Cook 1995; Stirrat 1990). The definition of RM remains the subject of debate. The World Health Organization (WHO) defines miscarriage as a pregnancy ending in the death or expulsion of the fetus or the embryo before the 20th week of gestational age (WHO 1977). Often RM is defined as three or more consecutive miscarriages. According to recent European Society for Human Reproduction & Embryology (ESHRE) guidelines, RM is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks' amenorrhoea (Jauniaux 2006). Some guidelines use the definition of two or more miscarriages for offering an evaluation of etiologic causes ((American College of Obstetrics and Gynecology (ACOG 2001); Dutch Society of Obstetrics and Gynecology (NVOG 2007)). However, the risk of a miscarriage after two or three consecutive miscarriages is almost similar (Regan 1988). Adequate characterisation of miscarriages and patients in RM studies is most important and, favourably, would be the same to make studies mutually comparable (Christiansen 2006). In this review we decided to use the broad definition of RM: two or more miscarriages (up to 20 weeks of amenorrhoea).

Miscarriage is associated with relevant maternal morbidity like bleeding and infection and, sometimes, maternal death (NHMRC
Thrombophilia are a diverse group of coagulation disorders associated with a predisposition to thrombosis and thus increased risk for thrombotic events as deep vein thrombosis and pulmonary embolism. These hypercoagulable states can be either acquired, as for instance the antiphospholipid syndrome, or inherited as the factor V Leiden mutation (which results in a decreased capacity to inactivate activated factor V by the protein C system, also known as activated protein C (APC) resistance), the deficiency of physiological anticoagulants like protein C, protein S and antithrombin and the prothrombin G20210A gene mutation (resulting in increased concentrations of prothrombin in plasma) or an elevated level of factor VIII-ac.

A growing body of evidence has implicated thrombophilia in adverse obstetrical events (such as intrauterine growth restriction, miscarriage, severe pre-eclampsia, and placental abruption) (Kupferminc 1999; Middeldorp 2007) and there is also reasonable evidence to suggest that some cases of recurrent miscarriage are associated with thrombosis of placental vessels and infarction. Firstly, microthrombi are a common finding in the placental vasculature of women with recurrent miscarriage (Rushton 1988). Secondly, placental thrombosis and infarction have been described in association with certain thrombophilic defects (Dixon 1997; Rai 1996), but other pathophysiological pathways than thrombosis could also be involved, since adverse pregnancy outcomes can occur in women with thrombophilia in the absence of placental thrombosis (Mousa 2000). Thirdly, thrombophilic defects are significantly more prevalent amongst women with such pregnancy complications (Rai 1995; Rey 2003). A meta-analysis showed that the magnitude of the association between thrombophilia and fetal loss varies according to the timing of fetal loss (Rey 2003). In particular, first trimester recurrent miscarriage was associated with factor V Leiden, APC resistance, and prothrombin G20210A mutation, while late non-recurrent fetal loss was associated with factor V Leiden, prothrombin G20210A mutation, and protein S deficiency. Also, family studies showed that women with hereditary thrombophilia, especially those with combined defects or antithrombin deficiency, have an increased risk of miscarriage and intrauterine fetal death compared to women without these defects (Meinardi 1999; Preston 1996; Sanson 1996).

The prognosis in subsequent pregnancies of women with recurrent miscarriage without antiphospholipid antibody syndrome is the live-birth rate of approximately 50% to 89% (Brigham 1999; Lindqvist 2006; Rai 2000; Stirrat 1990). For women with recurrent miscarriage and underlying thrombophilic disorders, these figures range from 63% to 80% (Preston 1996; Rai 2000). The differences between studies can probably be explained by differences in the populations of women participating in the studies.

The use of anticoagulants in pregnancy needs to be carefully monitored and evaluated for safety since it can carry risks for the mother and the fetus. In contrast to coumarin derivatives, neither unfractonated heparin nor low molecular weight heparin cross the placenta and therefore do not have the potential to cause fetal bleeding and teratogenicity (Ginsberg 2001). The maternal risks associated with heparin administration are uncommon but potentially serious and include bleeding, heparin-induced thrombocytopenia and heparin-induced osteopenia with fractures. Moreover, heparin administration may cause pain and slight bruising at injection sites. There is accumulating evidence that low molecular weight heparin is at least as effective and safe as unfractionated heparin with potential advantages during pregnancy, since they cause less heparin-induced thrombocytopenia, can be administered once daily, and are associated with a lower risk of heparin-induced osteoporosis (Ginsberg 2001; Sanson 1999). Based on current evidence, low-dose aspirin (less than 150 mg/d) during the second and third trimesters appears to be safe, while the safety of higher doses of aspirin and/or aspirin ingestion during the first trimester remains uncertain (Ginsberg 2001). The use of heparin in pregnancy has been covered in another Cochrane review (Walker 2003).

In clinical practice, women with recurrent miscarriage associated
with inherited thrombophilia or recurrent miscarriage without any other apparent predisposing disorder are frequently seeking advice about the indication for anticoagulant treatment. Some clinicians tend to extrapolate the beneficial effect of anticoagulant therapy in women with antiphospholipid antibody syndrome and recurrent miscarriage to all women with recurrent miscarriage without apparent cause or with inherited thrombophilia; whether there is evidence for this is the objective of this review.

**OBJECTIVES**

The objective of this review was to determine whether anticoagulant treatment improves pregnancy outcome in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised controlled trials and quasi-randomised controlled trials that assessed the effect of anticoagulant treatment on improving the live-birth rate in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia.

**Types of participants**

Participants were pregnant women or women who were actively trying to become pregnant with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. Studies that included women with apparent causes (other than familial thrombophilia) of recurrent miscarriage (antiphospholipid syndrome; uterine abnormalities; patients’ or their partners’ karyotype abnormalities; endocrine and toxic factors (diabetes mellitus); miscarriage due to documented fetal malformation or the result of an infectious complication) have been included only if the results from women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia could be extracted to be analysed separately. According to the WHO definitions and ESHRE guidelines, the term miscarriage referred to a miscarriage occurring before the 20th week of amenorrhoea. For the studies included in the review, the respective definition for recurrent miscarriage is reflected. The study populations are described whenever possible with regard to number of miscarriages, gestational age of the miscarriages, and maternal age.

**Types of interventions**

The interventions included were aspirin, unfractionated heparin, and low molecular weight heparin for the prevention of miscarriage. One treatment could be compared with another or with placebo. Combinations of therapy could be used.

**Types of outcome measures**

**Primary outcomes**

Live-birth rate

**Secondary outcomes**

1. Preterm delivery of a live infant between 24 and 28 weeks’ gestational age
2. Preterm delivery of a live infant between 28 and 32 weeks’ gestational age
3. Preterm delivery of a live infant between 32 and 37 weeks’ gestational age
4. Obstetric complications (pregnancy associated hypertension, pre-eclampsia, intrauterine growth retardation)
5. Congenital malformations
6. Admission to special care
7. Side effects of the drug used, both for the mother and the baby (maternal and/or neonatal bleeding, heparin-induced thrombocytopenia, heparin-induced osteopenia, pain and bruising at injection sites, allergic reactions to heparin, and teratogenicity)
8. Thromboembolic complications

**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 (April 2008).

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

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

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

Trials identified through the searching activities described above are 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 the Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 1), MEDLINE (January 1966 to March 2007), and EMBASE (1980 to March 2007) using the search strategy listed in Appendix 1.

Searching other resources
We scanned bibliographies of all located articles for any unidentified articles.
We did not apply any language restrictions.

Data collection and analysis
Two review authors independently reviewed titles and abstracts from the database searches to determine whether the inclusion criteria were satisfied. We made decisions regarding inclusion separately and compared results. We resolved any disagreements through discussion. Two authors independently reviewed the full text of identified articles, including those where there was disagreement in the initial title or abstract scanning, to ensure that the inclusion criteria were met. Where necessary, we contacted trial authors for additional information.

Two authors independently extracted the study characteristics using an agreed format and data from included studies, including assessments of quality. We resolved any disagreements by consensus and, if necessary, by involvement of a third author. If we could not reach agreement, we excluded the item until further information was available from the trialists. One author scanned conference proceedings and included them if adequate information could be obtained either from the abstract or from personal communication. One author identified articles from other sources (experts or reference lists) as possibly eligible and then two authors independently assessed them for inclusion, as above. Blinding of authors, journal of origin, or institutions did not occur. Two authors independently assessed the abstracts of non-English articles, which had to be translated, to ascertain if they met the inclusion criteria.

We obtained a translation of the full article of those that met the criteria. We assessed the validity of each included trial according to the criteria outlined in the Cochrane Reviewers’ Handbook (Clarke 2002). These include generation of randomisation sequence; allocation concealment; blinding of subject, investigator, and outcome assessor; less than 20% loss to follow up; and analysis by intention to treat. Where the method of allocation concealment was unclear, we attempted to contact authors to provide further details. Allocation concealment was judged adequate (A), unclear (B), inadequate (C), or not used (D), depending on the concealment schemes used. Blinding was considered double or single if both the physician and the participant or only one of them were unaware of the assigned intervention. We assessed other aspects of study quality in the studies which fulfilled the inclusion criteria.

We included all trials in the initial analyses and carried out sensitivity analyses to explore the effect of trial quality. We repeated analyses taking into account factors that could have introduced bias, such as the inclusion of quasi-randomised studies, high levels of exclusions which were unbalanced between the groups, or other insecure allocation concealment. We interpreted any differences cautiously and only used them to generate hypotheses. Despite this quality assessment, we did not exclude any study on the basis of quality. We carried out statistical analyses using the Review Manager software (RevMan 2000), with results presented as summary relative risks. We calculated risk ratios using a fixed-effect model (Mantel-Haenszel method).

In the case of homogenous data, we expressed summary statistics as risk difference (RD) and we used the number needed to treat (1/RD) to express the final results of the review.

We applied tests of heterogeneity between trials to assess the significance of any differences between trials ($I^2$ method, significant if greater than 0.3) and explored possible causes of any heterogeneity. If we detected heterogeneity, we planned to perform subgroup analyses for the main outcomes by individual quality criteria to assess the effect of poorer quality studies on the magnitude of the estimate of effect. If data were available, we also planned to perform subgroup analysis to compare outcomes in: (1) different inherited thrombophilic disorders; (2) preconceptional or periconceptional anticoagulant use; (3) type of anticoagulant(s) used (e.g. single drug, combination of anticoagulant agents); (4) dose of anticoagulant(s); (5) duration of anticoagulant use; and (6) women with a history of three or more miscarriages or two or more miscarriages.

We assessed publication bias using the funnel plot. Symmetry would be expected in the absence of any bias, although situations other than publication bias may result in asymmetry. We would have explored any anomaly, but it was anticipated that the number of eligible studies might be too few to allow adequate assessment.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
**Characteristics of included studies**

We included two studies (189 women) (Dolitzky 2006; Tulppala 1997) in this review. For the study by Tulppala (Tulppala 1997), we extracted data on the subgroup of women fulfilling the inclusion criteria of the review. Dolitzky 2006 evaluated the effect of aspirin or low-molecular-weight heparin in women with unexplained RM. RM was defined as three or more consecutive first trimester miscarriages or at least two consecutive second trimester miscarriages. The objective was to compare the effect of aspirin and enoxaparin on live-birth rate. Women were only included if there was no apparent cause for the miscarriages including absence of hereditary thrombophilia (factor V Leiden, prothrombin mutation (G20210A), homozogous MTHFR mutation, deficiency of protein C,S or antithrombin). The treatment with enoxaparin (40 mg/day) or aspirin (100 mg/day) was started from the time of detection of a fetal heart beat at 6 to 12 weeks gestation. Of the 107 included women, 54 received enoxaparin, 50 aspirin and 3 were lost to follow up. Besides the primary outcome measure of live-birth rate secondary outcomes like preterm delivery, intrauterine growth restriction, and pre-eclampsia were reported.

Tulppala 1997 evaluated the effect of low-dose aspirin (50 mg/day) on live-birth rate in pregnant women with preceding RM with or without detectable anticardiolipin antibodies and no other apparent cause for their previous miscarriages. RM was defined as three or more consecutive miscarriages (occurring before 22 weeks of gestational age). Aspirin was compared to placebo, with medication started as soon as a home urinary pregnancy test became positive. From this trial, we extracted data for the 54 women negative for anticardiolipin antibodies. Of these, 27 were assigned to aspirin and 27 to placebo. Secondary outcomes, such as preterm delivery, obstetric complications, and bleeding rate could not be extracted separately for the group of women with negative anticardiolipin antibodies. Overall, we excluded 18 studies from the review. We have provided the reasons for exclusion in the ‘Characteristics of excluded studies’ table.

**Effects of interventions**

We have included two trials, involving 189 participants, in this review. Given the paucity of data, we were unable to carry out the sensitivity and subgroup analysis as planned. In the study by Dolitzky et al (Dolitzky 2006), 54 patients were randomized to enoxaparin and 50 patients to aspirin. The mean age did not differ between the enoxaparin and aspirin groups, respectively 31.73 +/- 5.3 and 30.65 +/- 6.18. Also the number of previous miscarriages did not differ between the enoxaparin and aspirin groups, respectively 3.8 +/- 1.4 and 3.9 +/- 1.4. The number lost to follow up was three (2.8%). Both groups had similar live birth rates, 82% in the enoxaparin group and 84% in the aspirin group. The RR for enoxaparin versus aspirin was 0.97 (95% CI 0.81 to 1.16). In a post-hoc analysis of women who had no live children (primary aborters), women allocated to enoxaparin had a non-significantly increased live birth, 94% as compared to 81% in those who had been allocated to aspirin. The number of preterm deliveries and cases of intrauterine growth restriction did not differ between the two groups. Pre-eclampsia was found in three women in the aspirin group and in none in the enoxaparin group. Placental doppler blood flow studies were similar in both groups. No maternal side effects were seen. In the aspirin group, one infant was born with a necrotic testis and one had a convulsion caused by hypoglycaemia. In each group, one baby with a congenital anomaly was found. One fetus was detected with tricuspid insufficiency (the pregnancy was terminated) in the aspirin group and one infant had an imperforate hymen in the enoxaparin group.

For the study by Tulppala et al (Tulppala 1997), we extracted data for the subgroup of women fulfilling the inclusion criteria of the review. We could not extract data on mean age or mean number of miscarriages in the obstetric history in both groups. Fifty-four pregnant women with recurrent miscarriage without detectable anticardiolipin antibodies were randomised to low-dose aspirin or placebo. In both groups, 81% of the pregnancies resulted in a live birth (RR 1.00, 95% CI 0.78 to 1.29). We could not extract data on secondary outcomes, such as preterm delivery, obstetric complications, or bleeding rate.

**Risk of bias in included studies**

Details for the two included studies are in the ‘Characteristics of included studies’ table. The study by Dolitzky 2006 was not blinded and not placebo controlled. The randomisation method was clearly described with adequate concealment of allocation. The study by Tulppala 1997 was a double-blind, placebo-controlled trial. The method of randomisation was not stated and concealment of allocation was not clear.

**Discussion**

The results of this systematic review show a paucity of published intervention trials with anticoagulants in women with unexplained recurrent miscarriage without antiphospholipid antibodies. We included only two randomised controlled trials in this review; in one of them we could include data of only a small subgroup of women fulfilling the inclusion criteria of the review (Tulppala 1997). Neither study, one using low-dose aspirin and placebo (Tulppala 1997) and one comparing enoxaparin with aspirin (Dolitzky 2006), showed improvement of gestational outcome. Therefore, the use
of either aspirin or low-molecular-weight heparin to prevent miscarriage in women with two or more miscarriages without apparent causes other than inherited thrombophilia, is not based on evidence and should be discouraged. Currently, properly randomised controlled trials using placebo or no treatment arms are ongoing.

AUTHORS’ CONCLUSIONS

Implications for practice

There is a paucity in evidence on the efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. The two reviewed trials studied different treatments and only one study was placebo-controlled. None of the studies showed an effect of one treatment over the other. Therefore, the use of anticoagulants in this setting is not recommended. However, large, randomised, placebo-controlled trials are urgently needed.

Implications for research

From a public health perspective, even a moderate benefit from aspirin or anticoagulants in this high-risk group of women might be worthwhile, and large studies of strong methodological quality are awaited to clarify the real risk-benefit of such an approach. Moreover, the inclusion of a placebo or no-treatment arm in these studies is necessary since it would provide an adequate control to the active treatment and allows assessing a risk-benefit ratio.

ACKNOWLEDGEMENTS

Louisette Peters was an author on the first version of this review.

REFERENCES

References to studies included in this review

Dolitzky 2006 {published data only}

Tulppala 1997 {published data only}

References to studies excluded from this review

Bar 2000 {published data only}

Bar 2001 {published data only}
Bick 2000 [published data only]

Brenner 2000 [published data only]

Brenner 2005 [published and unpublished data]

Corrections for Bick 2000 and Brenner 2000 [published data only]

Carp 2003 [published data only]

Grandone 2002 [published data only]

Gris 1995 [published data only]

Gris 2004 [published data only]

Li 2003 [published data only]

Ogasawara 2001 [published data only]

Rai 2000 [published data only]

References to ongoing studies
ALIFE study [published data only]
Middeldorp S. Aspirin or low molecular weight heparin for women with unexplained recurrent miscarriage and/or intra-uterine fetal death. Netherlands Trial Register (http://www.trialregister.nl) (accessed 1 November 2005).
Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome (Review)

ETHIGII [published data only]

SPIN study [published data only]

TIPPS study [published data only]

Additional references


Levine 2002

Lindqvist 2006

Lockshin 1999

Meinardi 1999

Middeldorp 2007

Mousa 2000

NHMRC 2001

NVOG 2007

Porter 2006

Prescott 1996

Rai 1995

Rai 1996

Rai 1997

Regan 1988

RevMan 2000

Rey 2003

Rushton 1988

Sanson 1996

Sanson 1999

Stirrat 1990

Walker 2003
Walker MC, Ferguson SE, Allen VM. Heparin for pregnant women with acquired or inherited thrombophilias. Cochrane Database of Systematic Reviews 2003, Issue 2. [Art. No.: CD003580. DOI: 10.1002/14651858.CD003580]

WHO 1977

References to other published versions of this review

CDSR 2005

* Indicates the major publication for the study
Characteristics of included studies  [ordered by study ID]

Dolitzky 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>Open label, random allocation with adequate concealment.</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women (n = 107) with a history of three or more consecutive fetal losses in the first trimester or at least two second trimester fetal losses in whom no cause for their previous pregnancy losses was found.</td>
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<tr>
<td>Interventions</td>
<td>Subcutaneous enoxaparin (40 mg/daily) versus aspirin (100 mg/daily) from the time of detection of a fetal heart beat.</td>
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Risk of bias

<table>
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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
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</tbody>
</table>

Tulppala 1997

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<tr>
<th>Methods</th>
<th>Double-blind, placebo-controlled.</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Women (n = 82) with a history of at least 3 consecutive miscarriages in whom no obvious cause for their previous pregnancy losses was found.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Aspirin (50 mg/daily) versus placebo, started as soon as a urinary pregnancy test became positive.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>To assess the effect of low-dose aspirin on PGI2 and TXA2 production and on the rate of abortion in pregnant women with recurrent spontaneous abortion with or without detectable anticardiolipin antibodies.</td>
</tr>
<tr>
<td>Notes</td>
<td>Participants included in the present review: subcategory of 54 women negative for anticardiolipin antibodies.</td>
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</table>

Risk of bias

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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</table>

PGI2: prostacyclin 2
TXA2: thromboxane A2
Characteristics of excluded studies  [ordered by study ID]

<table>
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<tr>
<th>Study</th>
<th>Details</th>
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<tr>
<td>Bar 2000</td>
<td>Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
</tr>
<tr>
<td>Bar 2001</td>
<td>Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately. Uncontrolled trial.</td>
</tr>
<tr>
<td>Bick 2000</td>
<td>Non-randomised, uncontrolled trial.</td>
</tr>
<tr>
<td>Brenner 2000</td>
<td>Non-randomised trial, historical controls.</td>
</tr>
<tr>
<td>Brenner 2005</td>
<td>Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
</tr>
<tr>
<td>Carp 2003</td>
<td>Non-randomised trial, historical controls.</td>
</tr>
<tr>
<td>Grandone 2002</td>
<td>Non-randomised trial. Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
</tr>
<tr>
<td>Gris 1995</td>
<td>Moroxydine chloride is not an intervention of interest in this review.</td>
</tr>
<tr>
<td>Gris 2004</td>
<td>Not all included women had recurrent miscarriage; also women with one miscarriage with a gestational age of 10 or more weeks were included.</td>
</tr>
<tr>
<td>Li 2003</td>
<td>Non-randomised trial.</td>
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<tr>
<td>Ogasawara 2001</td>
<td>Non-randomised trial. Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
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<tr>
<td>Rai 2000</td>
<td>Non-randomised trial.</td>
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<td>Reznikoff-Etievant 1999</td>
<td>Non-randomised trial.</td>
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<tr>
<td>Sarig 2003</td>
<td>Data for women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
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<tr>
<td>Sarto 2001</td>
<td>Non-randomised trial, historical controls.</td>
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<td>Sorensen 2000</td>
<td>Non-randomised, uncontrolled trial. Data from women without apparent causes of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.</td>
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<tr>
<td>Tzafetas 2002</td>
<td>Non-randomised, uncontrolled trial.</td>
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<tr>
<td>Younis 2000</td>
<td>Non-randomised, uncontrolled trial.</td>
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### Characteristics of ongoing studies  
**[ordered by study ID]**

#### ALIFE study

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<th>Trial name or title</th>
<th>Anticoagulants for living fetuses study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Women with at least two or more pregnancy losses without apparent causes other than inherited thrombophilias.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Aspirin (100 mg/day) + nadroparine 2850 IE/day versus aspirin (100 mg/day) versus placebo. Medication is started preconceptional or with a gestation less than 6 weeks. Nadroparine is started when there is a fetal heart beat (+/- 6 weeks).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome is live birth rate, secondary outcomes are prevalence of adverse pregnancy outcomes: preeclampsia, HELLP, intrauterine growth restriction, premature delivery, congenital malformations, thromboembolic and hemorrhagic complications, thrombocytopenia, allergic reactions.</td>
</tr>
<tr>
<td>Starting date</td>
<td>2004</td>
</tr>
<tr>
<td>Contact information</td>
<td>Dr. S.Middeldorp, Leiden University Medical Center, departments of Clinical Epidemiology and General Internal Medicine C9-P, PO Box 9600, 3500 RC Leiden, The Netherlands. e-mail: <a href="mailto:alife@amc.uva.nl">alife@amc.uva.nl</a></td>
</tr>
<tr>
<td>Notes</td>
<td>Trial register number: ISRCTN 58496168</td>
</tr>
</tbody>
</table>

#### ETHIGII

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Effectiveness of dalteparin therapy as intervention in recurrent pregnancy loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Women with a history with at least two early pregnancy losses (&lt; 12 wks) or one late pregnancy loss (&gt; 12 wks) without apparent causes other than inherited thrombophilias.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Dalteparin (5000 IE/day) + two tablets multivitamin/day versus only two tablets multivitamin/day. Inclusion between 5 and 8 weeks' gestation and foetal heart activity.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome is an ongoing pregnancy at 24 weeks of gestation. Secondary outcomes: preterm delivery, placental insufficiency, intrauterine growth restriction, preeclampsia, abruptio placentae, structural anomalies, thromboembolic events, side effects of dalteparin.</td>
</tr>
<tr>
<td>Starting date</td>
<td>13-11-2006</td>
</tr>
<tr>
<td>Contact information</td>
<td>Prof E.Schleussner, department of Obstetrics, Friedrich Schiller University, Bachstr. 18 Jena, Germany.</td>
</tr>
<tr>
<td>Notes</td>
<td>Trial register number: ISRCTN 53717039</td>
</tr>
</tbody>
</table>
### SPIN study

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>The Scottish Pregnancy Intervention study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Women with at least two or more consecutive early pregnancy losses without apparent causes.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Low molecular weight heparin versus aspirin + intense surveillance versus intense surveillance only. Inclusion until 7 weeks of gestation.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome is live birth rate; secondary outcomes are: preeclampsia, intrauterine growth retardation, premature delivery, congenital malformations, admission to special care, side effects of the drug, thromboembolic complications.</td>
</tr>
<tr>
<td>Starting date</td>
<td>01-06-2004</td>
</tr>
<tr>
<td>Contact information</td>
<td>Dr. P. Clark, Scottish National Blood Transfusion Service, East of Scotland Blood Transfusion Centre, Ninewells Hospital, Dundee, DD1 9SY, United Kingdom</td>
</tr>
<tr>
<td>Notes</td>
<td>Trial register number: ISRCTN 06774126</td>
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</table>

### TIPPS study

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Thrombophilia in Pregnancy Prophylaxis Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Pregnant women with confirmed thrombophilia.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Dalteparin versus no medication. Inclusion until 17 weeks of gestation</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary objective is to identify if low-molecular-weight heparin prophylaxis in thrombophilic women reduces the relative risk in venous thromboembolism, pre-eclampsia, intrauterine growth restriction, and foetal loss.</td>
</tr>
<tr>
<td>Starting date</td>
<td>01-07-2000</td>
</tr>
<tr>
<td>Contact information</td>
<td>Dr Marc Rodger, The Ottawa hospital, 1053 Carling Ave, CEP F650, Canada.</td>
</tr>
<tr>
<td>Notes</td>
<td>Trial register number: ISRCTN 87441504</td>
</tr>
</tbody>
</table>
### DATA AND ANALYSES

**Comparison 1. Aspirin versus placebo**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live-birth rate</td>
<td>1</td>
<td>54</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.0 [0.78, 1.29]</td>
</tr>
</tbody>
</table>

**Comparison 2. Enoxaparin versus aspirin**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live-birth rate</td>
<td>1</td>
<td>104</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.81, 1.16]</td>
</tr>
<tr>
<td>2 Preterm delivery</td>
<td>1</td>
<td>104</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.28, 3.01]</td>
</tr>
<tr>
<td>3 Obstetric complications; preeclampsia</td>
<td>1</td>
<td>104</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.13 [0.01, 2.50]</td>
</tr>
<tr>
<td>4 Obstetric complications; intrauterine growth restriction</td>
<td>1</td>
<td>104</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.78 [0.12, 66.75]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Aspirin versus placebo, Outcome 1 Live-birth rate.

Review: Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Comparison: 1 Aspirin versus placebo

Outcome: 1 Live-birth rate

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aspirin n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tulppala 1997</td>
<td>22/27</td>
<td>22/27</td>
<td>1.00 %</td>
<td>1.00 [0.78, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>27</td>
<td>27</td>
<td>100.0 %</td>
<td>1.00 [0.78, 1.29]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 22 (Aspirin), 22 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)
Analysis 2.1. Comparison 2 Enoxaparin versus aspirin, Outcome 1 Live-birth rate.

Review: Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Comparison: 2 Enoxaparin versus aspirin

Outcome: 1 Live-birth rate

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Enoxaparin</th>
<th>Aspirin</th>
<th>Risk Ratio M-H,Fixed</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolitzky 2006</td>
<td>44/54</td>
<td>42/50</td>
<td>0.97 [0.81, 1.16]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 54 50

Total events: 44 (enoxaparin), 42 (aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.34 (P = 0.73)

Analysis 2.2. Comparison 2 Enoxaparin versus aspirin, Outcome 2 Preterm delivery.

Review: Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Comparison: 2 Enoxaparin versus aspirin

Outcome: 2 Preterm delivery

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Enoxaparin</th>
<th>Aspirin</th>
<th>Risk Ratio M-H,Fixed</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolitzky 2006</td>
<td>5/54</td>
<td>5/50</td>
<td>0.93 [0.28, 3.01]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 54 50

Total events: 5 (enoxaparin), 5 (aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.13 (P = 0.90)
Analysis 2.3. Comparison 2 Enoxaparin versus aspirin, Outcome 3 Obstetric complications; pre-eclampsia.

Review: Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Comparison: 2 Enoxaparin versus aspirin

Outcome: 3 Obstetric complications; pre-eclampsia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>enoxaparin n/N</th>
<th>aspirin n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolitzky 2006</td>
<td>0/54</td>
<td>3/50</td>
<td>0.13 [0.01, 2.50]</td>
<td>100.0</td>
<td>0.13 [0.01, 2.50]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>54</strong></td>
<td><strong>50</strong></td>
<td><strong>100.0</strong></td>
<td><strong>100.0</strong></td>
<td><strong>0.13 [0.01, 2.50]</strong></td>
</tr>
</tbody>
</table>

Total events: 0 (enoxaparin), 3 (aspirin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

Analysis 2.4. Comparison 2 Enoxaparin versus aspirin, Outcome 4 Obstetric complications; intrauterine growth restriction.

Review: Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

Comparison: 2 Enoxaparin versus aspirin

Outcome: 4 Obstetric complications; intrauterine growth restriction

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>enoxaparin n/N</th>
<th>aspirin n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolitzky 2006</td>
<td>1/54</td>
<td>0/50</td>
<td>2.78 [0.12, 66.75]</td>
<td>100.0</td>
<td>2.78 [0.12, 66.75]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>54</strong></td>
<td><strong>50</strong></td>
<td><strong>100.0</strong></td>
<td><strong>100.0</strong></td>
<td><strong>2.78 [0.12, 66.75]</strong></td>
</tr>
</tbody>
</table>

Total events: 1 (enoxaparin), 0 (aspirin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Appendix 1. Search Strategy

Cochrane Central Register of Controlled Trials ('The Cochrane Library' 2007, Issue 1), MEDLINE (January 1966 to April 2008), and EMBASE (1980 to March 2007), adapted for each database.

1 randomized controlled trial.pt.
2 randomized controlled trials/
3 controlled clinical trial.pt.
4 random allocation/
5 comparative study/
6 1 or 2 or 3 or 4 or 5
7 clinical trial.pt.
8 clinical trials/
9 (clin$ adj trial$).tw
10 random$.tw
11 7 or 8 or 9 or 10
12 6 or 11
13 miscarriage$.tw
14 recurrent miscarriage$.tw
15 abortion spontaneous/
16 recurrent abortion$.tw
17 abortion habitual/
18 spontaneous pregnancy loss$.tw
19 recurrent pregnancy loss$.tw
20 early pregnancy loss$.tw
21 early pregnancy bleeding$.tw
22 habitual fetal loss$.tw
23 fetal death/
24 fetal resorption/
25 stillbirth.tw
26 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 aspirin/
28 heparin/
29 low-molecular-weight heparin/
30 anticoagulants/
31 anticoagulant agent/
32 antithrombotic$.tw
33 27 or 28 or 29 or 30 or 31 or 32
34 12 and 26
35 33 and 34

Lines 1, 3 and 7 were omitted in the search of EMBASE as it does not have a .pt. field.
Lines 1-12 were not used for the search of CENTRAL.
The “/” refers to MeSH, medical subject headings, and (tw) to text word in the title or abstract.
The $ is a truncation character which allows all possible suffix variations of the root word.
Since aspirin was ineffective compared with placebo in increasing live births, it should not be used as the control treatment in randomised trials for this indication. The trial of low molecular weight heparin (enoxaparin) versus low dose aspirin ($n=20$) is much too small to assess the risk of potential adverse effects, such as heparin induced thrombocytopenia with thrombosis and bleeding. Observational or population based studies should be used to help assess these hazards. Major, fatal, and intracranial bleeding should be included in the primary or secondary endpoints. Rebound hypercoagulability after heparin withdrawal [1, 2] should also be assessed by follow up for at least two months after delivery. Due to potential risks to the mother and baby, heparin or low molecular weight heparin should not be used for this indication outside randomised trials.

The background section cites the prognosis in subsequent pregnancies of women without antiphospholipid antibody syndrome who have recurrent pregnancy loss ranges from 50% to 80%. Consequently, in this patient population, the chances for a healthy live baby within three pregnancies would range from 87.5% to 99.2% (i.e. $1 - (0.50 \times 0.50 \times 0.50) = 0.875$ and $1 - (0.20 \times 0.20 \times 0.20) = 0.992$). Given the risks of heparin and the potential for harm if tens of thousands of women have heparin treatment during pregnancy, the main endpoint in the recommended randomised trial, of anticoagulant versus placebo, should be a live healthy baby in up to three pregnancies rather than in a single pregnancy.

There is an undisclosed financial conflict of interest in this review, as one of the review authors, Dr. Middledorp, was also one of the Matisse investigators, who investigated fondaparinux supported by a grant from NV Organon (The Netherlands) and Sanofi-Synthelabo (France) [3].

References

(Summary of comment from David K Cundiff, September 2007)
(Reply from Stef Kaandorp, November 2007)

**Contributors**
Feedback: David K Cundiff

**WHAT'S NEW**
Last assessed as up-to-date: 29 April 2008.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 April 2008</td>
<td>New search has been performed</td>
<td>Search updated. Scope of review changed, resulting in a previously included study being excluded (<strong>Gris 2004</strong>). Please see 'Differences between protocol and review' for further details. Authors replied to feedback.</td>
</tr>
<tr>
<td>30 April 2008</td>
<td>New citation required but conclusions have not changed</td>
<td>Changes to scope of review and team of authors.</td>
</tr>
<tr>
<td>11 January 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
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</tbody>
</table>

**HISTORY**
Protocol first published: Issue 2, 2004
Review first published: Issue 2, 2005

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 November 2008</td>
<td>Feedback has been incorporated Feedback from David K Cundiff added.</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**

Stef Kaandorp updated the search and wrote the revised review. Mariette Goddijn commented on the revision.

Marcello Di Nisio wrote the first and the revised drafts of the protocol and review, and commented on the draft of the updated review.

Saskia Middeldorp supervised the development of the review in all of its phases.

Louisette Peters commented on the drafts of the first version of this review.
DEclarations of interest

Drs Kaandorp, Goddijn, and Middeldorp are involved in the running randomised controlled trial ÄLIFE study. This trial is assessing the efficacy and safety of aspirin, and aspirin combined with low-molecular-weight heparin, compared with placebo for the prevention of pregnancy loss in women with recurrent miscarriage (International Standard Randomised Controlled Trial Number Register: 58496168). Besides being the principal investigator of the ALIFE study, Dr. Middeldorp has also been and is involved in phase 2 and phase 3 trials that assessing the efficacy and safety of anticoagulant drugs for the indication of venous thrombosis or superficial thrombophlebitis. These trials were or are being sponsored by various pharmaceutical companies.

DiffErences Between protocol and reView

For this update, we decided to limit our systematic review to women with recurrent miscarriage only. In the first version of the review also women with one later intrauterine fetal death were included. However, given the presumed differences in etiology and different prognosis, we judged it not appropriate to pool results of interventions in these different patient populations. This decision has resulted in the exclusion of a trial (Gris 2004) in which a subgroup had been included in the former version of the review.

index terms

Medical Subject Headings (MeSH)

Abortion, Habitual [*drug therapy; etiology]; Anticoagulants [*therapeutic use]; Antiphospholipid Syndrome [complications]; Aspirin [therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Pregnancy Complications, Hematologic [*drug therapy; etiology]; Randomized Controlled Trials as Topic; Thrombophilia [complications; *drug therapy]

MeSH check words

Female; Humans; Pregnancy