Cochrane Library

Cochrane Database of Systematic Reviews

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia (Review)

de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S

de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S.
Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia.
Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD004734.
DOI: 10.1002/14651858.CD004734.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 4
METHODS 4
RESULTS 7
Figure 1. 9
DISCUSSION 11
AUTHORS' CONCLUSIONS 12
ACKNOWLEDGEMENTS 12
REFERENCES 13
CHARACTERISTICS OF STUDIES 18
DATA AND ANALYSES 27
Analysis 1.1. Comparison 1 Aspirin versus no treatment, Outcome 1 Live birth. 28
Analysis 1.2. Comparison 1 Aspirin versus no treatment, Outcome 2 Preterm delivery < 37 weeks. 29
Analysis 1.3. Comparison 1 Aspirin versus no treatment, Outcome 3 Preterm delivery 24-28 weeks. 29
Analysis 1.4. Comparison 1 Aspirin versus no treatment, Outcome 4 Preterm delivery 28-32 weeks. 29
Analysis 1.5. Comparison 1 Aspirin versus no treatment, Outcome 5 Preterm delivery 32-37 weeks. 29
Analysis 1.6. Comparison 1 Aspirin versus no treatment, Outcome 6 Obstetric complications; pre-eclampsia. 30
Analysis 1.7. Comparison 1 Aspirin versus no treatment, Outcome 7 Obstetric complications; IUGR. 30
Analysis 1.8. Comparison 1 Aspirin versus no treatment, Outcome 8 Congenital malformations. 30
Analysis 1.9. Comparison 1 Aspirin versus no treatment, Outcome 9 Side effects; any bleeding. 30
Analysis 1.10. Comparison 1 Aspirin versus no treatment, Outcome 10 HIT/thrombocytopenia. 30
Analysis 2.1. Comparison 2 LMWH versus aspirin, Outcome 1 Live birth. 31
Analysis 2.2. Comparison 2 LMWH versus aspirin, Outcome 2 Preterm delivery < 37 weeks. 32
Analysis 2.3. Comparison 2 LMWH versus aspirin, Outcome 3 Preterm delivery 24-28 weeks. 32
Analysis 2.4. Comparison 2 LMWH versus aspirin, Outcome 4 Preterm delivery 28-32 weeks. 32
Analysis 2.5. Comparison 2 LMWH versus aspirin, Outcome 5 Preterm delivery 32-37 weeks. 32
Analysis 2.6. Comparison 2 LMWH versus aspirin, Outcome 6 Obstetric complications; pre-eclampsia. 33
Analysis 2.7. Comparison 2 LMWH versus aspirin, Outcome 7 Obstetric complications; IUGR. 33
Analysis 2.8. Comparison 2 LMWH versus aspirin, Outcome 8 Obstetric complications; congenital malformations. 33
Analysis 2.9. Comparison 2 LMWH versus aspirin, Outcome 9 Side effects; any bleeding. 33
Analysis 3.1. Comparison 3 LMWH versus aspirin including studies at high risk of bias, Outcome 1 Live birth. 34
Analysis 4.1. Comparison 4 LMWH versus no treatment, Outcome 1 Live birth. 34
Analysis 5.1. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 1 Live birth. 35
Analysis 5.2. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 2 Preterm delivery < 37 weeks. 35
Analysis 5.3. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 3 Obstetric complications; pre-eclampsia. 35
Analysis 5.4. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 4 Obstetric complications; IUGR. 36
Analysis 5.5. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 5 Obstetric complications; congenital malformations. 36
Analysis 5.6. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 6 Side effects; any bleeding. 36
Analysis 5.7. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 7 Thromboembolic complications. 36
Analysis 6.1. Comparison 6 LMWH and aspirin versus no treatment, Outcome 1 Live birth. 37
Analysis 6.2. Comparison 6 LMWH and aspirin versus no treatment, Outcome 2 Preterm delivery < 37 weeks. 38
Analysis 6.3. Comparison 6 LMWH and aspirin versus no treatment, Outcome 3 Preterm delivery 24-28 weeks. 38
Analysis 6.4. Comparison 6 LMWH and aspirin versus no treatment, Outcome 4 Preterm delivery 28-32 weeks. 38

Analysis 6.5. Comparison 6 LMWH and aspirin versus no treatment, Outcome 5 Preterm delivery 32-37 weeks. 39
Analysis 6.6. Comparison 6 LMWH and aspirin versus no treatment, Outcome 6 Obstetric complications; pre-eclampsia. 39
Analysis 6.7. Comparison 6 LMWH and aspirin versus no treatment, Outcome 7 Obstetric complications; IUGR. 39
Analysis 6.8. Comparison 6 LMWH and aspirin versus no treatment, Outcome 8 Congenital Malformations. 39
Analysis 6.9. Comparison 6 LMWH and aspirin versus no treatment, Outcome 9 Side effects; any bleeding. 39
Analysis 6.10. Comparison 6 LMWH and aspirin versus no treatment, Outcome 10 Side effects; pain/itching/swelling at injection site. 40
Analysis 7.1. Comparison 7 LMWH and aspirin versus aspirin, Outcome 1 Live birth. 41
Analysis 7.2. Comparison 7 LMWH and aspirin versus aspirin, Outcome 2 Preterm delivery < 37 weeks. 41
Analysis 7.3. Comparison 7 LMWH and aspirin versus aspirin, Outcome 3 Preterm delivery 24-28 weeks. 42
Analysis 7.4. Comparison 7 LMWH and aspirin versus aspirin, Outcome 4 Preterm delivery; 28-32 weeks. 42
Analysis 7.5. Comparison 7 LMWH and aspirin versus aspirin, Outcome 5 Preterm delivery; 32-37 weeks. 42
Analysis 7.6. Comparison 7 LMWH and aspirin versus aspirin, Outcome 6 Obstetric complications; pre-eclampsia. 42
Analysis 7.7. Comparison 7 LMWH and aspirin versus aspirin, Outcome 7 Obstetric complications; IUGR. 42
Analysis 7.8. Comparison 7 LMWH and aspirin versus aspirin, Outcome 8 Congenital malformations. 42
Analysis 7.9. Comparison 7 LMWH and aspirin versus aspirin, Outcome 9 Side effects; any bleeding. 43
Analysis 7.10. Comparison 7 LMWH and aspirin versus aspirin, Outcome 10 Side effects; pain/itching/swelling at injection site. 43
Analysis 7.11. Comparison 7 LMWH and aspirin versus aspirin, Outcome 11 HIT/thrombocytopenia. 43
Analysis 8.1. Comparison 8 LMWH and aspirin versus LMWH, Outcome 1 Live birth. 44
Analysis 8.2. Comparison 8 LMWH and aspirin versus LMWH, Outcome 2 Preterm delivery < 37 weeks. 44
Analysis 8.3. Comparison 8 LMWH and aspirin versus LMWH, Outcome 3 Obstetric complications; pre-eclampsia. 45
Analysis 8.4. Comparison 8 LMWH and aspirin versus LMWH, Outcome 4 Obstetric complications; IUGR. 45
Analysis 8.5. Comparison 8 LMWH and aspirin versus LMWH, Outcome 5 Congenital malformations. 45
Analysis 8.6. Comparison 8 LMWH and aspirin versus LMWH, Outcome 6 Side effects; any bleeding. 45
Analysis 9.1. Comparison 9 LMWH with or without aspirin vs no treatment including studies at high risk of bias, Outcome 1 Live birth. 45
Analysis 10.1. Comparison 10 LMWH with or without aspirin vs no treatment, Outcome 1 Live birth. 46
APPENDICES 46
FEEDBACK 48
WHAT'S NEW 49
HISTORY 49
CONTRIBUTIONS OF AUTHORS 50
DECLARATIONS OF INTEREST 50
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 50
INDEX TERMS 50

[Intervention Review]

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia

Paulien G de Jong[1], Stef Kaandorp[2], Marcello Di Nisio[1,3], Mariëtte Goddijn[4], Saskia Middeldorp[1]

[1]Department of Vascular Medicine, Academic Medical Center, Amsterdam, Netherlands. [2]Obstetrics and Gynaecology, Westfriesgasthuis, Hoorn, Netherlands. [3]Department of Medical, Oral and Biotechnological Sciences, University "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy. [4]Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Contact address: Paulien G de Jong, Department of Vascular Medicine, Academic Medical Center, Meibergdreef 9, Amsterdam, 1105 AZ, Netherlands. P.G.deJong@amc.uva.nl.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2014.

Citation: de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No.: CD004734. DOI: 10.1002/14651858.CD004734.pub4.

ABSTRACT

Background

Since hypercoagulability might result in recurrent miscarriage, anticoagulant agents could potentially increase the chance of live birth in subsequent pregnancies in women with unexplained recurrent miscarriage, with or without inherited thrombophilia.

Objectives

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

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 October 2013) and 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 live birth in women with a history of at least two unexplained miscarriages with or without inherited thrombophilia were eligible. Interventions included aspirin, unfractionated heparin (UFH), and low molecular weight heparin (LMWH) for the prevention of miscarriage. One treatment could be compared with another or with no-treatment (or placebo).

Data collection and analysis

Two review authors (PJ and SK) assessed the studies for inclusion in the review and extracted the data. If necessary they contacted study authors for more information. We double checked the data.

Main results

Nine studies, including data of 1228 women, were included in the review evaluating the effect of either LMWH (enoxaparin or nadroparin in varying doses) or aspirin or a combination of both, on the chance of live birth in women with recurrent miscarriage, with or without inherited thrombophilia. Studies were heterogeneous with regard to study design and treatment regimen and three studies were considered to be at high risk of bias. Two of these three studies at high risk of bias showed a benefit of one treatment over the other, but

in sensitivity analyses (in which studies at high risk of bias were excluded) anticoagulants did not have a beneficial effect on live birth, regardless of which anticoagulant was evaluated (risk ratio (RR) for live birth in women who received aspirin compared to placebo 0.94, (95% confidence interval (CI) 0.80 to 1.11, n = 256), in women who received LMWH compared to aspirin RR 1.08 (95% CI 0.93 to 1.26, n = 239), and in women who received LMWH and aspirin compared to no-treatment RR 1.01 (95% CI 0.87 to 1.16) n = 322).

Obstetric complications such as preterm delivery, pre-eclampsia, intrauterine growth restriction and congenital malformations were not significantly affected by any treatment regimen. In included studies, aspirin did not increase the risk of bleeding, but treatment with LWMH and aspirin increased the risk of bleeding significantly in one study. Local skin reactions (pain, itching, swelling) to injection of LMWH were reported in almost 40% of patients in the same study.

Authors' conclusions

There is a limited number of studies on the efficacy and safety of aspirin and heparin in women with a history of at least two unexplained miscarriages with or without inherited thrombophilia. Of the nine reviewed studies quality varied, different treatments were studied and of the studies at low risk of bias only one was placebo-controlled. No beneficial effect of anticoagulants in studies at low risk of bias was found. Therefore, this review does not support the use of anticoagulants in women with unexplained recurrent miscarriage. The effect of anticoagulants in women with unexplained recurrent miscarriage and inherited thrombophilia needs to be assessed in further randomised controlled trials; at present there is no evidence of a beneficial effect.

PLAIN LANGUAGE SUMMARY

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia

Recurrent miscarriage is associated with inherited blood clotting disorders that could interfere with the placental blood circulation. Recurrent miscarriage can also be unexplained, with no known cause. Anticoagulant drugs such as aspirin or low molecular weight heparin may help women with recurrent miscarriage and such an underlying blood clotting problem. These drugs may also cause bleeding (including nose bleeds and haematomas) in the mother, though not in the baby. Data from nine included randomised controlled trials (involving 1228 women) analysed in this review, provided no evidence to support the use of anticoagulants in women with recurrent miscarriage, regardless of the presence of inherited blood clotting disorders (thrombophilia).

Irrespective of the type or combination of anticoagulant, no benefit of anticoagulant treatment was found for live births. Obstetric complications were not clearly affected by any treatment regimen. Injection of low molecular weight heparin caused local skin reactions (pain, itching, swelling) in one study (side effects were not regularly reported in all studies). In the nine reviewed studies quality varied and different treatments were studied. Three studies were considered at high risk of bias. The number of studies on this topic remains limited.

Thrombophilia refers to blood clotting disorders associated with a predisposition to thrombosis and thus increased risk for thrombotic events. It can be inherited as well as acquired, as is the case in the antiphospholipid syndrome. Both inherited and acquired thrombophilia are associated with vascular thrombosis as well as pregnancy complications including recurrent miscarriage and premature delivery.

BACKGROUND

Description of the condition

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 (recurrent miscarriage, RM), whereas 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). RM is devastating for women and their families. The definition of RM remains a subject of debate. The World Health Organization (WHO) defines miscarriage as the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestational age (WHO 2009). 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' gestation (Jauniaux 2006). Recent evidence shows that two miscarriages constitute RM (Bhattacharya 2010; Jaslow 2010). Adequate characterisation of miscarriages and patients in RM studies is most important and, favourably, would make studies mutually comparable (Christiansen 2006). The risk of miscarriage after two or three consecutive miscarriages is similar (Regan 1988).

Furthermore, the presence of parenteral chromosome abnormalities, which is a known risk factor for recurrent miscarriage (Franssen 2005), as well as the presence of antiphospholipid antibodies, another known risk factor for recurrent miscarriage (Jauniaux 2006), are not different in women with two or three miscarriages (van den Boogaard 2010; van den Boogaard 2012). We therefore chose to use the broad definition of RM in this review: two or more not necessarily consecutive miscarriages.

Miscarriage is associated with relevant maternal morbidity like bleeding and infection and, sometimes, maternal death (NHMRC 2001), particularly in low-income countries (Goyaux 2001). Moreover, miscarriage, especially if recurrent, might cause important psychological and emotional distress that can be further complicated by feelings of anxiety and depression as well as social withdrawal (Lee 1996; Lok 2007).

Several factors may be involved in the aetiology of RM. Women experiencing RM may have an underlying medical condition such as carrier status of a structural chromosome abnormality (Braekeleer 1990; Franssen 2005), antiphospholipid syndrome, or other blood clotting disorders generally referred to as thrombophilias (Robertson 2006) or a septate uterus (Chan 2011). Factors less strongly associated with RM are hyperhomocysteinemia and endocrine abnormalities (Christiansen 2005).

Thrombophilia is a diverse group of coagulation disorders associated with a predisposition to thrombosis and thus increased risk for thrombotic events such as deep vein thrombosis and pulmonary embolism. These hypercoagulable states can either be 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 (Middeldorp 2007a) or acquired, as for instance the antiphospholipid syndrome. In this latter syndrome, the predisposition to thrombosis is acquired due to the presence of antiphospholipid antibodies (Lim 2006).

A growing body of evidence has implicated thrombophilia in adverse obstetrical events (such as intrauterine growth restriction, (recurrent) miscarriage, severe pre-eclampsia, and placental abruption) (Kupferminc 1999; Middeldorp 2007), and there is also reasonable evidence to suggest that some cases of RM are associated with thrombosis of placental vessels and infarction. Firstly, microthrombi are a common finding in the placental vasculature of women with RM (Rushton 1988). Secondly, placental thrombosis and infarction have been described in association with certain thrombophilic defects (Dizon 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 of population-based studies showed that the magnitude of the association with thrombophilia varies according to the timing of fetal loss (Rey 2003). In particular, first trimester RM was associated with factor V Leiden mutation, APC resistance, and prothrombin G20210A mutation, while late non-recurrent fetal loss was associated with factor V Leiden mutation, prothrombin G20210A mutation, and protein S deficiency. Also, family studies showed that women with inherited 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 antiphospholipid syndrome is an acquired thrombophilia and associated both with vascular thrombosis and pregnancy complications (including RM and premature delivery) (Levine 2002). These adverse pregnancy outcomes may result from placental infarctions and thrombotic changes in decidual microvessels (Infante-Reviard 1991; Lockshin 1999). The use of antithrombotic agents heparin (unfractionated heparin or low-molecular-weight heparin (LMWH)) and aspirin has been studied in women with antiphospholipid syndrome. Both agents have anti-clotting properties, but these work differently: heparin increases the effect of the natural anticoagulant antithrombin; whereas aspirin inhibits platelet aggregation. Heparin and aspirin seem to be effective and safe in reducing miscarriage rates in women with antiphospholipid syndrome with significantly better pregnancy outcome than aspirin alone (rate of live births of 71% to 80% versus 42% to 44% respectively, an absolute risk difference of 36%) (Kutteh 1996; Rai 1997), although findings have not always been consistent (Farquharson 2002; Laskin 2009). Inconsistency in these study results may be explained by alternate treatment regimens, or the use of different diagnostic criteria, as these have been revised over time by consensus (Miyakis 2006). Both the therapy for RM associated with the antiphospholipid syndrome and other possible therapies currently considered for the prevention of RM (as progesterone and immunotherapy) are the topics covered in other Cochrane reviews (Empson 2005; Haas 2008; Porter 2006).

Estimates of the prognosis of subsequent pregnancies in women with RM without antiphospholipid syndrome range from live birth rates of approximately 50% to 89% (Brigham 1999; Cohn 2010;

Lindqvist 2006; Rai 2000; Stirrat 1990). For women with RM 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.

Description of the intervention

The use of anticoagulants in pregnancy needs to be carefully evaluated for efficacy and safety since it can carry risks for the mother and the fetus. Coumarin derivatives are anticoagulant drugs used most often in case of thrombosis, but cross the placenta and can display teratogenic effects. In contrast to coumarin derivatives, neither UFH nor LMWH 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 LMWH is at least as effective and safe as UFH 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 (Bates 2012; Ginsberg 2001; Sanson 1999). Based on current evidence, aspirin (less than 150 mg/d) during the second and third trimesters appears to be safe, while the safety of higher doses of aspirin during the first trimester remains uncertain (Askie 2007; Bates 2012; Ginsberg 2001). The use of heparin in pregnancy has been covered in another Cochrane review (Walker 2003).

Why it is important to do this review

In clinical practice, women with RM associated with inherited thrombophilia or RM 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 syndrome and RM to all women with RM. Whether there is evidence for an effect of anticoagulants in women with RM - either unexplained or associated with inherited thrombophilia - is the objective of this review.

OBJECTIVES

The objective of this review was to determine whether anticoagulant treatment improves the chance of a live birth in women with a history of at least two unexplained miscarriages with or without 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 unexplained miscarriages with or without inherited thrombophilia.

Types of participants

Participants were pregnant women with a history of at least two unexplained miscarriages with or without inherited thrombophilia. Of studies that included women attempting to conceive, but who were not pregnant upon randomisation only results of women who became pregnant were included. Studies that included women with apparent risk factors (other than inherited thrombophilia) of RM (antiphospholipid syndrome; uterine abnormalities; patients' or their partners' karyotype abnormalities) were included only if the results from women with a history of at least two unexplained miscarriages with or without inherited thrombophilia could be extracted to be analysed separately. For this review, we selected studies in women with two or more previous miscarriages up to 24 weeks' gestation. 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, UFH, and LMWH for the prevention of miscarriage. One treatment could be compared with another or with no treatment (or placebo). Combinations of therapy could be used. To exclude a potential lack of efficacy due to a limited duration of treatment, only studies in which the investigational treatment was started at a maximum of 12 weeks' gestation and continued beyond 32 weeks' gestation or until the end of pregnancy were eligible.

Types of outcome measures

Primary outcomes

Live birth.

Secondary outcomes

1. Preterm delivery of a live infant before 37 weeks' gestational age (not a prespecified outcome).
2. Preterm delivery of a live infant between 24 and 28 weeks' gestational age.
3. Preterm delivery of a live infant between 28 and 32 weeks' gestational age.
4. Preterm delivery of a live infant between 32 and 37 weeks' gestational age.
5. Obstetric complications (gestational hypertension, pre-eclampsia, intrauterine growth restriction).
6. Congenital malformations.
7. Admission to special care.
8. 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, itching or swelling at injection sites and allergic reactions to heparin).
9. Thromboembolic complications.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

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 (1 October 2013).

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

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

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

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

For additional searching performed for the previous version of the review, please see Appendix 1.

Searching other resources

We scanned bibliographies of all located articles for further studies.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 2.

For this update we used the following methods when assessing the reports identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager software (RevMan 2012) and checked for accuracy.

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

Dr Kaandorp, Dr Goddijn, and Dr Middeldorp were investigators of the randomised controlled trial ALIFE study (Kaandorp 2010) and so this trial was assessed by the other review authors.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

Performance bias and detection bias were not included as criterion for quality as we anticipated that the outcome live birth was not influenced by blinding.

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

Performance bias and detection bias were not included as criterion for quality as we anticipated that the outcome live birth was not influenced by blinding.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

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

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups; ≦ 20% participants missing);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation; more than 20% participants missing);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

We assessed the methods as:

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

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

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

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

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

(7) Overall risk of bias

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

Measures of treatment effect

Dichotomous data

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

Continuous data

We did not analyse any continuous data.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review. In future updates, if identified and eligible, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were excluded.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. However, none of the included studies were considered to be at high risk of attrition bias.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

Data were pooled based on type of intervention, but irrespective of the dose of LMWH or aspirin. Only studies in which the investigational treatment was started at a maximum of 12 weeks' gestation and continued beyond 32 weeks' gestation were included.

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We planned to consider whether an overall summary was meaningful, and if it was, use random-effects analysis to produce it.

We planned to carry out the following subgroup analyses:

1. inherited thrombophilia versus no inherited thrombophilia;
2. different inherited thrombophilic disorders;
3. preconceptional versus periconceptional anticoagulant use;
4. type of anticoagulant(s) used (e.g. single drug, combination of anticoagulant agents);
5. dose of anticoagulant(s);
6. duration of anticoagulant use;
7. women with a history of three or more miscarriages;
8. women with no previous live birth versus women with one or more previous live birth.

We planned to use the primary outcome, live birth, in subgroup analyses. However, due to lack of data, we were not able to conduct planned subgroup analysis. We included data from single subgroups in the analysis of the primary outcome, but due to lack of data, we did not explore the treatment effect between the pre-specified subgroups as outlined above.

In future updates, if more data become available, we will assess subgroup differences by interaction tests available within RevMan (RevMan 2012) and report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We performed sensitivity 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. Only studies at an overall low risk of bias were included in the initial analyses and we carried out sensitivity analyses to explore the effect of quality.

RESULTS

Description of studies

Included studies

Details for the studies included are in the Characteristics of included studies.

We included nine studies (1228 women for the primary outcome live birth) (Badawy 2008; Clark 2010; Dolitzky 2006; Fawzy 2008; Giancotti 2012 Kaandorp 2010; Martinelli 2012; Tulppala 1997; Visser 2011) in this review. In the studies Badawy 2008 and Dolitzky 2006, full study populations were included. For the studies Clark 2010; Fawzy 2008; Giancotti 2012; Kaandorp 2010; Martinelli 2012; Tulppala 1997; and Visser 2011, we could not include full study populations, but had to extract data on the women fulfilling the inclusion criteria of the review. Reasons for including only part of the original study population are explained for each study.

Badawy 2008 evaluated the effect of LMWH (enoxaparin 20 mg/day) in women with three or more consecutive first trimester miscarriages. Women were included if no risk factors for RM could be identified (women with inherited thrombophilia were excluded) and randomised to either treatment or no-treatment (no placebo). Therapy was commenced once fetal viability was detected on ultrasound and continued until 34 weeks' gestation. The primary outcome was pregnancy loss and pregnancy complications, but live births could be calculated from the report and were confirmed by the study author. Of 350 women enrolled, 10 women (four (2.3%) and six (3.4%) in both arms) were lost to follow-up, leaving 170 women in each study arm for analysis. Side effects of treatment were only reported for women randomised to treatment, not in those randomised to no-treatment.

Clark 2010 studied the effect of LMWH (enoxaparin 40 mg/day) and aspirin (75 mg/day) from before seven weeks' gestation until 36 weeks' gestation on live birth in 296 women with RM, defined as a minimum of two consecutive early pregnancy losses (at or before 24 weeks' gestation). Intervention with LMWH and aspirin combined with intense pregnancy surveillance was compared with intense pregnancy surveillance without pharmacological intervention. Women were included upon a positive pregnancy test (before seven weeks' gestation). Investigations for uterine or chromosomal abnormalities and antiphospholipid syndrome were conducted only for women with three or more previous miscarriages. Women who were included because of two previous miscarriages were excluded from our analysis, because it could not be confirmed that previous miscarriages were 'unexplained'. The primary outcome measure in the study was live birth. Adverse events of intervention were reported, though could not be extracted for the women with three or more previous miscarriages. One-hundred and twenty-two women were included in the review (64 randomised to LMWH and aspirin versus 58 randomised to surveillance).

Dolitzky 2006 evaluated the effect of LMWH compared with aspirin in 104 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 enoxaparin and aspirin on live birth rate. Women were only included if there was no apparent risk factors for the miscarriages and women with inherited thrombophilia

were excluded. 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 six to 12 weeks' gestation and continued until a gestational age of 37 weeks. Of the 107 included women, 54 received enoxaparin, 50 aspirin and three were lost to follow-up. Besides the primary outcome measure of live birth, secondary outcomes like preterm delivery, intrauterine growth restriction, and pre-eclampsia were reported.

Fawzy 2008 assessed the effect of LMWH (enoxaparin 20 mg/day) compared with combination treatment (oral prednisone and progesterone from the onset of pregnancy until 12 weeks of gestation and aspirin from the onset of pregnancy until 32 weeks of gestation) compared with placebo (for oral intervention) in women with three or more consecutive unexplained miscarriages (before 24 weeks' gestation) with the same partner. Women with inherited thrombophilia were excluded. From this study, we extracted data for the 107 women receiving enoxaparin or placebo. Of these women, 57 were assigned to enoxaparin and 50 to placebo. Treatment was started when a fetal pole was detected and continued until term. The primary outcome was live birth, but secondary outcomes such as obstetric complications and neonatal outcomes were also reported.

Giancotti 2012 evaluated the effect of LMWH or aspirin or a combination of these in 167 women with a history of two or more unexplained miscarriages before 12 weeks' gestation. Women with uterine or chromosomal abnormalities were excluded, but women with inherited thrombophilia or antiphospholipid syndrome were eligible. Women were randomised to LMWH (enoxaparin 40 mg/day from diagnosis of intrauterine pregnancy until delivery) or aspirin (100 mg/day from diagnosis of pregnancy until 32 weeks' gestation) or first aspirin (100 mg/day from diagnosis of pregnancy), which was replaced by LMWH at 32 weeks' gestation (enoxaparin 40 mg/day continued until delivery). For this analysis, we included only data from women without antiphospholipid antibodies randomised to either LMWH (n = 40) or aspirin (n = 46). The primary outcome of the study was live birth, and no secondary outcome measures were reported.

Kaandorp 2010 evaluated the effect of open label LMWH (nadroparin 2850 IU/day) combined with aspirin (80 mg/day) or aspirin only (80 mg/day) compared with placebo in 364 women with unexplained RM with or without inherited thrombophilia. Previous miscarriage was defined as pregnancy loss at a gestational age of 20 weeks or less. Women were included in the study if they were attempting to conceive or were less than six weeks pregnant. From this study, we extracted data of the 299 women who became pregnant (97 were assigned to aspirin plus nadroparin, 99 were assigned to aspirin only and 103 were assigned to placebo). LMWH was initiated when a viable intrauterine pregnancy was confirmed on ultrasonography at six weeks' gestation until the start of labour. Aspirin or placebo was started at randomisation and continued until a gestational age of 36 weeks. The primary outcome was live birth, and secondary outcomes were adverse pregnancy outcomes and maternal adverse events. Secondary outcomes such as obstetric complications and neonatal events were evaluated for 200 women with ongoing pregnancy beyond 12 weeks of gestation.

Martinelli 2012 evaluated the effect of open label LMWH (nadroparin 3800 IU/day), compared with no treatment in 135 women with previous placenta-mediated pregnancy complications. Women with antiphospholipid syndrome, uterine anomalies or abnormal karyotype were excluded from the study. Inherited thrombophilia was not an exclusion criterion. LMWH was compared with medical surveillance only and treatment was initiated upon randomisation and continued until delivery. Randomisation was performed around the 12th week of gestation, after pregnancy was confirmed on ultrasonography. The primary outcome of the study was a composite outcome of several pregnancy complications. For this review we included data of six women, who had a history of two or more unexplained miscarriages up to 24 weeks' gestation.

Tulppala 1997 evaluated the effect of aspirin (50 mg/day) on live birth rate in 66 pregnant women with preceding RM with or without detectable anticardiolipin antibodies and no other apparent risk factors for their previous miscarriages. RM was defined as three or more consecutive miscarriages (occurring before 22 weeks of gestational age). Aspirin was compared with placebo, and medication was started as soon as a home urinary pregnancy test became positive and continued until delivery. From this study, we extracted data for 54 women who were 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.

Visser 2011 evaluated the effect of LMWH (enoxaparin 40 mg/day) plus oral placebo (n = 68) compared with LMWH (enoxaparin 40 mg/day) plus aspirin (100 mg/day) (n = 63), compared with aspirin only (100 mg/day) (n = 76) in women with unexplained RM with or without inherited thrombophilia. RM was defined as three or more consecutive first trimester miscarriages, two or more second trimester miscarriages or one third trimester fetal loss combined with at least one first trimester miscarriage. Treatment was initiated upon randomisation (before seven weeks' gestation); aspirin and placebo were discontinued at 36 weeks' gestation whereas enoxaparin was continued until the first signs of labour. The primary outcome was live birth and secondary outcomes were adverse pregnancy outcomes and bleeding. Premature delivery, obstetrical complications and congenital malformations were reported only for women who had live birth. Study authors stated that only one woman was included in the study because of RM based on one fetal loss before, and two fetal losses after 24 weeks' gestation; her data were excluded from this review. Furthermore, data of 10 women (allocated to enoxaparin plus placebo (n = 3, one live birth), enoxaparin plus aspirin (n = 2, one live birth), aspirin only (n = 5, four live births)) were excluded because of the presence of Beta-2 glycoprotein antibodies. One-hundred and ninety-six women were included in this trial.

As can be noted, no study compared the same treatment regimen. Studies compared different doses of LMWH and aspirin or combinations of these, and treatment was started at various gestational ages. As described in the Methods section, we pooled data based on type of intervention, but irrespective of the dose of LMWH or aspirin. Only studies in which the investigational treatment was started at a maximum of 12 weeks' gestation and continued beyond 32 weeks' gestation were included.

Excluded studies

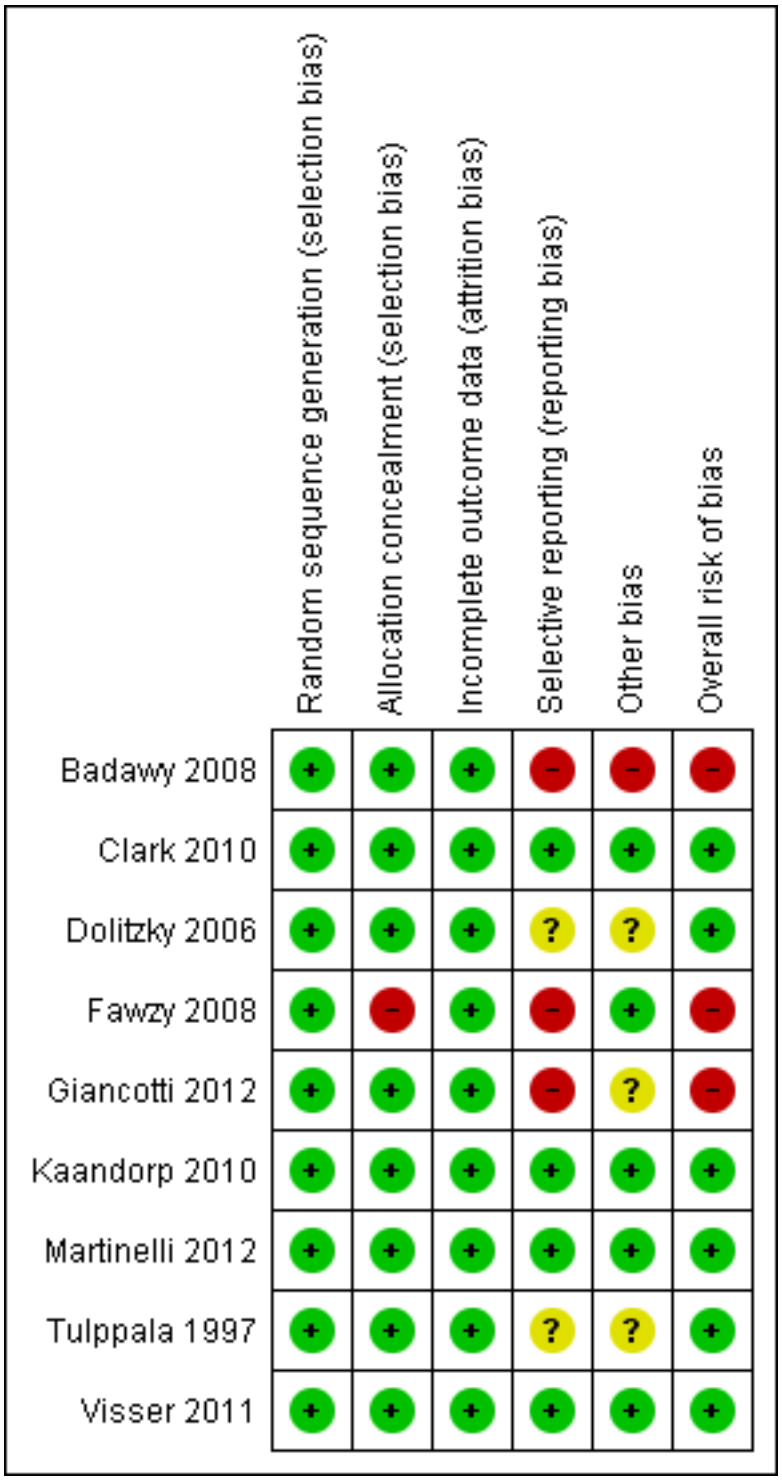
Overall, we excluded 22 studies from the review. We have provided the reasons for exclusion in the Characteristics of excluded studies table.

Three studies are only available in abstract form (Rodger 2009; Salman 2012; Schleussner 2013) and we are awaiting the full study report, see Characteristics of studies awaiting classification.

Risk of bias in included studies

Details for the included studies are shown in the Characteristics of included studies and in Figure 1.

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



The studies by Clark 2010; Kaandorp 2010; Martinelli 2012 and Visser 2011 were considered to be at low risk of bias for all assessed criteria.

Allocation

Procedures for adequate allocation concealment were well described in the studies by Badawy 2008; Clark 2010; Dolitzky 2006; Giancotti 2012; Kaandorp 2010; Martinelli 2012; and Visser 2011. Dr Tulppala provided information about allocation in her study (Tulppala 1997), which was then judged to be at low risk of bias. Based on the report and information provided by Dr Fawzy regarding treatment allocation, we judged this study (Fawzy 2008) to be at high risk of selection bias.

Blinding

As explained in the methods sections, performance bias and detection bias were not included as criterion for quality.

Incomplete outcome data

The study by Kaandorp 2010 was analysed on intention-to-treat basis, including women lost to follow-up. Other studies reported outcomes for randomised women minus any participants whose outcomes were missing. Numbers of women lost to follow-up were small and well balanced for each group and not enough to have a clinically relevant impact on the intervention effect estimate. All studies were therefore considered to be at low risk of attrition bias.

Selective reporting

Assessment of reporting bias was impossible for Dolitzky 2006; and Tulppala 1997 as trial registration was not operative at time of inclusion.The studies by Badawy 2008, Fawzy 2008 and Giancotti 2012 were considered to be at high risk of bias because they were not registered in a prospective trial register. Other studies were considered to be at low risk of reporting bias.

Other potential sources of bias

There were inconsistencies in the report by Badawy 2008, and the report by Giancotti 2012 provided no baseline table, which made it impossible to determine whether prognostic factors were evenly distributed between groups.

Effects of interventions

We included nine studies, involving 1228 participants, in this review. Since treatment regimens varied among included studies, pooled analysis could not include more than three studies, except for when LMWH with or without aspirin was compared to no treatment. Only one study (Kaandorp 2010) included women who used anticoagulants preconceptionally. This yielded insufficient data to perform the planned subgroup analysis for pre- and periconceptional anticoagulant use. Where studies reported pregnancy complications, different denominators (e.g. all pregnant women, only ongoing pregnancies, only women with live births) were used in different studies and results could not be pooled. This is explained for the comparisons of treatment concerned.

Aspirin versus no treatment

Pooled analysis from 256 patients showed that compared to placebo, aspirin did not increase live birth (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.80 to 1.11), Analysis 1.1, (Kaandorp 2010; Tulppala 1997). Subgroup analyses for the outcome live birth for women with no previous live births (RR 0.93, 95% CI 0.72 to 1.21), inherited thrombophilia (RR 1.08, 95% CI 0.63 to 1.85) or more than two miscarriages (RR 0.95, 95% CI 0.70 to 1.28) could only be performed for the study by Kaandorp 2010 and also showed no effect of treatment.

Secondary outcomes were not reported by Tulppala 1997. Preterm delivery, obstetric complications and congenital malformations as reported by Kaandorp 2010 for women with ongoing pregnancies beyond 12 weeks' gestation did not differ between the two groups. Bleeding as a side effect from treatment (mainly nose or gum bleeds or haematomas) was reported for 30% of women receiving aspirin and for 27% women receiving placebo (RR 1.11, 95% CI 0.72 to 1.72, Analysis 1.9). It should be noted that bleeding was reported for all women included in the study, including women who did not become pregnant during the course of the study.

LMWH versus aspirin

Three studies compared enoxaparin with aspirin (Dolitzky 2006; Giancotti 2012; Visser 2011). Pooled analysis (n = 325) showed an average RR of live birth for women treated with aspirin of 1.16 (95% CI 0.93 to 1.45; Heterogeneity: $Tau^2 = 0.03$; $I^2 = 67\%$, Analysis 3.1). Due to substantial statistical heterogeneity being detected, we used random-effects meta-analysis in Analysis 3.1. After excluding the study by Giancotti 2012 at high risk of bias, both groups had similar live birth rates, 76% in the enoxaparin group and 70% in the aspirin group (RR 1.08, 95% CI 0.93 to 1.26, Analysis 2.1). In the subgroup of women with no previous live births, the RR of live birth with LMWH was 1.24 (95% CI 1.02 to 1.49) compared to aspirin.

The study by Giancotti 2012 reported no secondary outcome measures. Results of secondary outcome measures for the studies by Dolitzky 2006 and Visser 2011 could not be pooled, as both studies used different denominators (i.e. all pregnancies in the study by Dolitzky 2006 and only women with live birth in the study by Visser 2011). In the individual studies, the number of preterm deliveries (before 37 weeks), cases of intrauterine growth restriction, pre-eclampsia and congenital malformations did not differ between the two groups, Bleeding complications did not differ between the two groups in both studies, though results of bleeding were very different; 0% versus 0.04% in the study by Dolitzky 2006 and 49% versus 50% in the study by Visser 2011 in women treated with LMWH versus aspirin respectively.

LMWH versus no treatment

The effect of LMWH was evaluated in three studies (Badawy 2008; Fawzy 2008; Martinelli 2012). Pooled analysis (n = 453) showed an average RR of live birth for women treated with LMWH of 1.23 (95% CI 0.84 to 1.81; Heterogeneity: $Tau^2 = 0.09$; $I^2 = 80\%$, Analysis 5.1). Due to substantial statistical heterogeneity being detected, we used random-effects meta-analysis in Analysis 5.1. When excluding studies at high risk of bias, only the data of six women included in the study by Martinelli 2012 could be analysed. Of these six women, four were randomised to LMWH and two to no treatment and all six had a live birth during the study (Analysis 4.1). Secondary outcomes were only reported by studies at high risk of bias, and could not be pooled due to a difference in denominators (pregnancies continued beyond 21 weeks in the study by Badawy 2008 and all pregnancies in the study by Fawzy 2008). No difference between

treatment groups were found in individual studies for pregnancy complications, bleeding or thromboembolic events. The study by Badawy 2008 reported that 22% of women treated with LMWH experienced symptoms of bleeding and 30% local skin reactions.

LMWH and aspirin versus no treatment

The effect of LMWH and aspirin on live birth compared to no treatment or placebo was evaluated in two studies (n = 322) (Clark 2010; Kaandorp 2010). Live birth occurred as often in women receiving LMWH and aspirin (n = 161) as in women who received no treatment (n = 161) (RR for women who received LMWH and aspirin 1.01, 95% CI 0.87 to 1.16), Analysis 6.1). Subgroup analyses for the outcome live birth could only be performed for the study by Kaandorp 2010. For women with no previous live births (RR 1.05, 95% CI 0.83 to 1.34), or more than two miscarriages (RR 1.00, 95% CI 0.75 to 1.33) no effect of treatment was found. Data of women with inherited thrombophilia suggested a potential benefit in these women when treated with LMWH and aspirin, but the subgroup was underpowered for firm conclusions (RR 1.25, 95% CI 0.74 to 2.12).

Data of secondary outcomes were not available for the study by Clark 2010 and are therefore only described for the study by Kaandorp 2010. The occurrence of obstetric complications did not differ between the two study arms. Maternal bleeding (mainly nose or gum bleeds or haematomas) occurred significantly more frequently in women who received treatment; resulting in a RR of any bleeding of 2.28 (95% CI 1.60 to 3.24, Analysis 6.9). Pain, itching and swelling at injection site was reported by 51% of the women treated with LMWH and aspirin.

LMWH and aspirin versus aspirin

In the studies by Kaandorp 2010 and Visser 2011 the effect of LMWH and aspirin was compared with aspirin only (n = 327). Live birth did not differ significantly between both groups; 68% and 61% respectively (RR 1.11, 95% CI 0.94 to 1.30, Analysis 7.1). Subgroup analyses for the outcome live birth in women with either no previous live births, inherited thrombophilia or more than two previous miscarriages (study by Kaandorp 2010 only) also showed no effect of treatment.

Again, results for secondary outcome measures could not be pooled because different denominators (ongoing pregnancies in the study by Kaandorp 2010 and pregnancies that ended in live birth in the study by Visser 2011) were used. The incidence of preterm delivery, pre-eclampsia, intrauterine growth restriction (IUGR) and congenital malformations was similar in both groups in the individual studies. A significant difference was seen in bleeding (mainly nose or gum bleeds or haematomas) between the two groups, favouring treatment with aspirin only (RR for bleeding in women treated with LMWH and aspirin 2.04, 95% CI 1.46 to 2.86, Analysis 7.9), in the study by Kaandorp 2010, 62% of women treated with LMWH and aspirin experienced bleeding compared to 30% in women treated with aspirin only. In the study by Visser 2011, bleeding (reported as first trimester, second/third trimester bleeding or postpartum haemorrhage) was reported more often in women treated with aspirin (38% in women treated with LMWH and aspirin and 50% in women treated with aspirin only), though this difference was not significant (RR 0.75, 95% CI 0.45 to 1.24, Analysis 7.9).

LMWH with aspirin versus LMWH

One study evaluated the effect of LMWH and aspirin (n = 61) in comparison with LMWH only (n = 65) (Visser 2011). Neither live birth, nor any of the secondary outcomes including bleeding were different between the two groups (RR of live birth in women treated with LMWH plus aspirin 0.91, 95% CI 0.72 to 1.15, Analysis 8.1). Subgroup analyses in women with inherited thrombophilia or no previous live birth were small and showed no benefit of one treatment over the other.

LMWH with or without aspirin versus no treatment

Results of studies were combined, to evaluate the effect of LMWH with or without aspirin on the chance of live birth. Pooled results from 793 patients of five studies (Badawy 2008; Clark 2010; Fawzy 2008; Kaandorp 2010; Martinelli 2012) showed no effect of treatment (RR 1.07, 95% CI 0.99 to 1.15, Analysis 9.1). After excluding studies at high risk of bias the point estimate shifted towards 1 and no effect of treatment was observed (n = 324, RR for live birth in women treated with LMWH 0.98, 95% CI 0.85 to 1.12, Analysis 10.1).

DISCUSSION

Since the last update of this review (Kaandorp 2009), seven randomised controlled trials on the efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent risk factors other than inherited thrombophilia were published, but the number of studies on this topic remains limited. Although in total nine studies were included, three studies were considered to be at high risk of bias and from one study, data of only six women could be included. Different treatment doses of anticoagulants compared, prescribed for different time periods, resulted in maximally three studies per comparison that could be pooled and only three of seven comparisons included a placebo- or no treatment-arm.

Irrespective of the type of or combinations of anticoagulants used, no benefit of anticoagulant treatment for live birth was found.

Data for subgroup analyses were scarce. Subgroup analyses in women with more than two previous miscarriages showed no effect of treatment, regardless which treatment regimens were compared. A trend towards a significant effect from LMWH when compared to aspirin (risk ratio (RR) of live birth 1.21, 95% confidence interval (CI) 0.79 to 1.87) and of LMWH and aspirin when compared to no treatment (RR of live birth 1.25, 95% CI 0.74 to 2.12) was observed in women with inherited thrombophilia but the subgroups were underpowered for firm conclusions. As the clinical question of efficacy of anticoagulants for women with recurrent miscarriage (RM) and inherited thrombophilia remains relevant, randomised controlled trials focussing on women with inherited thrombophilia only are urgently needed.

In subgroup analyses of women with no previous live birth, a beneficial effect of LMWH over aspirin was found in pooled analyses of two studies (n = 112, RR 1.24, 95% CI 1.02 to 1.49). Some evidence of a similar trend toward a beneficial effect for LMWH versus LMWH and aspirin was observed in a small subgroup in one study (n = 72, RR of live birth in women treated with LMWH and aspirin 0.77, 95% CI 0.59 to 1.02). In comparisons of LMWH and aspirin with either no treatment or with aspirin, no beneficial effect of LMWH and aspirin was found for women with no previous live birth. All subgroup

analyses in women with no previous live birth were limited due to small numbers.

Reporting of secondary outcomes varied widely among studies. In studies that reported pregnancy complications, different denominators (e.g. all pregnant women, only ongoing pregnancies, only live births) were used and results could not be pooled. In the individual studies, no effect of treatment on any pregnancy complication was found. Especially reporting of side effects of treatment, such as bleeding and local skin reactions (for LMWH) was inconsistent. The risk of bleeding (mainly nose or gum bleeds or haematomas) was more than two-fold increased in women treated with LMWH and aspirin, compared to either aspirin only or no treatment in the study by Kaandorp 2010. This was not confirmed in the study by Visser 2011 (reporting first-trimester, second/third trimester bleeding and postpartum haemorrhage, results could not be pooled). Local skin reactions to administered LMWH were not reported in several studies, whereas 50% of women treated with LMWH and aspirin in the study by Kaandorp 2010 reported these side effects.

Besides the limited number of studies on this topic, we must appreciate the heterogeneity between studies. Study designs vary regarding dose, duration and type of treatment, blinding, reporting of secondary outcomes and study quality. Furthermore, lack of a no-treatment (or placebo) arm in some studies impedes assessing a risk-benefit ratio for the individual interventions.

Although in approximately half of women with RM risk factors can be identified, in 50% this remains unexplained. One could argue that the group of women with unexplained RM is in fact a heterogeneous collection of subgroups of women with as yet unidentified risk factors. Once identified, these risk factors may render them ineligible for the study. For this review, we have studied women with unexplained RM (with or without inherited thrombophilia) as one group and where possible we performed a subgroup analysis in women with inherited thrombophilia. Obvious risk factors of RM such as antiphospholipid syndrome, abnormal parental karyotypes and uterine abnormalities were exclusion criteria. This approach yields results that can be applied to all women with unexplained RM, with or without inherited thrombophilia. If future research leads to the identification of other risk factors for RM, therapeutic options for that newly identified subgroup will have to be considered.

Our review of currently available (though limited) data, does not support the use of anticoagulants heparin, LMWH and aspirin, or combinations of these, for women with unexplained RM with or without inherited thrombophilia. Included studies were not sufficiently powered to evaluate an effect of heparin, LMWH or aspirin or combinations in women with confirmed inherited thrombophilia and unexplained recurrent miscarriage. Large randomised controlled trials assessing this subgroup are urgently needed, but until results are available, anticoagulants in these women are also not recommended in this setting.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence on the efficacy and safety of aspirin and low molecular weight heparin (LMWH) in women with a history of at least two miscarriages without apparent risk factors other than inherited thrombophilia is limited, but now includes several high-quality randomised controlled trials. Based on the results of the (pooled) analyses in this review, there is no evidence to support the use of anticoagulants in women with recurrent miscarriage (RM), regardless of the presence of inherited thrombophilia. Large randomised controlled trials assessing an effect of anticoagulants in women with RM and inherited thrombophilia are urgently needed.

Implications for research

Although several studies included women with inherited thrombophilia, subgroup analyses were never sufficiently powered to assess an effect of anticoagulation in these women with RM. We can not exclude a beneficial effect in these women and therefore, large randomised trials are urgently needed and because of a counterbalancing effect of heparin and aspirin, a placebo or no intervention arm is necessary, since it would provide an adequate control to the active treatment and allows assessing a risk-benefit ratio.

ACKNOWLEDGEMENTS

We kindly acknowledge Professor Badawy, Professor Carp, Dr Fawzy, Dr Giancotti, Dr Martinelli, Dr Perna, Dr Ruggenenti, Dr Clark, Dr Tulppala, Dr Kaaja and Dr Visser for providing data or additional information requested for the review.

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

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

REFERENCES

References to studies included in this review

Badawy 2008 *{published data only}*

Badawy AM, Khiary M, Sherif LS, Hassan M, Ragab A, Abdelall I. Low-molecular weight heparin in patients with recurrent early miscarriages of unknown aetiology. *Journal of Obstetrics and Gynaecology* 2008;**28**(3):280-4.

Clark 2010 *{published data only}*

Clark P. The Scottish pregnancy intervention study: the effect of low molecular weight heparin and aspirin therapy on recurrent pregnancy loss (ongoing trial). National Research Register (www.nrr.nhs.uk) (accessed 6 July 2006).

* Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood* 2010;**115**(21):4162-7.

Dolitzky 2006 *{published data only}*

Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. *Fertility and Sterility* 2006;**86**(2):362-6.

Fawzy 2008 *{published data only}*

Fawzy M, Shokeir T, El-Tatongy M, Warda O, El-Refaiey AA, Mosbah A. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study. *Archives of Gynecology and Obstetrics* 2008;**278**(1):33-8.

Giancotti 2012 *{published data only}*

Chistolini A, Torelli F, Giancotti A, Pignoloni P, Muto B, Cosimo C, et al. Recurrent fetal loss: prospective evaluation of the efficacy of three different thromboprophylaxis regimens: aspirin versus low molecular weight heparin versus low molecular weight heparin plus aspirin [abstract]. *Hematology Journal* 2006;**91**(Suppl 1):146.

* Giancotti A, Torre RL, Spagnuolo A, D'Ambrosio V, Cerekja A, Piazze J, et al. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. *Journal of Maternal-Fetal and Neonatal Medicine* 2012;**25**(7):1191-4. [PUBMED: 21988715]

Kaandorp 2010 *{published data only (unpublished sought but not used)}*

* Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyak K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *New England Journal of Medicine* 2010;**362**(17):1586-96.

Middeldorp S. Aspirin and/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).

Martinelli 2012 *{published data only}*

Martinelli I. Low molecular weight heparin in pregnant women with previous obstetrical complications. A multicenter, randomized trial. *Pathophysiology of Haemostasis and Thrombosis* 2010;**37 Suppl 1**:A3.

* Martinelli I, Ruggenenti P, Cetin I, Pardi G, Perna A, Vergani P, et al. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood* 2012;**119**(14):3269-75. [PUBMED: 22289887]

Tulppala 1997 *{published data only}*

Tulppala M, Marttunen M, Soderstrom-Anttila V, Ailus K, Palosuo T, Ylikorkala O. Low dose aspirin in the prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. *Human Reproduction* 1997;**12**(1):191.

* Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, et al. Low-dose aspirin in the prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. *Human Reproduction* 1997;**12**(7):1567-72.

Visser 2011 *{published data only}*

Visser J, Ulander V, Bloemenkamp K, Kaaja R. A randomised controlled multicenter study: the effect of enoxaparin and/or aspirin on prevention of recurrent miscarriage in women with or without thrombophilia, HABENOX-study. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S371.

* Visser J, Ulander V-M, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KWM, et al. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia - HABENOX*: a randomised multicentre trial. *Thrombosis and Haemostasis* 2011;**105**(2):295-301.

References to studies excluded from this review

Bar 2000 *{published data only}*

Bar J, Cohen-Sacher B, Hod M, Blickstein D, Lahav J, Merlob P. Low-molecular-weight heparin for thrombophilia in pregnant women. *International Journal of Gynecology & Obstetrics* 2000;**69**:209-13.

Bar 2001 *{published data only}*

Bar J, Mashiah R, Cohen-Sacher B, Hod M, Orvieto R, Ben-Rafael Z, et al. Effect of thromboprophylaxis on uterine and fetal circulation in pregnant women with a history of pregnancy complications. *Thrombosis Research* 2001;**101**:235-41.

Bick 2000 *{published data only}*

Bick RL. Recurrent miscarriage syndrome due to blood coagulation protein/platelet defects: prevalence, treatment and outcome results. DRW Metroplex Recurrent Miscarriage Syndrome Cooperative Group. *Clinical and Applied Thrombosis/Hemostasis* 2000;**6**(3):115-25.

Brenner 2000 *{published data only}*

Brenner B, Hoffman, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. *Thrombosis and Haemostasis* 2000;**83**:693-7.

Brenner 2005 *{published and unpublished data}*

* Brenner B, Bar J, Ellis M, Yarom I, Yohai D, Samueloff A. Effects of enoxaparin on late pregnancy complications and neonatal outcome in women with recurrent pregnancy loss and thrombophilia: results from the Live-Enox study. *Fertility and Sterility* 2005;**84**(3):770-3.

Brenner B, Hoffman R, Carp H, Dulitsky M, Samueloff A, Yohai D, et al. Enoxaparin treatment improves the gestational outcome of pregnant women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study [abstract]. *Blood* 2003;**102**(11):16a.

Brenner B, Hoffman R, Carp H, Dulitsky M, Samueloff A, Yohal D, et al. Efficacy and safety of two doses of enoxaparin in pregnant women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. *Journal of Thrombosis and Haemostasis* 2003;**1 Suppl 1**:Abstract number: OC084.

Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. *Journal of Thrombosis and Haemostasis* 2005;**3**(2):227-9.

Brenner B, for the LIVE-ENOX Investigators. Efficacy and safety of two doses of enoxaparin in pregnant women with thrombophilia and recurrent pregnancy loss. The LIVE-ENOX study. *Blood* 2002;**100**(11 Pt 1):702a.

Thaler I, Brenner B. Efficacy of enoxaparin for improving pregnancy outcomes and uteroplacental blood flow in women with thrombophilia and recurrent pregnancy loss. *American Journal of Obstetrics and Gynecology* 2004;**191**(6 Suppl 1):S7.

Carp 2003 *{published data only}*

Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. *Journal of Thrombosis and Haemostasis* 2003;**1**:433-8.

Grandone 2002 *{published data only}*

Grandone E, Brancaccio V, Colaizzo D, Sciannamé N, Pavone G, Di Minno G, et al. Preventing adverse obstetric outcomes in women with genetic thrombophilia. *Fertility and Sterility* 2002;**78**(2):371-5.

Gris 1995 *{published data only}*

Gris JC, Neveu S, Tailland ML, Courtieu C, Mares P, Schved JF. Use of a low-molecular-weight heparin (enoxaparin) or of a phenformin-like substance (moroxydine chloride) in primary early recurrent aborters with an impaired fibrinolytic capacity. *Thrombosis and Haemostasis* 1995;**73**(3):362-7.

Gris 2004 *{published data only}*

Gris JC, Mercier E, Quéré I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood* 2004;**103**:3695-9.

Gris 2010 *{published data only}*

Gris JC, Chauleur C, Faillie JL, Baer G, Mares P, Fabbro-Peray P, et al. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae: the pilot randomised controlled NOH-AP trial. Thrombosis and Haemostasis 2010; Vol. 104, issue 4:771-9.

Gris 2011 *{published data only}*

Gris JC, Chauleur C, Molinari N, Mares P, Fabbro-Peray P, Quere I, et al. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. *Thrombosis and Haemostasis* 2011;**106**(6):1053-61. [PUBMED: 21946915]

Li 2003 *{published data only}*

Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003;**327**:368-72.

Ogasawara 2001 *{published data only}*

Ogasawara MS, Iinuma Y, Aoki K, Katano K, Ozaki Y, Suzumori K. Low-dose aspirin is effective for treatment of recurrent miscarriage in patients with decreased coagulation factor XII. *Fertility and Sterility* 2001;**76**(1):203-4.

Rai 2000 *{published data only}*

Rai R, Backos M, Baxter N, Chilcott I, Regan L. Recurrent miscarriage-an aspirin a day?. *Human Reproduction* 2000;**15**(10):2220-3.

Rey 2009 *{published data only}*

Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *Journal of Thrombosis and Haemostasis* 2009;**7**(1):58-64.

Reznikoff-Etievant 1999 *{published data only}*

Reznikoff-Etievant MF, Cayol V, Zou GM, Abuaf N, Robert A, Johanet C, et al. Habitual abortions in 678 healthy patients: investigation and prevention. *Human Reproduction* 1999;**14**(8):2106-9.

Sarig 2003 *{published data only}*

Sarig G, Aharon A, Lanir N, Goshen H, Drugan A, Blumenfeld Z, et al. Modulation of systemic and placental hemostatic mechanisms by enoxaparin in women with gestational vascular complications. *Journal of Thrombosis and Haemostasis* 2003;**1 Suppl 1**:Abstract number: OC083.

Sarto 2001 *{published data only}*

Sarto A, Rocha M, Geller M, Capmany C, Martinez M, Quintans C, et al. Treatment with enoxaparin adapted to the fertility programs in women with recurrent abortion and thrombophilia. *Medicina* 2001;**61**(4):406-12.

Sorensen 2000 *{published data only}*

Sorensen HT, Johnsen SP, Larsen H, Pedersen L, Nielsen GL, Moller M. Birth outcomes in pregnant women treated with low-molecular-weight heparin. *Acta Obstetricia et Gynecologica Scandinavica* 2000;**79**:655-9.

Tzafettas 2002 *{published data only}*

Tzafettas J, Mamopoulos A, Anapliotis A, Loufopoulos A, Psarra A, Klearchou N, et al. Thromboprophylaxis throughout pregnancy in women with previous history of recurrent miscarriage of unknown etiology. *Clinical and Experimental Obstetrics and Gynecology* 2002;**29**(4):267-70.

Younis 2000 *{published data only}*

Younis JS, Ohel G, Brenner B, Haddad S, Lanir N, Ben-Ami M. The effect of thromboprophylaxis on pregnancy outcome in patients with recurrent pregnancy loss associated with factor V mutation. *BJOG: an international journal of obstetrics and gynaecology* 2000;**107**:415-9.

Zolghadri 2010 *{published data only}*

Zolghadri J, Ahmadpour F, Momtahan M, Tavana Z, Foroughinia L. Evaluation of the efficacy of aspirin and low molecular weight heparin in patients with unexplained recurrent spontaneous abortions. *Iranian Red Crescent Medical Journal* 2010;**12**(5):548-52.

References to studies awaiting assessment

Rodger 2009 *{published data only}*

Abou-Nassar K, Kovacs MJ, Kahn SR, Wells P, Doucette S, Ramsay T, et al. The effect of dalteparin on coagulation activation during pregnancy in women with thrombophilia. A randomized trial. *Thrombosis and Haemostasis* 2007;**98**(1):163-71.

Abou-Nassar K, Rodger M, Kovacs MJ, Doucette S, Tim R, Kahn S, et al. The effect of dalteparin on coagulation activation during pregnancy in women with thrombophilia: a randomised trial. *Blood* 2006;**108**(11 Pt 1):262.

Rodger M, Hague WM, Kingdom J, Kahn SR, Karovitch A, Wells PS, et al. The Thrombophilia in Pregnancy Prophylaxis Study (TIPPS): a multi-national randomized trial of dalteparin vs. no dalteparin to prevent pregnancy complications in pregnant thrombophilic women. *Journal of Thrombosis and Haemostasis* 2013;**11**(Suppl 2):78.

Rodger MA. TIPPS: Thrombophilia in pregnancy prophylaxis study. ClinicalTrials.gov (accessed 21 May 2013). NCT00967382 2009.

Rodger MA, Kahn S, Cranney A, Hodson A, Kovacs M, Clement AM, et al. Prophylactic low molecular weight heparin (LMWH) during pregnancy is not associated with a decrease in bone mineral density (BMD) [abstract]. *Hypertension in Pregnancy* 2006;**25**(Suppl 1):8.

Rodger MA, Kahn SR, Cranney A, Hodsman A, Kovacs MJ, Clement AM, et al. Long-term dalteparin in pregnancy not associated with a decrease in bone mineral density: substudy of a randomized controlled trial. *Journal of Thrombosis and Haemostasis* 2007;**5**(8):1600-6.

Rodger MA, Lazo-Langner A, Kahn S, Kovacs M, Robinson S, Blostein M, et al. Prophylactic low molecular weight heparin (LMWH) during pregnancy is not associated with a decrease in bone mineral density (BMD). The TIPPS (Thrombophilia in Pregnancy Prophylaxis Study) BMD substudy. *Blood* 2005;**106**(11):Abstract no 548.

Rodgers M. Thrombophilia in pregnancy prophylaxis study (TIPPS). Ottawa Health Research Institute (http://www.ohri.ca) (accessed 17 July 2002).

Salman 2012 *{published data only}*

Salman SA, Shaaban OM, Zahran KM, Fathalla MM, Anan MA. Low molecular weight heparin (LMWH) for treatment of recurrent miscarriage negatively tested for anti phospholipid antibodies: A randomized controlled trial. *Fertility and Sterility* 2012;**98**(3 Suppl 1):S191.

Schleussner 2013 *{published data only}*

Kamin G, Rogenhofer N, Pildner V, Steinberg S, Neuhoffer A, Seeger S, et al. Therapy with dalteparin for habitual abortion - presentation of the ETHiG II-Studie [Therapie mit Dalteparin bei habitueller Abortneigung - Vorstellung der ETHiG II-Studie]. *Geburtshilfe und Frauenheilkunde* 2008;**68**:S51.

Schleussner E. Effectiveness of dalteparin therapy as intervention in recurrent pregnancy loss. http://controlled-trials.com (accessed 15.02.2007).

Schleussner E, Bohlmann M, Kamin G, Rogenhofer N, Seeger S, Toth B. Low molecular weight heparin for the prevention of habitual abortion - introduction of the multicentre study EThIG2 and discussion of the current data [Niedermolekulares heparin zur pravention habitueller aborte - vorstellung der multizentrischen EThIG2-studie und diskussion der aktuellen datenlage]. *Archives of Gynecology and Obstetrics* 2012;**286**(Suppl 1):S220.

Schleussner E, Kamin G, Seeliger G, Rogenhofer N, Toth B. Low-molecular-weight heparin in recurrent pregnancy loss-Results of the ETHIG II study. *Thrombosis Research* 2013;**131**(Suppl 1):S73.

Additional references

Askie 2007

Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007;**369**(9575):1791-8. [PUBMED: 17512048]

Bates 2012

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**(2 Suppl):e691S-736S. [PUBMED: 22315276]

Bhattacharya 2010

Bhattacharya S, Townend J, Bhattacharya S. Recurrent miscarriage: Are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2010;**150**(1):24-7. [PUBMED: 20207064]

Braekeleer 1990

Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Human Reproduction* 1990;**5**:519-28.

Brigham 1999

Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. *Human Reproduction* 1999;**14**:2868-71.

Chan 2011

Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. *Human Reproduction Update* 2011;**17**(6):761-71. [PUBMED: 21705770]

Christiansen 2005

Christiansen OB, Nybo Andersen AM, Bosch E, Daya S, Delves PJ, Hviid TV, et al. Evidence-based investigations and treatments of recurrent pregnancy loss. *Fertility and Sterility* 2005;**83**(4):821-39.

Christiansen 2006

Christiansen OB. Evidence-based investigations and treatments of recurrent pregnancy loss. *Current Opinion in Obstetrics and Gynecology* 2006;**18**:304-12.

Clifford 1994

Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. *Human Reproduction* 1994;**9**:1328-32.

Cohn 2010

Cohn DM, Goddijn M, Middeldorp S, Korevaar JC, Dawood F, Farquharson RG. Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy. *Journal of Thrombosis and Haemostasis* 2010;**8**(10):2208-13. [PUBMED: 20704646]

Cook 1995

Cook CL, Pridman DD. Recurrent pregnancy loss. *Current Opinion in Obstetrics and Gynecology* 1995;**7**:357-66.

Dizon 1997

Dizon TD, Meline L, Nelson LM, Varner M, Ward K. Fetal carriers of the factor V Leiden mutation are prone to miscarriage and placental infarction. *American Journal of Obstetrics and Gynecology* 1997;**177**:402-5.

Empson 2005

Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD002859.pub2]

Everett 1997

Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *BMJ* 1997;**315**:32-4.

Farquharson 2002

Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstetrics & Gynecology* 2002;**100**:408-13.

Franssen 2005

Franssen MT, Korevaar JC, Leschot NJ, Bossuyt PM, Knegt AC, Gerssen-Schoorl KB, et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. *BMJ* 2005;**331**:137-41.

Ginsberg 2001

Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest* 2001;**119**(Suppl):122-31.

Goyaux 2001

Goyaux N, Alihonou E, Diadhiou F, Leke R, Thonneau PF. Complications of induced abortion and miscarriage in three African Countries: a hospital-based study among WHO collaborating centres. *Acta Obstetricia et Gynecologica Scandinavica* 2001;**80**:568-73.

Haas 2008

Haas DM, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD003511.pub2]

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Huisjes 1984

Huisjes HJ. Spontaneous Abortion. London: Churchill Livingstone, 1984:6.

Infante-Reviard 1991

Infante-Reviard C, David M, Gauthier R, Rivard GE. Lupus anticoagulants, anticardiolipin antibodies, and fetal loss. A case-control study. *New England Journal of Medicine* 1991;**325**:1063-6.

Jaslow 2010

Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. *Fertility and Sterility* 2010;**93**(4):1234-43. [PUBMED: 19338986]

Jauniaux 2006

Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical

treatment of recurrent miscarriage. *Human Reproduction* 2006;**21**:2216-22.

Kupferminc 1999

Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *New England Journal of Medicine* 1999;**340**:9-13.

Kutteh 1996

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *American Journal of Obstetrics and Gynecology* 1996;**174**:1584-9.

Laskin 2009

Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker GA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *Journal of Rheumatology* 2009;**36**(2):279-87. [PUBMED: 19208560]

Lee 1996

Lee C, Slade P. Miscarriage as a traumatic event: a review of the literature and new implications for intervention. *Journal of Psychosomatic Research* 1996;**40**(3):235-44.

Levine 2002

Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. *New England Journal of Medicine* 2002;**346**:752-63.

Lim 2006

Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA* 2006;**295**(9):1050-7. [PUBMED: 16507806]

Lindqvist 2006

Lindqvist PG, Merlo J. The natural course of women with recurrent fetal loss. *Journal of Thrombosis and Haemostasis* 2006;**4**:896-7.

Lockshin 1999

Lockshin MD. Pregnancy loss in the antiphospholipid syndrome. *Thrombosis and Haemostasis* 1999;**82**:641-8.

Lok 2007

Lok IH, Neugebauer R. Psychological morbidity following miscarriage. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2007;**21**(2):229-47. [PUBMED: 17317322]

Meinardi 1999

Meinardi JR, Middeldorp S, de Kam PJ, Koopman MMW, van Pampus ECM, Hamulyak K, et al. Increased risk for fetal loss in carriers of the factor V Leiden. *Annals of Internal Medicine* 1999;**130**:736-9.

Middeldorp 2007

Middeldorp S. Thrombophilia and pregnancy complications: cause or association?. *Journal of Thrombosis and Haemostasis* 2007;**5 Suppl 1**:276-82.

Middeldorp 2007a

Middeldorp S, Levi M. Thrombophilia: an update. *Seminars in Thrombosis and Hemostasis* 2007;**33**(6):563-72. [PUBMED: 17768688]

Miyakis 2006

Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Journal of Thrombosis and Haemostasis* 2006;**4**(2):295-306. [PUBMED: 16420554]

Mousa 2000

Mousa HA, Alfirevic Z. Do placental lesions reflect thrombophilia state in women with adverse pregnancy outcome?. *Human Reproduction* 2000;**15**:1830-3.

NHMRC 2001

National Health and Medical Research Council. Report on Maternal Deaths in Australia 1994-96. Canberra. Australian Institute of Health and Welfare National Perinatal Statistics Unit, 2001.

Porter 2006

Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD000112.pub2]

Preston 1996

Preston F, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;**348**:913-6.

Rai 1995

Rai RS, Regan L, Clifford K, Pickering W, Dave M, Mackie I, et al. Antiphospholipid antibodies and beta2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive approach. *Human Reproduction* 1995;**10**:2001-5.

Rai 1996

Rai RS, Regan L, Chitolie A, Donald JG, Cohen H. Placental thrombosis and second trimester miscarriage in association with activated protein C resistance. *British Journal of Obstetrics and Gynaecology* 1996;**103**:842-4.

Rai 1997

Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;**314**:253-7.

Regan 1988

Regan L. A prospective study of spontaneous abortion. Early Pregnancy Loss: Mechanisms and Treatment. RCOG, 1988.

RevMan 2012 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2012.

Rey 2003

Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003;**361**:901-8.

Robertson 2006

Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al. Thrombophilia in pregnancy: a systematic review. *British Journal of Haematology* 2006;**132**(2):171-96. [PUBMED: 16398652]

Rushton 1988

Rushton DI. Placental pathology in spontaneous miscarriage. In: Beard RW, Sharp F editor(s). Early Pregnancy Loss: Mechanisms and Treatment. London: RCOG, 1988:149-58.

Sanson 1996

Sanson BJ, Friederich PW, Simioni P, Zanardi S, Huisman MV, Girolami A, et al. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. *Thrombosis and Haemostasis* 1996;**75**(3):387-8.

Sanson 1999

Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E. Safety of low-molecular-weight heparin in pregnancy. A systematic review. *Thrombosis and Haemostasis* 1999;**81**:668-72.

Stirrat 1990

Stirrat GM. Recurrent miscarriage: definition and epidemiology. *Lancet* 1990;**336**:673-5.

van den Boogaard 2010

van den Boogaard E, Kaandorp SP, Franssen MT, Mol BW, Leschot NJ, Wouters CH, et al. Consecutive or non-consecutive recurrent miscarriage: is there any difference in carrier status?. *Human Reproduction (Oxford, England)* 2010;**25**(6):1411-4. [PUBMED: 20382970]

van den Boogaard 2012

van den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, et al. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertility and Sterility 2012 Oct 6 [Epub ahead of print]. [DOI: 10.1016/j.fertnstert.2012.09.002.]

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. [DOI: 10.1002/14651858.CD003580]

WHO 2009

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Human Reproduction (Oxford, England)* 2009;**24**(11):2683-7. [PUBMED: 19801627]

References to other published versions of this review

Di Nisio 2005

Di Nisio M, Peters LW, Middeldorp S. Aspirin or anticoagulants for the treatment of recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD004734.pub2]

Kaandorp 2009

Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004734.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Badawy 2008

Methods	Multicentre, open label; random allocation with adequate concealment.
Participants	Pregnant women (< 8 weeks) (n = 340) with a history of 3 or more consecutive first trimester miscarriages.
Interventions	Subcutaneous enoxaparin 20 mg once daily from detection of fetal viability on ultrasound until 34 weeks' gestation vs no pharmacological intervention.
Outcomes	Primary: termination of pregnancy. Secondary: maternal and fetal complications, adverse effects such as bleeding, thrombocytopenia and local reactions.
Notes	Live birth rates were not reported in the article; upon request, study authors confirmed that all women who were not reported to have a miscarriage or placental abruption had a live birth.

Badawy 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly allocated by using prefilled sealed envelopes drawn by investigators for each patient.
Allocation concealment (selection bias)	Low risk	Women were randomly allocated by using prefilled sealed envelopes drawn by investigators for each patient.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 women lost to follow-up in group A and 6 women lost to follow-up in group B; these women were excluded from analyses.
Selective reporting (reporting bias)	High risk	Study was not registered in trial register.
Other bias	High risk	Inconsistencies throughout article; 95% confidence intervals do not correspond to odds ratios reported.
Overall risk of bias	High risk	Because of the high risk of reporting bias and other bias due to inconsistencies throughout the article this study was judged as to be at high risk of bias.

Clark 2010

Methods	Open label, random allocation with adequate concealment.
Participants	Pregnant women (n = 294) (< 7 weeks' gestation, n = 294) with a history of 2 or more consecutive pregnancy losses (at or before 24 weeks' gestation) in whom no risk factor for their previous losses was found.
Interventions	Subcutaneous enoxaparin (40 mg daily) and aspirin (75 mg daily) vs no pharmacological treatment from randomisation until 36 weeks' gestation.
Outcomes	Primary: live birth. Secondary: haemorrhage, anaemia, thrombocytopenia, skin reactions.
Notes	We included only data of women with 3 or more previous miscarriages, as of these women tests for abnormal karyotype, uterine abnormalities and antiphospholipid syndrome were performed (n = 122) and found to be negative.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally using consecutively numbered randomisation envelopes supplied by the statistics unit.
Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study analyses were performed on an intention-to-treat basis. Of 294 women, 11 were lost to follow-up. These women were excluded from analyses.

Clark 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study was prospectively registered (ISRCTN06774126).
Other bias	Low risk	No other sources of bias were detected.
Overall risk of bias	Low risk	Overall, the study was considered at low risk of bias.

Dolitzky 2006

Methods	Multicentre, open label, random allocation with adequate concealment.
Participants	Women (n = 107) with a history of 3 or more consecutive fetal losses in the first trimester or at least 2 second trimester fetal losses in whom no risk factor for their previous pregnancy losses was found.
Interventions	Subcutaneous enoxaparin (40 mg/daily) vs aspirin (100 mg/daily) from the time of detection of a fetal heart beat.
Outcomes	Data of 104 women were available for analysis. Primary: live birth rates. Secondary: intrauterine growth restriction, birthweight, uterine and umbilical blood flow, pre-eclampsia, haemorrhage, thrombocytopenia, allergic reactions and congenital malformations.
Notes	Study authors were contacted and provided information that all women included in the review had at least 2 miscarriages before 25 weeks' gestation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally in blocks of 8 by an independent co-ordinator.
Allocation concealment (selection bias)	Low risk	The randomisation code per patient number was held by the monitor and blinded from the investigator.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 107 women 3 women were lost to follow-up. These women were excluded from analyses.
Selective reporting (reporting bias)	Unclear risk	Trial registration was not yet operative at time of inclusion.
Other bias	Unclear risk	Initial power analysis aimed to include more patients; study was closed after interim analyses because it was estimated that too many patients needed to be included to reach statistical significance.
Overall risk of bias	Low risk	As trial registration was not operative at time of inclusion, the overall risk of bias was judged as low risk.

Fawzy 2008

Methods	Single centre, placebo-controlled.

Fawzy 2008 *(Continued)*

Participants	Women (n = 170) with a history of 3 or more spontaneous consecutive pregnancy losses < 24 weeks' gestation in whom no risk factor of previous pregnancy losses was found.
Interventions	Subcutaneous enoxaparin (20 mg daily) until spontaneous labour or miscarriage vs combination treatment of oral prednisone (20 mg daily) and progesterone (20 mg daily) for the first 12 weeks of gestation vs placebo.
Outcomes	Primary: live birth. Secondary: obstetric complications including pre-eclampsia, preterm delivery, gestational diabetes, haemorrhage, allergic reactions and neonatal outcome.
Notes	Unclear treatment allocation and placebo procedure. Participants included in the present review: 107 (of 170 randomised women, 6 were lost to follow-up and 4 women stopped treatment; 53 women were randomised to a combined intervention arm (prednisone, progesterone and aspirin) and they were excluded from our analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was performed according to a computer-generated list of study numbers.
Allocation concealment (selection bias)	High risk	Authors describe that a list of study numbers was used, and that only patients were blinded for allocation. In personal communication authors could not confirm allocation concealment was adequate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women randomised to enoxaparin were lost to follow-up and 1 woman randomised to enoxaparin stopped treatment; these women were excluded from analyses.
Selective reporting (reporting bias)	High risk	Study was not registered in a trial register.
Other bias	Low risk	No other sources of bias were detected.
Overall risk of bias	High risk	Because of the high risk of selection bias and reporting bias this study was judged to be at high risk of bias.

Giancotti 2012

Methods	Single centre university hospital, open label.
Participants	Non-pregnant women with a history of 2 or more unexplained miscarriages before 12 weeks' gestation were recruited. 167 women became pregnant and were randomised after positive plasma Beta HCG test with corresponding ultrasonography.
Interventions	Aspirin (100 mg daily) from confirmation of pregnancy until 32 weeks' gestation vs subcutaneous enoxaparin (40 mg daily) from confirmation of pregnancy until delivery vs combination of aspirin (100 mg daily) from confirmation of pregnancy until 32 weeks' gestation and enoxaparin (40 mg daily) from 32 weeks' gestation until delivery.
Outcomes	Primary: live birth. Secondary: none.

Giancotti 2012 *(Continued)*

Notes	Women randomised to the third study arm received aspirin before and enoxaparin after 32 weeks' gestation. Data of these women were excluded from analyses. 46 women randomised to aspirin and 40 women randomised to enoxaparin were included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistical advisor performed randomised selection as stated by the statistical data management program.
Allocation concealment (selection bias)	Low risk	Once informed consent was obtained, randomised selection was performed as stated by the statistical data management program.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data are available for all randomised women.
Selective reporting (reporting bias)	High risk	Study was not registered in trial register.
Other bias	Unclear risk	Baseline table was not provided; unclear if baseline imbalances between groups existed.
Overall risk of bias	High risk	Because of the high risk of reporting bias and risk of other bias due to baseline imbalances this study was judged to be at high risk of bias.

Kaandorp 2010

Methods	Double blind (for aspirin)/open label (for nadroparin) placebo-controlled with adequate allocation concealment.
Participants	364 women with a history of 2 or more miscarriages attempting to conceive or < 6 weeks pregnant, in whom no risk factor of their previous miscarriages could be found, with or without inherited thrombophilia.
Interventions	Subcutaneous nadroparin (2850 IU daily, from 6 weeks of gestation until labour) and aspirin (80 mg daily) vs aspirin only (80 mg daily) vs placebo. Aspirin or placebo was initiated at randomisation and continued until 36 weeks' gestation or stopped at miscarriage, ectopic pregnancy or premature delivery.
Outcomes	Primary: live birth. Secondary: miscarriage, intrauterine fetal death, obstetrical complications (HELLP syndrome, small size for gestational age, placental abruption, premature delivery), thrombocytopenia, haemorrhage, skin reactions, congenital abnormalities.
Notes	Participants included in the present review: 299 women who became pregnant during the course of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally by a computer program with minimisation for maternal age and the number of miscarriages, stratified according to study centre.

Kaandorp 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Women were randomised preconceptionally. Respectively 26, 21 and 18 women were either lost to follow-up, did not become pregnant or were still in the study when the trial ended in the combination, aspirin and placebo arm. Study analyses were performed on an intention-to-treat basis. Only data of women who became pregnant were included in this review.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered (ISRCTN58496168).
Other bias	Low risk	No other sources of bias were detected.
Overall risk of bias	Low risk	Overall, the study was considered at low risk of bias.

Martinelli 2012

Methods	Multicentre, open label, random allocation with adequate concealment.
Participants	135 pregnant women with previous pregnancies complicated by either pre-eclampsia, HELLP syndrome, spontaneous fetal loss > 15 weeks' gestation, birthweight < 10th percentile or placental abruptio followed by emergency delivery > 24 weeks.
Interventions	Subcutaneous nadroparin (3800 IU once daily) and medical surveillance vs medical surveillance only. Treatment was initiated upon randomisation and continued until delivery.
Outcomes	Primary: a composite endpoint of pregnancy complications. Secondary: maternal, fetal adverse events related to study, miscarriage (< 15 weeks' gestation), mode of delivery, Apgar scores.
Notes	Upon request, the authors provided data on live birth in women who had 2 or more previous miscarriages up to 24 weeks' gestation that were unexplained. Only this subgroup of 6 women could be included in the current review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer randomisation list was generated by the laboratory of biostatistics.
Allocation concealment (selection bias)	Low risk	The patient randomisation number and study arm were requested by phone or fax and centrally assigned by the treatment secretariat.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 women and 3 women randomised to intervention and surveillance respectively were reported as drop-outs. These were excluded from analyses.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered (EudraCT 2006-004205-26).
Other bias	Low risk	No other sources of bias were detected.
Overall risk of bias	Low risk	Overall, the study was considered at low risk of bias.

Tulppala 1997

Methods	Double-blind, placebo-controlled.
Participants	Women (n = 82) with a history of at least 3 consecutive miscarriages in whom no obvious risk factor for their previous pregnancy losses was found.
Interventions	Aspirin (50 mg/daily) vs placebo, started as soon as a urinary pregnancy test became positive.
Outcomes	To assess the effect of 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.
Notes	Participants included in the present review: subcategory of 54 women negative for anticardiolipin antibodies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally by a medical company who supplied the study medication (aspirin and placebo).
Allocation concealment (selection bias)	Low risk	Aspirin and placebo tablets were identical and were supplied after randomisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For the complete study population, 2 women with blighted ovum and 1 ectopic pregnancy were reported in the aspirin group, compared to 2 and 3 in the placebo group. There were no losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Trial registration was not yet operative at time of inclusion.
Other bias	Unclear risk	Unclear if baseline imbalances were present.
Overall risk of bias	Low risk	Dr Tulppala provided information on random sequence generation and allocation concealment which was not available from the article. As trial registration was not operative at time of inclusion, the overall risk of bias was judged as low risk.

Visser 2011

Methods	Multicentre, double blind (for aspirin)/open label (for enoxaparin) placebo controlled (for aspirin).
Participants	Pregnant women with 3 or more first trimester miscarriages (< 13 weeks), 2 or more second trimester miscarriages (13-24 weeks) or 1 third trimester fetal loss (> 24 weeks).
Interventions	Subcutaneous enoxaparin (40 mg daily) and placebo for aspirin (n = 68) vs subcutaneous enoxaparin (40 mg daily) (n = 63) and aspirin (100 mg daily) vs aspirin (100 mg daily) (n = 76).
Outcomes	Primary: live birth (live birth after 24 weeks' gestation). Secondary: pre-eclampsia, abruptio placentae, premature delivery (24-37 weeks' gestation) intrauterine growth restriction, adverse effects and vaginal bleeding complications.

Visser 2011 *(Continued)*

Notes	Data of 1 woman (randomised to aspirin only) were excluded from analyses because she did not have RM < 24 weeks' gestation and data of 10 women were excluded from analyses because they had beta-2 glycoprotein antibodies and therefore did not meet inclusion criteria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by computer in blocks of 6 patients, stratified by centre and history of early or late miscarriage.
Allocation concealment (selection bias)	Low risk	Patients were allocated to randomisation code numbers in chronological order. The allocation list was stored at an independent secretary and randomisation was performed by telephone.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No women were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered (NCT0095962).
Other bias	Low risk	No other sources of bias were detected.
Overall risk of bias	Low risk	Overall, the study was considered at low risk of bias.

HCG: human chorionic gonadotropin
HELLP: haemolysis, elevated liver enzymes, low platelet count
IU: international units
PGI2: prostacyclin 2
RM: recurrent miscarriage
TXA2: thromboxane A2
vs: versus

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

Study	Reason for exclusion
Bar 2000	Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately. Non-randomised trial.
Bar 2001	Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately. Non- randomised, uncontrolled trial.
Bick 2000	Non-randomised, uncontrolled trial.
Brenner 2000	Non-randomised trial, historical controls.
Brenner 2005	Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.
Carp 2003	Non-randomised trial, historical controls.
Grandone 2002	Non-randomised trial. Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.

Study	Reason for exclusion
Gris 1995	Moroxydine chloride is not an intervention of interest in this review.
Gris 2004	Study does not include women with a history of RM.
Gris 2010	Study does not include women with a history of RM.
Gris 2011	Study does not include women with a history of RM.
Li 2003	Non-randomised trial.
Ogasawara 2001	Non-randomised trial. Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.
Rai 2000	Non-randomised trial.
Rey 2009	Study author confirmed that no women were included in the study because of RM only.
Reznikoff-Etievant 1999	Non-randomised trial.
Sarig 2003	Data for women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.
Sarto 2001	Non-randomised trial, historical controls.
Sorensen 2000	Non-randomised, uncontrolled trial. Data from women without apparent risk factors of recurrent pregnancy loss other than inherited thrombophilia cannot be extracted to be analysed separately.
Tzafettas 2002	Non-randomised, uncontrolled trial.
Younis 2000	Non-randomised, uncontrolled trial.
Zolghadri 2010	Unclear at what gestational age previous pregnancy losses occurred.

RM: recurrent miscarriage

Characteristics of studies awaiting assessment *[ordered by study ID]*

Rodger 2009

Methods	Multi-national randomised controlled trial.
Participants	Women with laboratory confirmed thrombophilia at increased risk of placenta-mediated pregnancy complications or VTE.
Interventions	Dalteparin 5000 units daily until 20 weeks' gestation and then 5000 units twice daily until at least 37 weeks' gestation vs no dalteparin.
Outcomes	Primary composite outcome: independently adjudicated placenta-mediated pregnancy complications (severe or early onset preeclampsia, birth of a small-for-gestational-age child (< 10th percentile) and/or pregnancy loss) and/or major VTE up to 6 weeks postpartum.
Notes	Abstract only, awaiting full study report.

Salman 2012

Methods	Randomised controlled trial.
Participants	Women with unexplained recurrent pregnancy loss.
Interventions	Tinzaparin sodium 4500 IU combined with 500 micrograms folic acid vs folic acid only.
Outcomes	Primary outcome: continuation of a viable pregnancy up to 20 weeks' gestation.
Notes	Abstract only, awaiting full study report.

Schleussner 2013

Methods	Multicentre randomised controlled trial.
Participants	Women with at least 2 early or 1 late miscarriage.
Interventions	Dalteparin 5000 units combined with multi-vitamins vs vitamins only.
Outcomes	Primary outcome ongoing pregnancy at 24 weeks' gestation.
Notes	Abstracts only, awaiting full study report.

IU: international units
vs: versus
VTE: venous thromboembolism

DATA AND ANALYSES

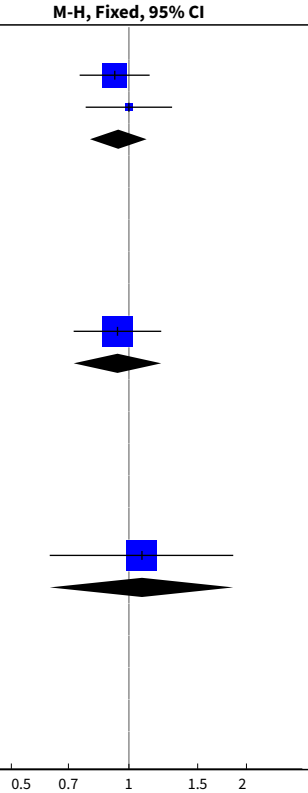
Comparison 1. Aspirin versus no treatment

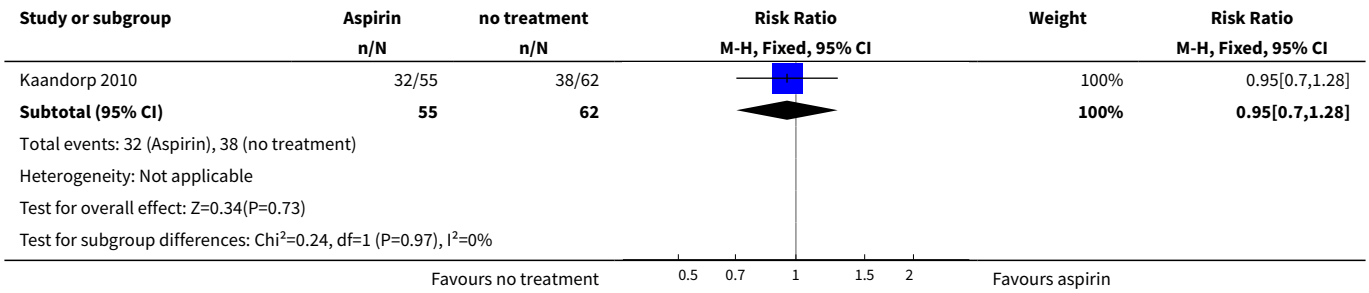
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Live birth in all women	2	256	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.11]
1.2 Live birth in women with no previous live birth	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
1.3 Live birth in women with inherited thrombophilia	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.63, 1.85]
1.4 Live birth in women with more than two previous miscarriages	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
2 Preterm delivery < 37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Preterm delivery 24-28 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Preterm delivery 28-32 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Preterm delivery 32-37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Obstetric complications; pre-eclampsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Obstetric complications; IUGR	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Congenital malformations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Side effects; any bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 HIT/thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

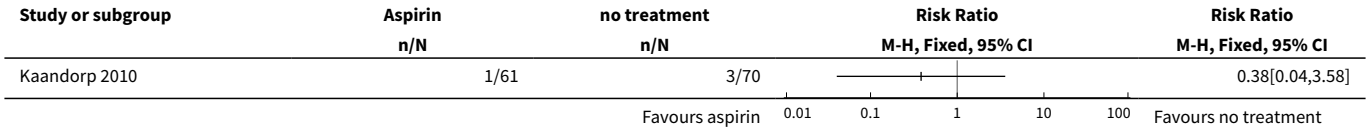
Analysis 1.1. Comparison 1 Aspirin versus no treatment, Outcome 1 Live birth.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Live birth in all women					
Kaandorp 2010	61/99	69/103		75.46%	0.92[0.75,1.13]
Tulppala 1997	22/27	22/27		24.54%	1[0.78,1.29]
Subtotal (95% CI)	**126**	**130**		**100%**	**0.94[0.8,1.11]**
Total events: 83 (Aspirin), 91 (no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.73(P=0.46)					
1.1.2 Live birth in women with no previous live birth					
Kaandorp 2010	38/60	42/62		100%	0.93[0.72,1.21]
Subtotal (95% CI)	**60**	**62**		**100%**	**0.93[0.72,1.21]**
Total events: 38 (Aspirin), 42 (no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.51(P=0.61)					
1.1.3 Live birth in women with inherited thrombophilia					
Kaandorp 2010	11/17	9/15		100%	1.08[0.63,1.85]
Subtotal (95% CI)	**17**	**15**		**100%**	**1.08[0.63,1.85]**
Total events: 11 (Aspirin), 9 (no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.78)					
1.1.4 Live birth in women with more than two previous miscarriages					

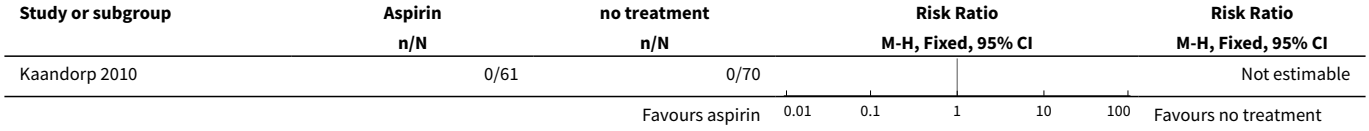




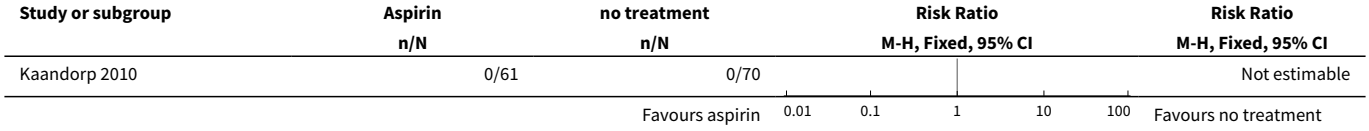
Analysis 1.2. Comparison 1 Aspirin versus no treatment, Outcome 2 Preterm delivery < 37 weeks.



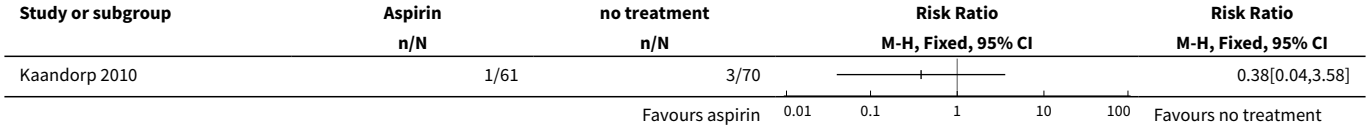
Analysis 1.3. Comparison 1 Aspirin versus no treatment, Outcome 3 Preterm delivery 24-28 weeks.



Analysis 1.4. Comparison 1 Aspirin versus no treatment, Outcome 4 Preterm delivery 28-32 weeks.

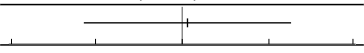


Analysis 1.5. Comparison 1 Aspirin versus no treatment, Outcome 5 Preterm delivery 32-37 weeks.



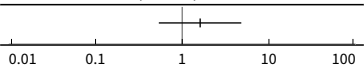
Analysis 1.6. Comparison 1 Aspirin versus no treatment, Outcome 6 Obstetric complications; pre-eclampsia.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	1/61	1/70		1.15[0.07,17.96]



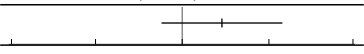
Analysis 1.7. Comparison 1 Aspirin versus no treatment, Outcome 7 Obstetric complications; IUGR.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	7/61	5/70		1.61[0.54,4.8]



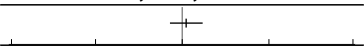
Analysis 1.8. Comparison 1 Aspirin versus no treatment, Outcome 8 Congenital malformations.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	5/61	2/70		2.87[0.58,14.26]



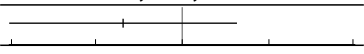
Analysis 1.9. Comparison 1 Aspirin versus no treatment, Outcome 9 Side effects; any bleeding.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	30/99	28/103		1.11[0.72,1.72]



Analysis 1.10. Comparison 1 Aspirin versus no treatment, Outcome 10 HIT/thrombocytopenia.

Study or subgroup	Aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	0/99	2/103		0.21[0.01,4.28]



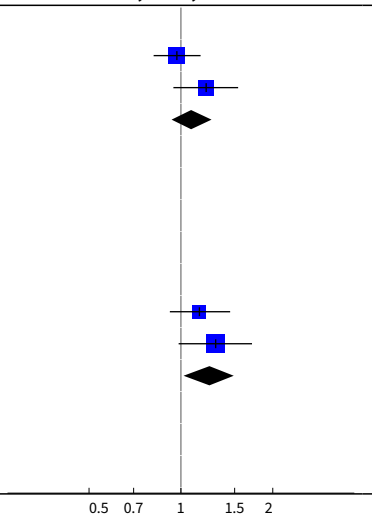
Comparison 2. LMWH versus aspirin

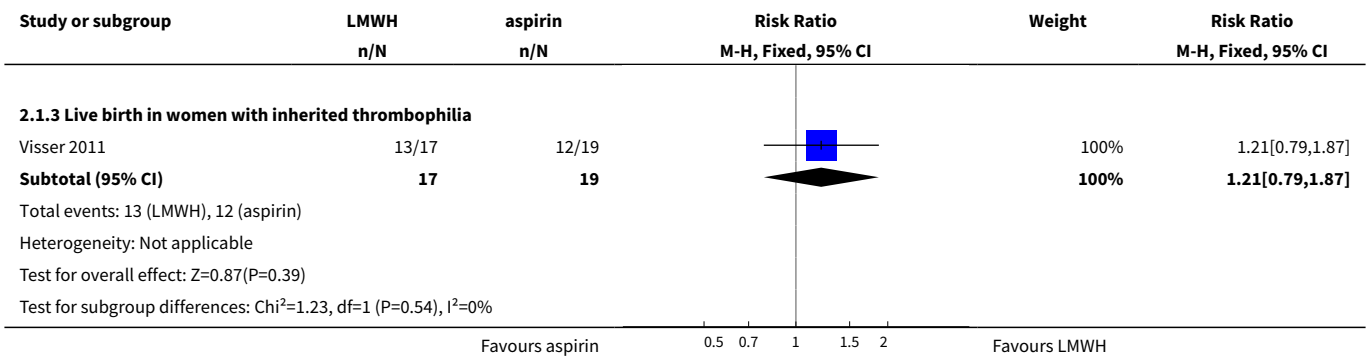
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth in all women	2	239	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
1.2 Live birth in women with no previous live birth	2	112	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.02, 1.49]
1.3 Live birth in women with inherited thrombophilia	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.79, 1.87]
2 Preterm delivery < 37 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Preterm delivery 24-28 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Preterm delivery 28-32 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Preterm delivery 32-37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Obstetric complications; pre-eclampsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Obstetric complications; IUGR	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Obstetric complications; congenital malformations	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Side effects; any bleeding	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

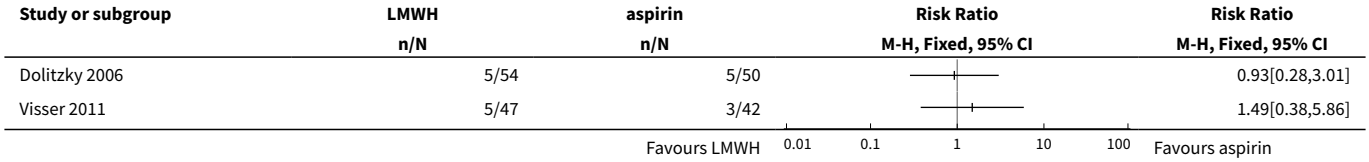
Analysis 2.1. Comparison 2 LMWH versus aspirin, Outcome 1 Live birth.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Live birth in all women					
Dolitzky 2006	44/54	42/50		51.89%	0.97[0.81,1.16]
Visser 2011	47/65	42/70		48.11%	1.21[0.94,1.54]
Subtotal (95% CI)	**119**	**120**		**100%**	**1.08[0.93,1.26]**
Total events: 91 (LMWH), 84 (aspirin)					
Heterogeneity: Tau^2=0; Chi^2=2.26, df=1(P=0.13); I^2=55.68%					
Test for overall effect: Z=1.04(P=0.3)					
2.1.2 Live birth in women with no previous live birth					
Dolitzky 2006	17/18	18/22		41.86%	1.15[0.92,1.45]
Visser 2011	25/30	27/42		58.14%	1.3[0.98,1.71]
Subtotal (95% CI)	**48**	**64**		**100%**	**1.24[1.02,1.49]**
Total events: 42 (LMWH), 45 (aspirin)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=2.21(P=0.03)					

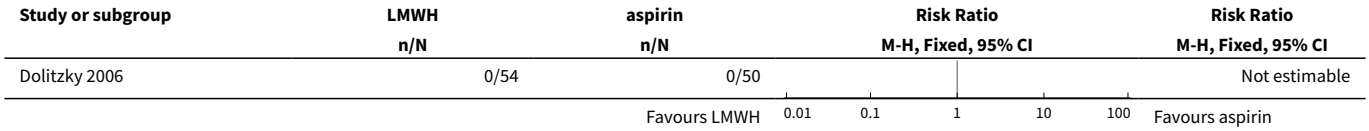




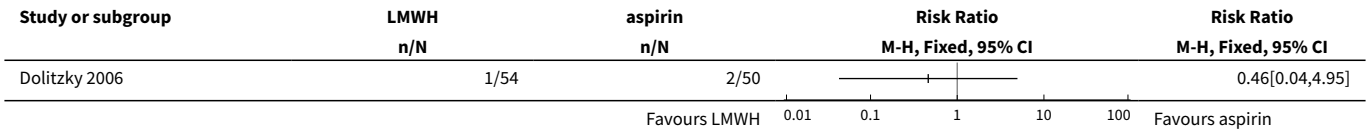
Analysis 2.2. Comparison 2 LMWH versus aspirin, Outcome 2 Preterm delivery < 37 weeks.



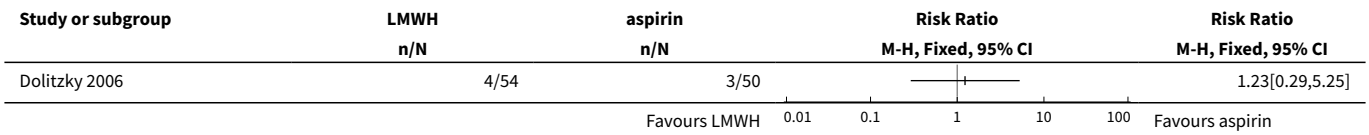
Analysis 2.3. Comparison 2 LMWH versus aspirin, Outcome 3 Preterm delivery 24-28 weeks.



Analysis 2.4. Comparison 2 LMWH versus aspirin, Outcome 4 Preterm delivery 28-32 weeks.

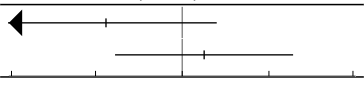


Analysis 2.5. Comparison 2 LMWH versus aspirin, Outcome 5 Preterm delivery 32-37 weeks.



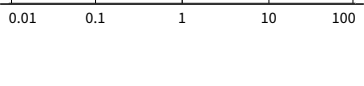
Analysis 2.6. Comparison 2 LMWH versus aspirin, Outcome 6 Obstetric complications; pre-eclampsia.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Dolitzky 2006	0/54	3/50		0.13[0.01,2.5]
Visser 2011	2/47	1/42		1.79[0.17,19.01]



Analysis 2.7. Comparison 2 LMWH versus aspirin, Outcome 7 Obstetric complications; IUGR.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Dolitzky 2006	1/54	0/50		2.78[0.12,66.75]
Visser 2011	4/47	1/42		3.57[0.42,30.73]



Analysis 2.8. Comparison 2 LMWH versus aspirin, Outcome 8 Obstetric complications; congenital malformations.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Dolitzky 2006	0/54	2/50		0.19[0.01,3.77]
Visser 2011	2/47	0/42		4.48[0.22,90.72]

Analysis 2.9. Comparison 2 LMWH versus aspirin, Outcome 9 Side effects; any bleeding.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Dolitzky 2006	0/54	2/50		0.19[0.01,3.77]
Visser 2011	23/47	21/42		0.98[0.64,1.49]

Comparison 3. LMWH versus aspirin including studies at high risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	325	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.93, 1.45]

Analysis 3.1. Comparison 3 LMWH versus aspirin including studies at high risk of bias, Outcome 1 Live birth.

Study or subgroup	LMWH n/N	aspirin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dolitzky 2006	44/54	42/50		38.15%	0.97[0.81,1.16]
Giancotti 2012	35/40	29/46		30.59%	1.39[1.08,1.78]
Visser 2011	47/65	42/70		31.26%	1.21[0.94,1.54]
Total (95% CI)	**159**	**166**		**100%**	**1.16[0.93,1.45]**
Total events: 126 (LMWH), 113 (aspirin)					
Heterogeneity: Tau^2=0.03; Chi^2=6.02, df=2(P=0.05); I^2=66.75%					
Test for overall effect: Z=1.3(P=0.19)					

Comparison 4. LMWH versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.56, 1.79]

Analysis 4.1. Comparison 4 LMWH versus no treatment, Outcome 1 Live birth.

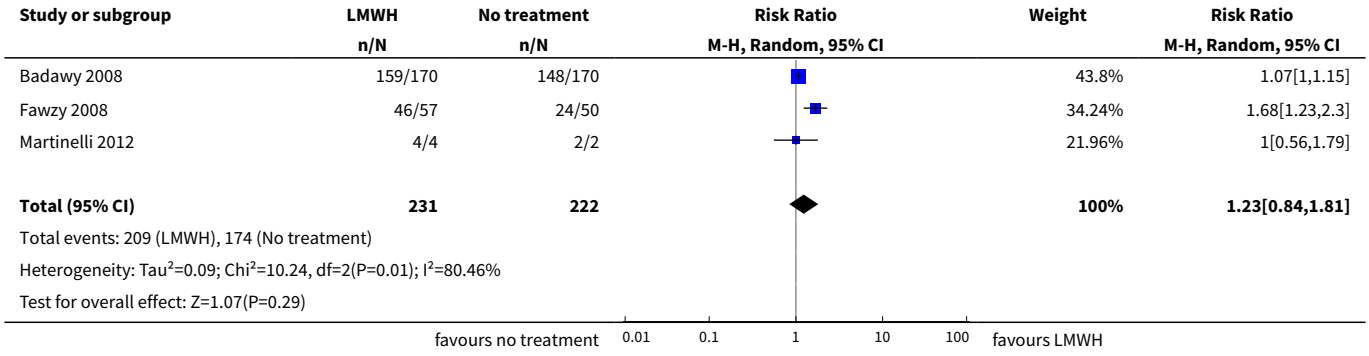
Study or subgroup	LMWH n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Martinelli 2012	4/4	2/2		100%	1[0.56,1.79]
Total (95% CI)	**4**	**2**		**100%**	**1[0.56,1.79]**
Total events: 4 (LMWH), 2 (no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Comparison 5. LMWH versus no treatment including studies at high risk of bias

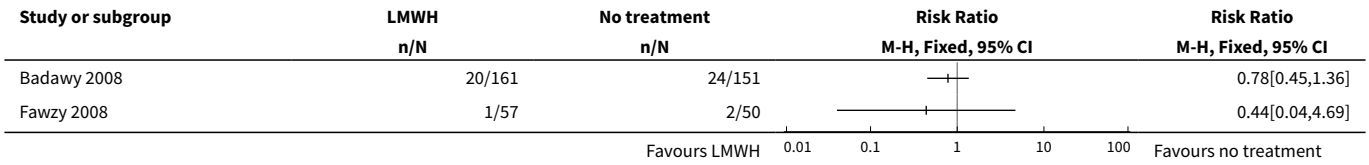
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	453	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.81]
2 Preterm delivery < 37 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Obstetric complications; pre-eclampsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Obstetric complications; IUGR	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Obstetric complications; congenital malformations	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Side effects; any bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Thromboembolic complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

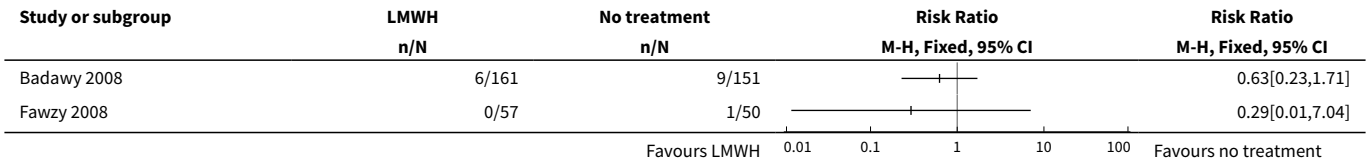
Analysis 5.1. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 1 Live birth.



Analysis 5.2. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 2 Preterm delivery < 37 weeks.



Analysis 5.3. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 3 Obstetric complications; pre-eclampsia.



Analysis 5.4. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 4 Obstetric complications; IUGR.

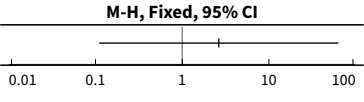
Study or subgroup	LMWH n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Badawy 2008	30/161	28/151		1[0.63,1.6]
Fawzy 2008	1/57	2/50		0.44[0.04,4.69]

Analysis 5.5. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 5 Obstetric complications; congenital malformations.

Study or subgroup	LMWH n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Badawy 2008	2/161	0/151		4.69[0.23,96.93]
Fawzy 2008	1/57	0/50		2.64[0.11,63.33]

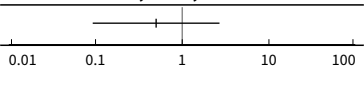
Analysis 5.6. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 6 Side effects; any bleeding.

Study or subgroup	LMWH n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fawzy 2008	1/57	0/50		2.64[0.11,63.33]



Analysis 5.7. Comparison 5 LMWH versus no treatment including studies at high risk of bias, Outcome 7 Thromboembolic complications.

Study or subgroup	LMWH n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Badawy 2008	2/170	4/170		0.5[0.09,2.69]

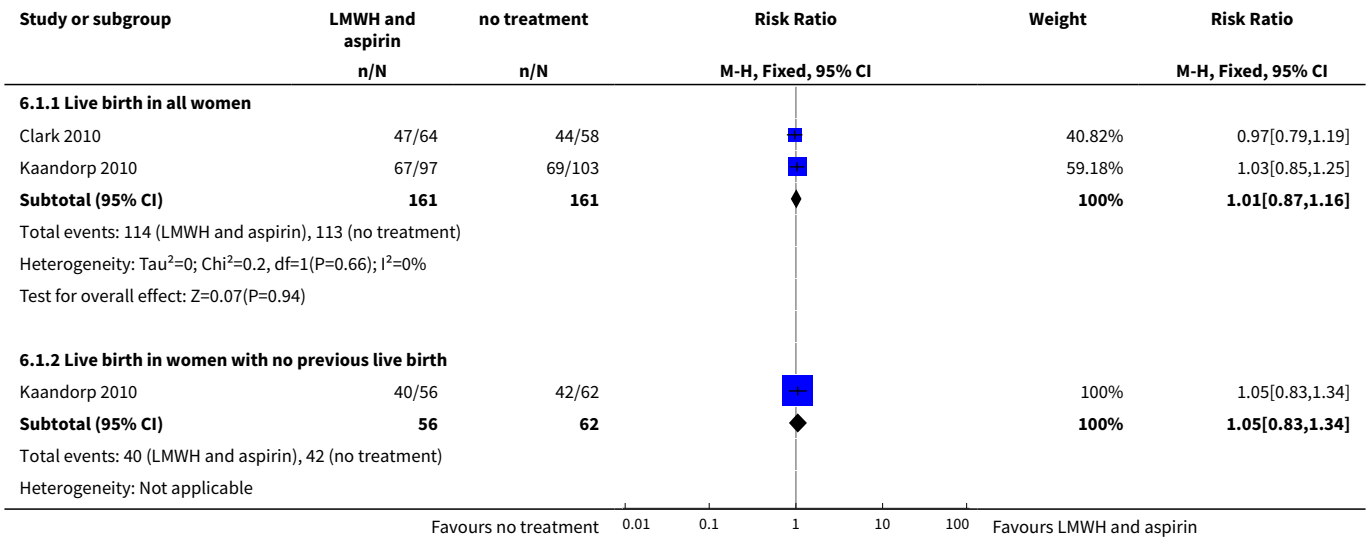


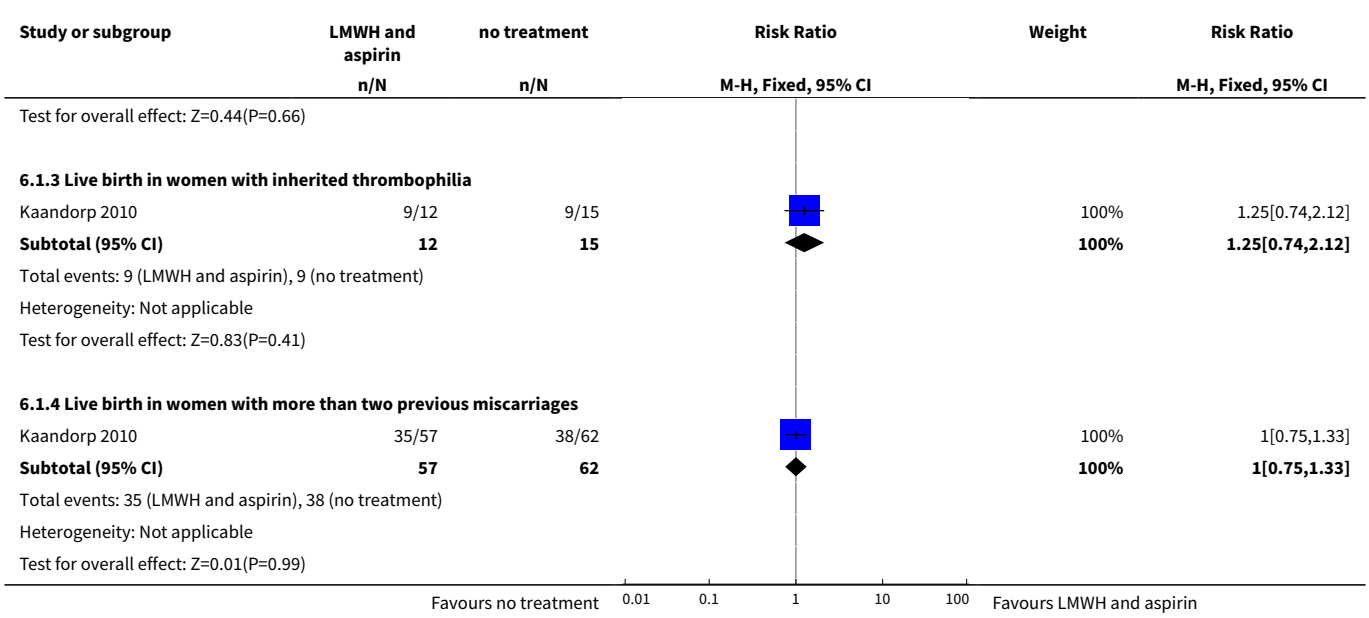
Comparison 6. LMWH and aspirin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Live birth in all women	2	322	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.16]
1.2 Live birth in women with no previous live birth	1	118	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.83, 1.34]

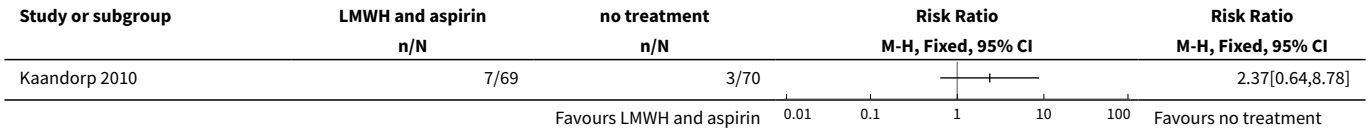
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Live birth in women with inherited thrombophilia	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.74, 2.12]
1.4 Live birth in women with more than two previous miscarriages	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
2 Preterm delivery < 37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Preterm delivery 24-28 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Preterm delivery 28-32 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Preterm delivery 32-37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Obstetric complications; pre-eclampsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Obstetric complications; IUGR	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Congenital Malformations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Side effects; any bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Side effects; pain/itching/swelling at injection site	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6 LMWH and aspirin versus no treatment, Outcome 1 Live birth.

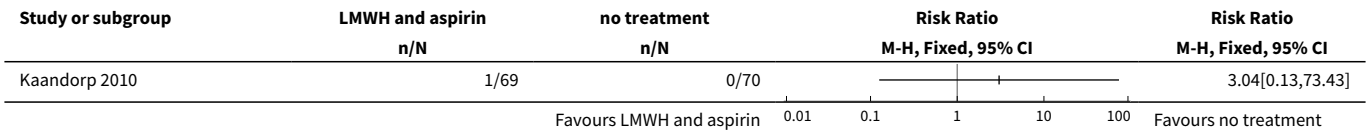




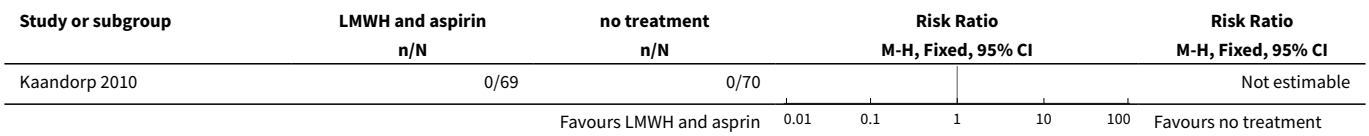
Analysis 6.2. Comparison 6 LMWH and aspirin versus no treatment, Outcome 2 Preterm delivery < 37 weeks.



Analysis 6.3. Comparison 6 LMWH and aspirin versus no treatment, Outcome 3 Preterm delivery 24-28 weeks.

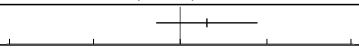


Analysis 6.4. Comparison 6 LMWH and aspirin versus no treatment, Outcome 4 Preterm delivery 28-32 weeks.



Analysis 6.5. Comparison 6 LMWH and aspirin versus no treatment, Outcome 5 Preterm delivery 32-37 weeks.

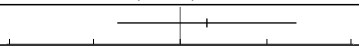
Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	6/69	3/70		2.03[0.53,7.79]



Favours LMWH and aspirin — Favours no treatment

Analysis 6.6. Comparison 6 LMWH and aspirin versus no treatment, Outcome 6 Obstetric complications; pre-eclampsia.

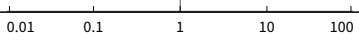
Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	2/69	1/70		2.03[0.19,21.86]



Favours LMWH and aspirin — Favours no treatment

Analysis 6.7. Comparison 6 LMWH and aspirin versus no treatment, Outcome 7 Obstetric complications; IUGR.

Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	6/69	5/70		1.22[0.39,3.8]



Favours LMWH and aspirin — Favours no treatment

Analysis 6.8. Comparison 6 LMWH and aspirin versus no treatment, Outcome 8 Congenital Malformations.

Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	3/69	2/70		1.52[0.26,8.83]

Favours LMWH and aspirin — Favours no treatment

Analysis 6.9. Comparison 6 LMWH and aspirin versus no treatment, Outcome 9 Side effects; any bleeding.

Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	60/97	28/103		2.28[1.6,3.24]

Favours LMWH and aspirin — Favours no treatment

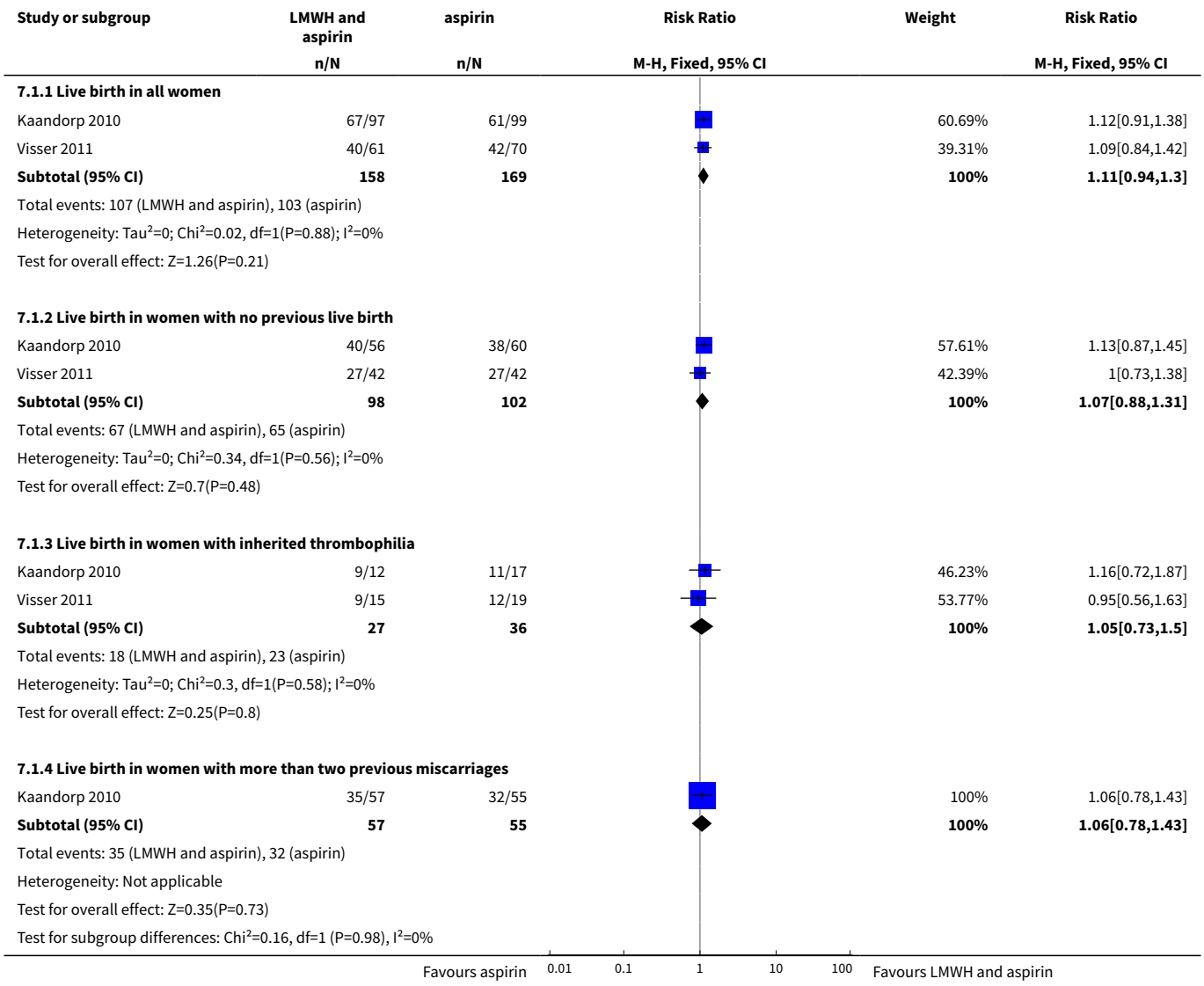
Analysis 6.10. Comparison 6 LMWH and aspirin versus no treatment, Outcome 10 Side effects; pain/itching/swelling at injection site.

Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	49/97	1/103		0%	52.03[7.33,369.51]

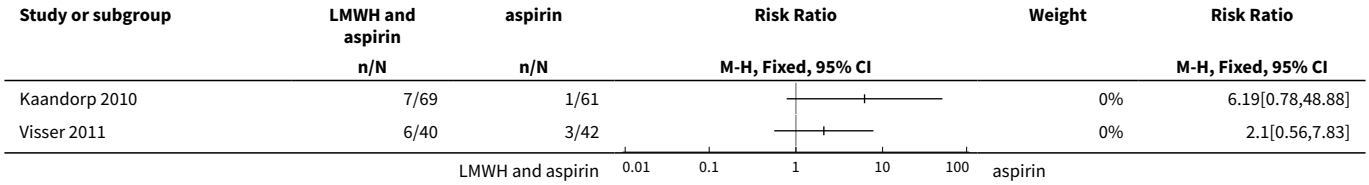
Comparison 7. LMWH and aspirin versus aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Live birth in all women	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.30]
1.2 Live birth in women with no previous live birth	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.31]
1.3 Live birth in women with inherited thrombophilia	2	63	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.73, 1.50]
1.4 Live birth in women with more than two previous miscarriages	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.78, 1.43]
2 Preterm delivery < 37 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Preterm delivery 24-28 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Preterm delivery; 28-32 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Preterm delivery; 32-37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Obstetric complications; pre-eclampsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Obstetric complications; IUGR	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Congenital malformations	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Side effects; any bleeding	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Side effects; pain/itching/swelling at injection site	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 HIT/thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 LMWH and aspirin versus aspirin, Outcome 1 Live birth.



Analysis 7.2. Comparison 7 LMWH and aspirin versus aspirin, Outcome 2 Preterm delivery < 37 weeks.



Analysis 7.3. Comparison 7 LMWH and aspirin versus aspirin, Outcome 3 Preterm delivery 24-28 weeks.

Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	1/69	0/61		2.66[0.11,64.04]

Favours LMWH and aspirin 0.01 0.1 1 10 100 Favours aspirin

Analysis 7.4. Comparison 7 LMWH and aspirin versus aspirin, Outcome 4 Preterm delivery; 28-32 weeks.

Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	0/69	0/61		Not estimable

Favours LMWH and aspirin 0.01 0.1 1 10 100 Favours aspirin

Analysis 7.5. Comparison 7 LMWH and aspirin versus aspirin, Outcome 5 Preterm delivery; 32-37 weeks.

Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	6/69	0/61		11.51[0.66,200.27]

Favours LMWH and aspirin 0.01 0.1 1 10 100 Favours aspirin

Analysis 7.6. Comparison 7 LMWH and aspirin versus aspirin, Outcome 6 Obstetric complications; pre-eclampsia.

Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	2/69	1/61		1.77[0.16,19.02]
Visser 2011	1/40	1/42		1.05[0.07,16.23]

Favours aspirin 0.01 0.1 1 10 100 Favours LMWH and aspirin

Analysis 7.7. Comparison 7 LMWH and aspirin versus aspirin, Outcome 7 Obstetric complications; IUGR.

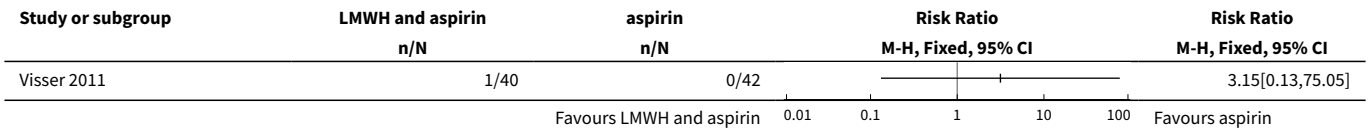
Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	6/69	7/61		0.76[0.27,2.13]
Visser 2011	4/40	1/42		4.2[0.49,35.99]

Favours aspirin 0.01 0.1 1 10 100 Favours LMWH and aspirin

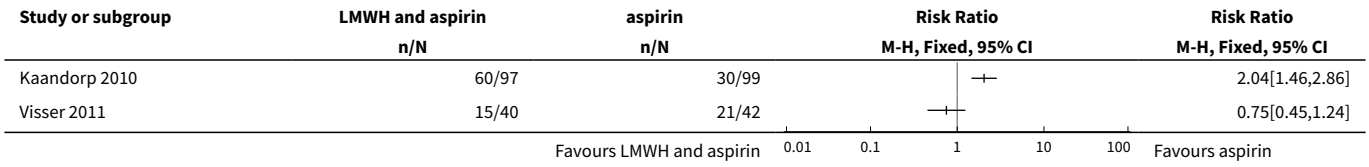
Analysis 7.8. Comparison 7 LMWH and aspirin versus aspirin, Outcome 8 Congenital malformations.

Study or subgroup	LMWH and aspirin n/N	aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kaandorp 2010	3/69	5/61		0.53[0.13,2.13]

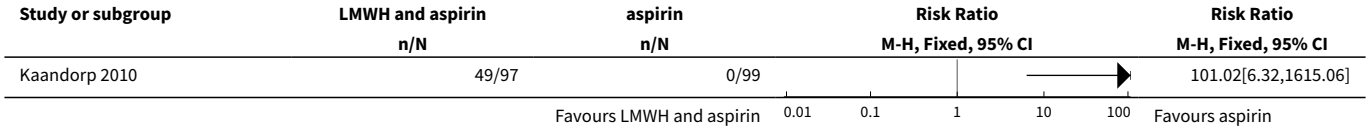
Favours LMWH and aspirin 0.01 0.1 1 10 100 Favours aspirin



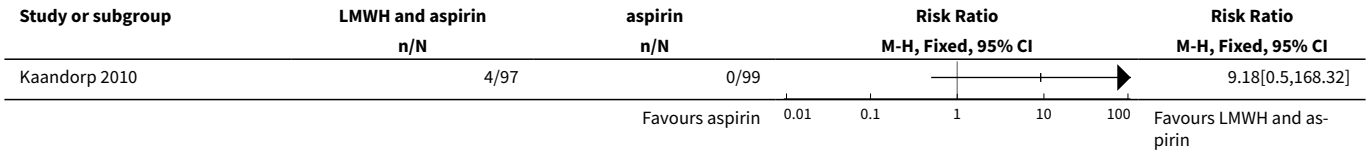
Analysis 7.9. Comparison 7 LMWH and aspirin versus aspirin, Outcome 9 Side effects; any bleeding.



Analysis 7.10. Comparison 7 LMWH and aspirin versus aspirin, Outcome 10 Side effects; pain/itching/swelling at injection site.



Analysis 7.11. Comparison 7 LMWH and aspirin versus aspirin, Outcome 11 HIT/thrombocytopenia.

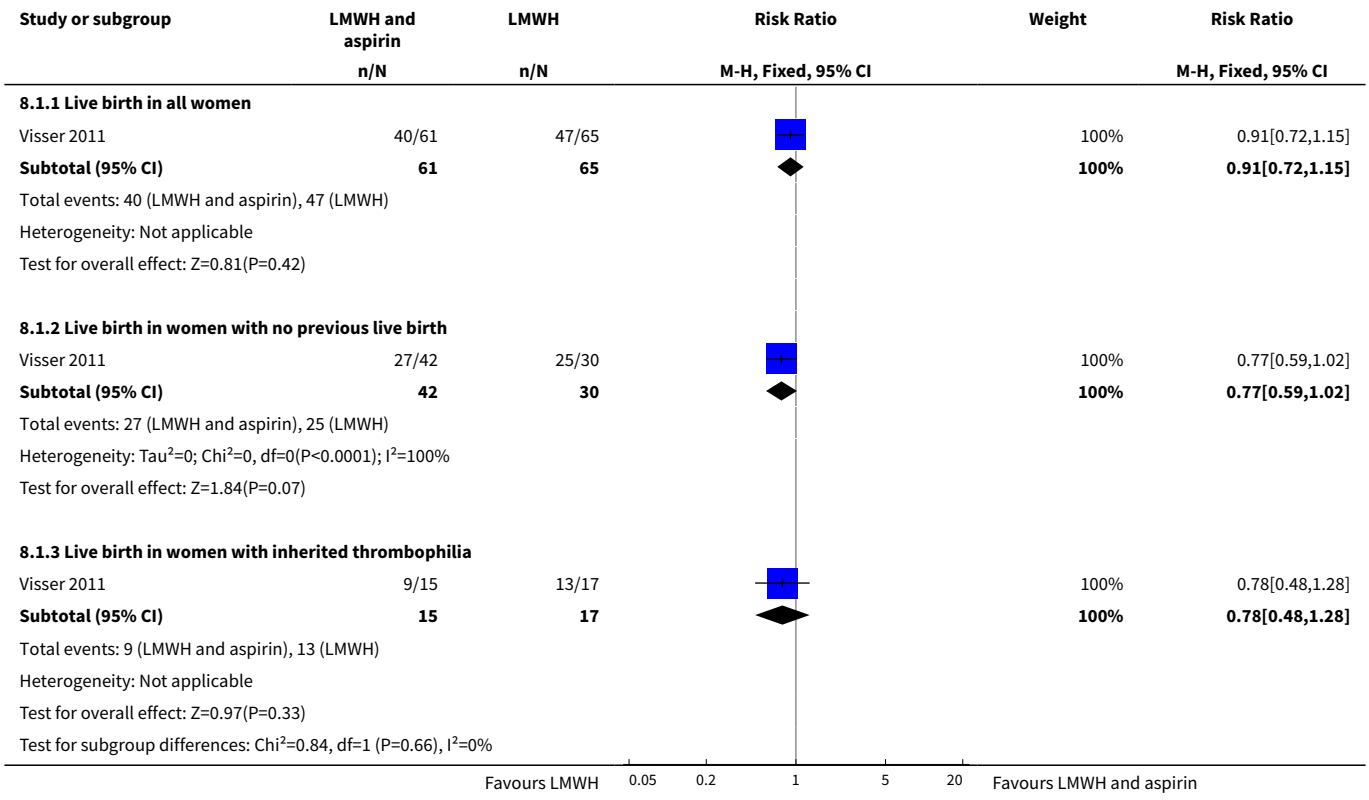


Comparison 8. LMWH and aspirin versus LMWH

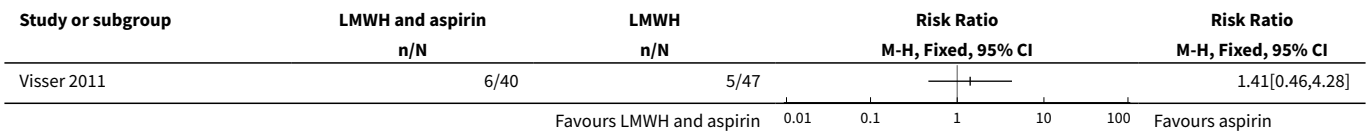
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Live birth in all women	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.15]
1.2 Live birth in women with no previous live birth	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.59, 1.02]
1.3 Live birth in women with inherited thrombophilia	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.48, 1.28]
2 Preterm delivery < 37 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Obstetric complications; pre-eclampsia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Obstetric complications; IUGR	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Congenital malformations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Side effects; any bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 LMWH and aspirin versus LMWH, Outcome 1 Live birth.

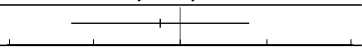


Analysis 8.2. Comparison 8 LMWH and aspirin versus LMWH, Outcome 2 Preterm delivery < 37 weeks.



Analysis 8.3. Comparison 8 LMWH and aspirin versus LMWH, Outcome 3 Obstetric complications; pre-eclampsia.

Study or subgroup	Favours LMWH and aspirin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Visser 2011	1/40	2/47		0.59[0.06,6.24]

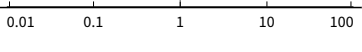


Analysis 8.4. Comparison 8 LMWH and aspirin versus LMWH, Outcome 4 Obstetric complications; IUGR.

Study or subgroup	LMWH and aspirin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Visser 2011	4/40	4/47		1.18[0.31,4.4]

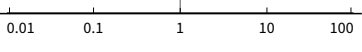
Analysis 8.5. Comparison 8 LMWH and aspirin versus LMWH, Outcome 5 Congenital malformations.

Study or subgroup	LMWH and aspirin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Visser 2011	1/40	2/47		0.59[0.06,6.24]



Analysis 8.6. Comparison 8 LMWH and aspirin versus LMWH, Outcome 6 Side effects; any bleeding.

Study or subgroup	LMWH and aspirin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Visser 2011	15/40	23/47		0.77[0.47,1.26]

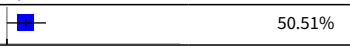


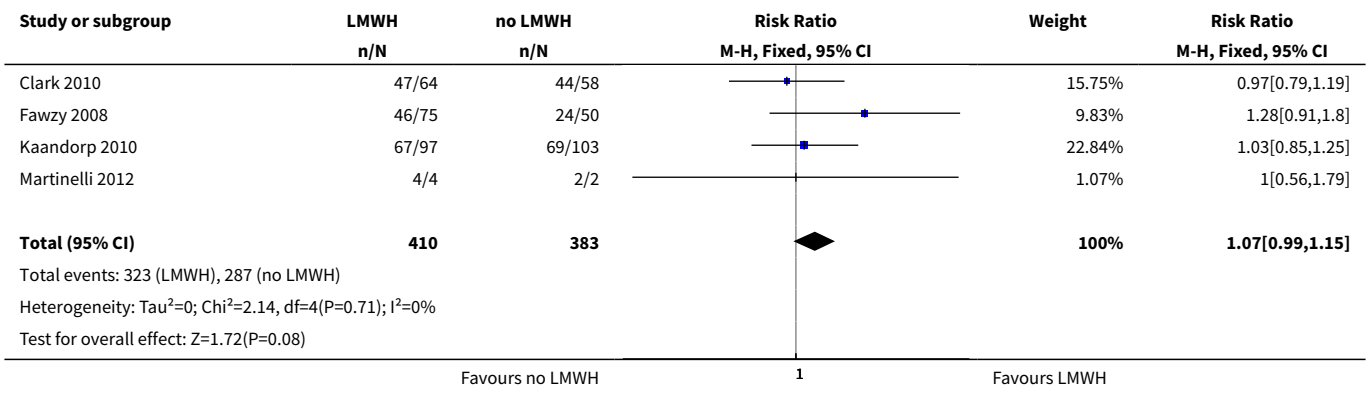
Comparison 9. LMWH with or without aspirin vs no treatment including studies at high risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	5	793	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.99, 1.15]

Analysis 9.1. Comparison 9 LMWH with or without aspirin vs no treatment including studies at high risk of bias, Outcome 1 Live birth.

Study or subgroup	LMWH n/N	no LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Badawy 2008	159/170	148/170		50.51%	1.07[1,1.15]

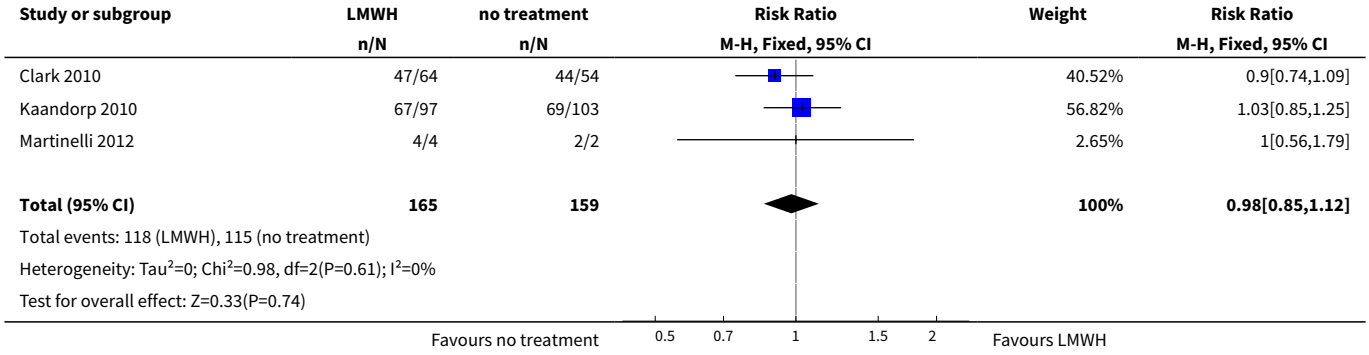




Comparison 10. LMWH with or without aspirin vs no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	324	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.12]

Analysis 10.1. Comparison 10 LMWH with or without aspirin vs no treatment, Outcome 1 Live birth.



APPENDICES

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.

Appendix 2. Methods used when assessing the trials identified in the previous version of this review

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.

F E E D B A C K

Cundiff, September 2007

Summary

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 x 0.50 x 0.50] = .875 and [1 - 0.20 x 0.20 x0.20] = .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
1. Granger CB, Miller JM, Bovill EG, et al. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. Circulation 1995; 91(7):1929-1935.
2. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Lancet 1996; 347(9001):561-568.
3. The Matisse Investigators. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. N Engl J Med 2003; 349(18):1695-1702.

(Summary of comment from David K Cundiff, September 2007)

Reply

We agree aspirin was ineffective compared with placebo in increasing live births, and so should not be used as the control treatment in randomised trials assessing anticoagulants for women with recurrent miscarriage. As we describe in 'Implications for research', the inclusion of a placebo or no treatment arm in these studies is necessary to provide an adequate control for active treatment.

We also agree that trials in this field are generally too small to assess the risk of rare but potentially serious adverse effects. Observational and population-based studies are useful to assess these hazards; however this review is limited to randomised trials.

Following recurrent miscarriage, the calculation that the chance of having a healthy live baby within three pregnancies ranges from 87.5% to 99.2% is probably slightly optimistic. It does not take account of the fact that the chance of a successful pregnancy declines after each miscarriage, thus the chance of live birth will also decline.

The proposal that a live healthy baby in up to three pregnancies, rather than in one, would be a better endpoint is interesting. However, the primary outcome of a live birth in a single pregnancy in a well-designed randomised placebo controlled trial will allow better assessment of possible hazards of the intervention. Also, we doubt whether couples with recurrent miscarriage would regard a healthy baby after three pregnancies as the ideal outcome.

Finally, although Dr. Middeldorp has been involved in trials of anticoagulants for venous thrombosis that were sponsored by pharmaceutical companies, this does not necessarily lead to a conflict of interest. She has published papers in which she has opposed the use of anticoagulants for the prevention of pregnancy loss or pregnancy complications. She is also principle investigator of the ALIFE study that is assessing the efficacy and safety of aspirin, and aspirin combined with low-molecular-weight heparin, compared with placebo (International Standard Randomised Controlled Trial Number Register: 58496168).

(Reply from Stef Kaandorp, November 2007)

Contributors

Feedback: David K Cundiff

WHAT'S NEW

Date	Event	Description
1 October 2013	New citation required but conclusions have not changed	Search updated. Seven studies added to the review (Badawy 2008; Clark 2010; Fawzy 2008; Giancotti 2012; Kaandorp 2010; Martinelli 2012; Visser 2011).
25 June 2013	New search has been performed	Change to team of authors. Title changed since last version as detailed below: **Previous version title**: Aspirin or anticoagulants for the treatment of recurrent miscarriage in women without antiphospholipid syndrome. **Current title**: Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia.

HISTORY

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

Date	Event	Description
13 November 2008	Feedback has been incorporated	Feedback from David K Cundiff added.
30 April 2008	New citation required but conclusions have not changed	Changes to scope of review and team of authors.
30 April 2008	New search has been performed	Search updated. Scope of review changed, resulting in a previously included study being excluded (Gris 2004). Please see 'Differences between protocol and review' for further details. Authors replied to feedback.

Date	Event	Description
11 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr de Jong wrote the current revised review. Dr Kaandorp commented on the revision.
Dr Di Nisio wrote the first and the revised drafts of the protocol and review, and commented on the draft of the updated review. Dr Kaandorp updated the search and wrote the first revised review. Dr Goddijn and Dr Middeldorp commented on and supervised the development of the first review and both revisions.

DECLARATIONS OF INTEREST

Dr Kaandorp, Dr Goddijn, and Dr Middeldorp were investigators of the randomised controlled trial ALIFE study (Kaandorp 2010). Dr Middeldorp has also been and is involved in phase 2 and phase 3 trials that assess 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 the first 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 aetiology and different prognosis, we judged it not appropriate to pool results of interventions in these different patient populations. This decision resulted in the exclusion of a study (Gris 2004) in which a subgroup had been included in the first version of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Habitual [blood] [etiology] [*prevention & control]; Anticoagulants [*therapeutic use]; Antiphospholipid Syndrome [complications]; Aspirin [therapeutic use]; Enoxaparin [therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Live Birth; Nadroparin [therapeutic use]; Pregnancy Complications, Hematologic [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Thrombophilia [complications] [*drug therapy]

MeSH check words

Female; Humans; Pregnancy