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Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction (Review)

Dodd JM, McLeod A, Windrim RC, Kingdom J

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[Intervention Review]

Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction

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ABSTRACT

Background

Pregnancy complications such as pre-eclampsia and eclampsia, intrauterine growth restriction and placental abruption are thought to have a common origin related to abnormalities in the development and function of the placenta.

Objectives

To compare, using the best available evidence, the benefits and harms of antenatal antithrombotic therapy to improve maternal or infant health outcomes in women considered at risk of placental dysfunction, when compared with other treatments, placebo or no treatment.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (17 July 2012).

Selection criteria

Randomised controlled trials comparing antenatal antithrombotic therapy (either alone or in combination with other agents) with placebo or no treatment, or any other treatment in the antenatal period to improve maternal or infant health outcomes in women considered at risk of placental dysfunction.

Data collection and analysis

Two review authors evaluated trials under consideration for appropriateness for inclusion and methodological quality without consideration of their results according to the prestated eligibility criteria. We used a fixed-effect meta-analysis for combining study data if the trials were judged to be sufficiently similar. We investigated heterogeneity by calculating I^2 statistic, and if this indicated a high level of heterogeneity among the trials included, we used a random-effects model.

Main results

Our search strategy identified 18 reports of 14 studies for consideration. The original review included five studies (484 women) which met the inclusion criteria, with a further five studies included in the updated review, involving an additional 655 women. The overall quality of the included trials was considered fair to good.

Nine studies compared heparin (alone or in combination with dipyridamole or low-dose aspirin) with no treatment; and one compared trapidil (triazolopyrimidine).

While this review identified the use of heparin to be associated with a statistically significant reduction in risk of perinatal mortality (six studies; 653 women; risk ratio (RR) 0.40; 95% confidence intervals (CI) 0.20 to 0.78), preterm birth before 34 (three studies; 494 women; RR 0.46; 95% CI 0.29 to 0.73) and 37 (five studies; 621 women; RR 0.72; 95% CI 0.58 to 0.90) weeks' gestation, and infant birthweight below the 10th centile for gestational age (seven studies; 710 infants; RR 0.41; 95% CI 0.27 to 0.61), there is a lack of reliable information available related to clinically relevant, serious adverse infant health outcomes, which have not been reported to date.

Authors' conclusions

While treatment with heparin for women considered to be at particularly high risk of adverse pregnancy complications secondary to placental insufficiency was associated with a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birthweight below the 10th centile for gestational age when compared with no treatment for women considered at increased risk of placental dysfunction, to date, important information about serious adverse infant and long-term childhood outcomes is unavailable.

PLAIN LANGUAGE SUMMARY

Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction

Pregnancy complications such as pre-eclampsia and eclampsia, intrauterine fetal growth restriction and placental abruption are thought to be related to abnormalities in the development and function of the placenta. Treatment with heparin to prevent the development of blood clots within the placenta appears to be a promising intervention to prevent these complications. The numbers of pregnant women with pre-eclampsia, preterm birth, perinatal death and a low birthweight infant (weighing less than the 10th centile for gestational age) were reduced with this treatment. Ten randomised trials involving 1139 women met the inclusion criteria for the review. Nine studies compared heparin (alone or in combination with dipyridamole) with no treatment; and one compared triazolopyrimidine with placebo. The most commonly recognised side effect for women related to this treatment was mild skin bruising. To date, important information about serious adverse infant and long-term childhood outcomes with using anti-clotting medications is unavailable. Further research is required.

BACKGROUND

Description of the condition

Pregnancy complications such as pre-eclampsia and eclampsia, restricted growth of the baby in the uterus (intrauterine fetal growth restriction (IUGR)) and placental abruption are thought to be related to problems with the development and function of the placenta. Pre-eclampsia and its complications remain a common cause of maternal and infant morbidity and mortality throughout the world (Sibai 2005). Infants born to women with pre-eclampsia have an increased risk of IUGR, preterm birth and perinatal mortality (Laws 2004). Infants who are small-for-gestational age (SGA) at birth are recognised to be at increased risk of adverse health outcomes (Bernstein 2000; McIntire 1999), including mortality (Cnattingius 1998; Kok 1998), birth hypoxia (Cnattingius 1998), and developmental problems during infancy and childhood (Kok 1998; Roth 1999). The risk of infant mortality is further increased in both term and preterm infants in the presence of growth restriction (Tan 2005). Fetal growth restriction is estimated to complicate 5% to 10% of perinatal deaths, with over 75% of stillborn infants being of low birthweight (Laws 2004). For women and their families, the loss of a pregnancy through intrauterine fetal death is an emotionally devastating event.

Central to the development and continuation of a normal healthy pregnancy is the optimal development of the placenta. The placenta is required to form an effective exchange system for the transfer of oxygen, nutrients and waste products between the mother and the fetus (Khong 2004; Robson 2002). Crucial to this development is the transformation of the usually high resistance spiral arteries into large calibre, low resistance uteroplacental vessels by a process of extra-villous trophoblast infiltration (Burton 2009; Khong 2004; Robson 2002). When this process does not occur, the placenta that develops is small (Egbor 2006; Khong 2004; Sander 2005; Toal 2008), and there is a poor maternal cardiovascular response to pregnancy, resulting in haemoconcentration, a lack of second trimester blood pressure reduction (Dekker 2005a; Sibai 2005). These changes in the placenta precede the development of severe early-onset pre-eclampsia (Dekker 2001; Dekker 2005a; Dekker 2005b; Sibai 2005). Pathological examination of the placenta after birth, which has occurred secondary to pre-eclampsia or IUGR occurring in early pregnancy, may identify the presence of ischaemic thrombotic lesions, including infarction (or damage to the placental tissue due to clots forming in the placental blood vessels on the maternal side) (Ferrazzi 1999; Franco 2011; Viero 2004; Walker 2012).

Description of the intervention

An intervention that may be able to prevent the development of vascular pathology (specifically to prevent the development of blood clots within the placenta and the subsequent death or infarction of placental tissue) may be effective in reducing the risk or preventing the development of clinical complications such as fetal death, pre-eclampsia or IUGR. Therapies that may be effective include the use of antithrombotic medications, which act by preventing the formation of blood clots, in addition to some immune mediating functions. These medications include unfractionated heparin (UFH), and low molecular weight heparin (LMWH), and are administered by injection below the skin of the abdomen (called subcutaneous injection).

How the intervention might work

There have been a number of reports in the literature related to the use of antithrombotic medications in women with a history of placental infarction in a previous pregnancy, as a means of preventing placental dysfunction in a subsequent pregnancy, and improving infant outcomes (Alkazaleh 2004; Bonnar 1975; Buyse 1974; Chupin 1978; Fuke 1994 Moe 1982). These studies are in the form of case series and cohort studies, which have inherent bias, involve a small number of pregnant women only, and variably report important clinical outcomes. Furthermore, two reports (Bonnar 1975; Buyse 1974) involved the use of warfarin from the second trimester of pregnancy before converting to heparin therapy from 36 weeks' gestation. Warfarin is an oral anticoagulant medication that is currently not recommended for use in pregnancy as it is associated with the development of fetal anomalies when used in the first trimester of pregnancy. The results of these case series and cohort studies should be interpreted with caution.

The use of antithrombotic medications, while potentially beneficial in reducing the occurrence of adverse pregnancy outcome, are not without potential harm. The most commonly recognised minor side effects for the woman related to antithrombotic therapy include local skin reactions and skin bruising (Greer 2006). More serious complications for the woman are uncommon with the relatively short-term use of medication as seen during pregnancy (Greer 2006). Other potential complications include bone loss (called osteopaenia), and subsequent osteoporotic bone fractures. These complications occur in less than 1% of patients exposed to long-term heparin therapy (rather than the short duration associated with use during pregnancy), and predominantly occur with the use of UFH (rather than LMWH) (Greer 2006). Heparin-induced thrombocytopenia (or a fall in platelet count; platelets are components of the blood which assist in clotting) is estimated to occur in less than 1% of women exposed to long-term heparin therapy, is reversible with cessation of medication, and again, is more common when UFH is used (Greer 2006). Placental bleeding or abruption has been reported to occur in 0.04% of women using long-term heparin therapy during pregnancy (Greer 2006). Furthermore, the use of heparin may be associated with an increased risk of bleeding at the time of epidural or spinal anaesthesia, as well as increasing risks of post-operative bleeding (Greer 2006). Antithrombotic medications, such as UFH and LMWH, do not cross the placenta, and are therefore, safe for the fetus when used during pregnancy (Greer 2006).

Why it is important to do this review

While there may be benefits in the use of antenatal antithrombotic therapy for women considered to be at risk of complications related to placental dysfunction, in terms of improved maternal and infant health outcomes, there may also be harms related to the potential side effects of medication. The aim of this review is to use the best available evidence to assess the benefits and harms of antenatal antithrombotic therapy for women where the intention is to improve maternal or infant health outcomes associated with placental dysfunction when compared with other treatments, placebo or no treatment.

This review will not consider the use of heparin in pregnant women with acquired or inherited thrombophilias (predisposition to thrombosis) (Walker 2003), its use in recurrent miscarriage or recurrent pregnancy loss in women with (Empson 2005) or without

(Kaandorp 2009) antiphospholipid syndrome, or as prophylaxis for venous thromboembolic disease in pregnancy and the postpartum period (Gates 2002) as the use of antithrombotic agents for these indications are covered in other Cochrane reviews.

OBJECTIVES

To compare, using the best available evidence, the benefits and harms of antenatal antithrombotic therapy to improve maternal or infant health outcomes in women considered at risk of placental dysfunction, when compared with other treatments, placebo, or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion all published, unpublished, and ongoing randomised controlled trials (RCTs) comparing antenatal antithrombotic therapy (either alone or in combination with other agents) with placebo or no treatment, or any other treatment in the antenatal period to improve maternal or infant health outcomes in women considered at risk of placental dysfunction.

We excluded trials assessing the role of heparin in pregnant women with acquired or inherited thrombophilias, its use in recurrent miscarriage or recurrent pregnancy loss in women with or without antiphospholipid syndrome, or as prophylaxis for venous thromboembolic disease in pregnancy and the postpartum period. We excluded quasi-randomised trials (e.g. those randomised by date of birth or hospital number). We also excluded studies where low-dose aspirin was used alone. We included studies reported only in abstract form in the Studies awaiting classification category; if relevant we will include these in the analyses when published as full reports.

Types of participants

Women undergoing antenatal treatment with antithrombotic therapy where the intention is to improve maternal or infant health outcomes in women considered at particularly high risk of complications related to placental dysfunction.

Types of interventions

Antenatal antithrombotic therapy (alone or in combination with other agents) versus placebo or no treatment, or any other treatment in the antenatal period to improve maternal or infant health outcomes in women considered at risk of placental dysfunction. We considered for inclusion studies reporting comparisons between different antithrombotic agents or different doses of antithrombotic agents.

Types of outcome measures

Primary outcomes

- Perinatal mortality
- Preterm birth (less than 34 weeks' gestation)
- Major neurodevelopmental handicap at childhood follow-up

Secondary outcomes

Maternal

- Pre-eclampsia or eclampsia
- Placental abruption
- Antepartum haemorrhage (beyond 20 weeks and requiring hospital admission)
- Length of antenatal stay
- Use of antenatal corticosteroids for fetal lung maturation
- Antibiotic use after birth
- Postpartum haemorrhage (defined as blood loss greater than 500 mL at vaginal birth or greater than 1000 mL at caesarean birth)
- Need for blood transfusion
- Anaesthetic complications (as defined by trial authors)
- Adverse drug reaction (including bruising, local skin reaction, minor haemorrhage, heparin-induced thrombocytopaenia, osteopaenia, bone fractures)
- Maternal death

Infant

- Birth before 37, 32, and 28 completed weeks
- Birthweight less than the 10th centile for gestational age
- Birthweight less than 2500 g
- Apgar score of less than seven at five minutes
- Respiratory distress syndrome
- Use of mechanical ventilation
- Duration of mechanical ventilation
- Intraventricular haemorrhage - Grades III or IV
- Periventricular leucomalacia
- Retinopathy of prematurity
- Retinopathy of prematurity - Grades III or IV
- Chronic lung disease
- Necrotising enterocolitis
- Neonatal sepsis
- Fetal death
- Neonatal death
- Admission to neonatal intensive care unit
- Neonatal length of hospital stay

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 (17 July 2012).

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.

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 1.

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 person.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

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

Assessment of risk of bias in included studies

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias 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 is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We assessed methods as:

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

- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest 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 are at high risk of bias, according to the criteria given in the *Cochrane 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 planned to explore 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

For continuous data, we used the mean difference for outcomes measured in the same way between trials. In future updates, if appropriate, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were included in this 2013 updated. In future updates, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* Section 16.3.4 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 are not an appropriate study design in this setting and will not be included.

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. This has not been performed for this update.

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 analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

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

Assessment of reporting biases

In future updates, 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

We carried out statistical analysis using the Review Manager software (RevMan 2011). 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 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 T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We did not carry out any subgroup analysis in this 2013 update.

In future updates, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Antithrombotic agent administered (UFH versus LMWH versus other).
2. Gestational age treatment commenced (first trimester versus second trimester versus third trimester).

The primary outcomes will be used in subgroup analysis (perinatal mortality; preterm birth less than 34 weeks' gestation; and major neurodevelopmental delay at childhood follow-up).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2011). We will report the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

Sensitivity analyses will be conducted to evaluate the effect of trial quality in future updates.

RESULTS

Description of studies

Results of the search

The search of the Pregnancy and Childbirth Group's Trials Register found 22 reports of 15 studies. The original review included five studies, and this updated review has included an additional five studies; for further details, see Characteristics of included studies. Two studies were excluded (Airoldi 1988; Eid 2006) as they were not randomised (see Characteristics of excluded studies). Four reports of two studies (Bonnar 1980; Ferrier 2000) have been reported in abstract form only, and further information is required to assess their methodological quality and relevance to this review. One further report is also awaiting classification (Yu 2004b) (see Studies awaiting classification).

Included studies

Our search strategy identified 22 reports of 15 studies for consideration. The original review included five studies (484 women) which met the inclusion criteria (Kincaid-Smith 1995; Mello 2005; Nieder 1995; Rey 2009; Yu 2004a). The updated review has included a further five studies (Gris 2010; Gris 2011; Kingdom 2011; Martinelli 2012; Yu 2010), involving an additional 655 women.

Nine studies compared heparin (alone or in combination with dipyridamole or low-dose aspirin) with no treatment (Gris 2010; Gris 2011; Kincaid-Smith 1995; Kingdom 2011; Martinelli 2012; Mello 2005; Rey 2009; Yu 2004a; Yu 2010). The study by Yu and colleagues involved a comparison between UFH and LMWH also (Yu 2004a). A single study compared trapidil (triazolopyrimidine) with placebo (Nieder 1995).

Participant population

The included studies recruited women considered to be at particularly high risk of adverse outcomes from placental insufficiency, predominantly based on a past history (particularly pre-eclampsia, eclampsia, renal disease, placental abruption, fetal growth restriction, or fetal death).

Reported outcomes

There was variable reporting of the pre-specified outcomes.

Refer to Characteristics of included studies for further information.

Excluded studies

Two studies were excluded (Airoldi 1988; Eid 2006) as they were not randomised (see Characteristics of excluded studies).

Risk of bias in included studies

The overall quality of the included trials was considered fair to good.

Please refer to the table Characteristics of included studies for further details and Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

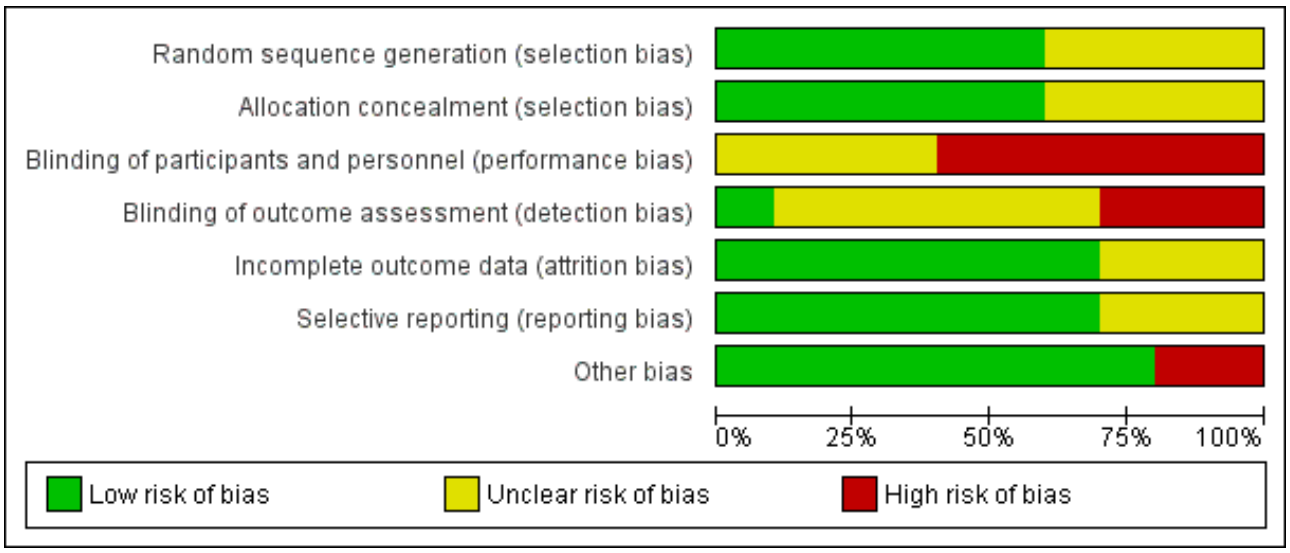
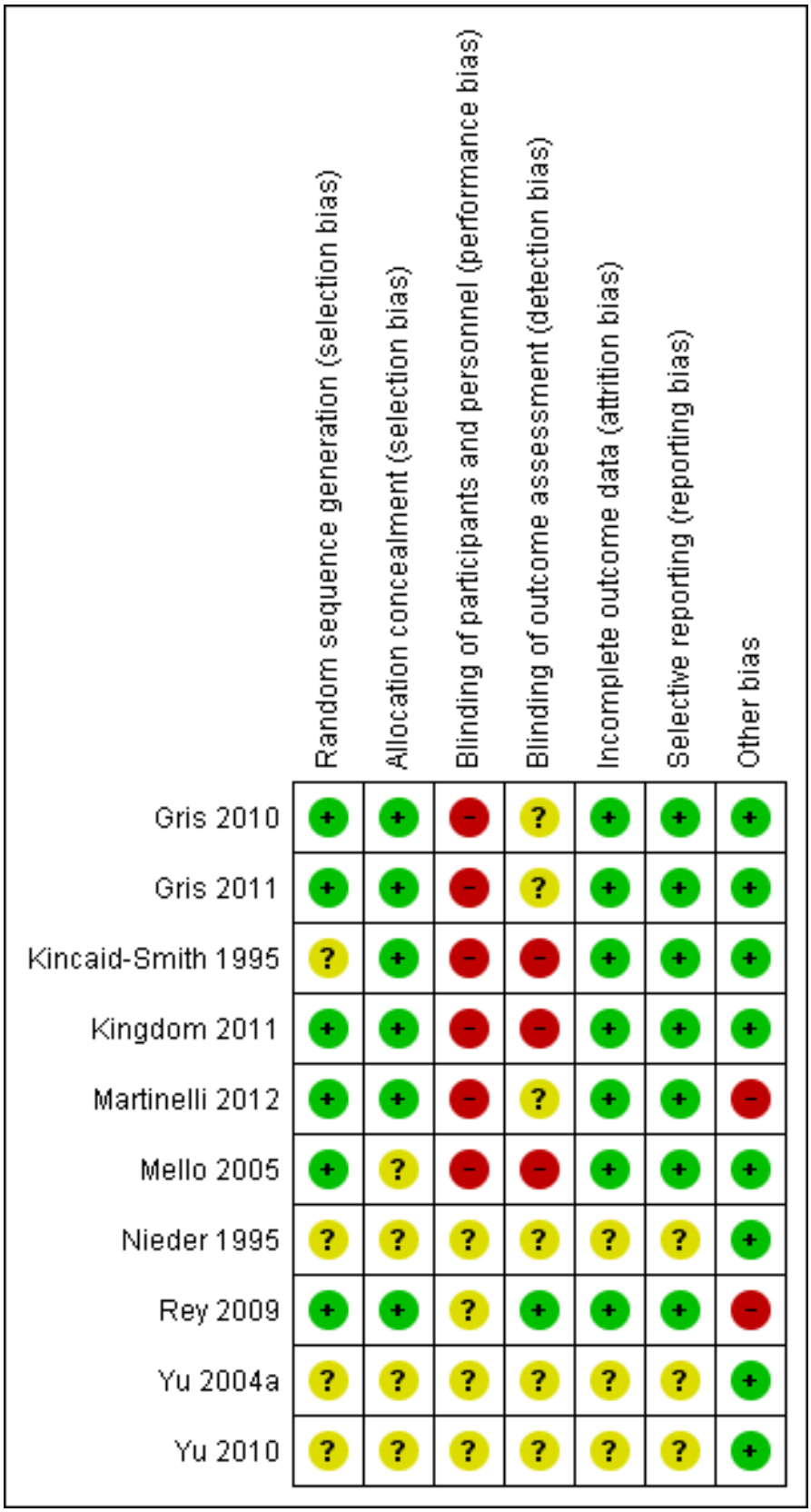


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All trials were stated to be randomised, with Gris 2010, Gris 2011, Kingdom 2011, Martinelli 2012, Mello 2005 and Rey 2009 utilising computer-generated random number tables. The precise method of randomisation was unclear or not stated in Kincaid-Smith 1995, Nieder 1995, Yu 2004a and Yu 2010. Allocation concealment utilised a central telephone randomisation service in Kingdom 2011 and Martinelli 2012, while sealed opaque envelopes were utilised by Gris 2010, Gris 2011, Kincaid-Smith 1995 and Rey 2009. The method of allocation concealment was unclear or not stated for Mello 2005, Nieder 1995, Yu 2004a, and Yu 2010.

Blinding

The study by Rey 2009 was the only one to ensure blinding of outcome assessors; blinding of participants and caregivers was not achieved or not stated in any of the included trials (Gris 2010; Gris 2011; Kingdom 2011; Kincaid-Smith 1995; Martinelli 2012; Mello 2005; Nieder 1995; Rey 2009; Yu 2004a; Yu 2010).

Incomplete outcome data

The majority of the studies appeared to be at low risk of attrition bias, with low levels of missing data.

Selective reporting

The majority of the studies appeared to be at low risk of selective reporting, although without access to a pre-specified trial protocol, this is difficult to assess.

Other potential sources of bias

The baseline characteristics of participants in the included studies appeared comparable at the time of trial entry. However, the trials by Martinelli 2012 and Rey 2009 were both halted prior to achieving their intended sample size for reasons of slow recruitment and futility.

Effects of interventions

Heparin (alone or with other medications) versus no treatment

We included nine studies involving 979 women.

Primary outcomes

For the primary outcomes, women who were administered heparin during pregnancy were at significantly lower risk of perinatal death (six studies; 653 women; risk ratio (RR) 0.40; 95% confidence intervals (CI) 0.20 to 0.78; Analysis 1.1), or of giving birth prior to 34 weeks' gestation (three studies; 494 women; RR 0.46; 95% CI 0.29 to 0.73; Analysis 1.2). There was no available information for the outcome major neurodevelopmental delay at child follow-up (one study; 107 infants; RR not estimable).

Secondary outcomes

Women administered heparin during pregnancy were at significantly lower risk of developing pre-eclampsia (seven studies; 761 women; RR 0.43; 95% CI 0.28 to 0.65). However a high degree of heterogeneity was identified, and when a random-effects model was used, the results were no longer statistically significant (seven studies; 761 women; average RR 0.47; 95% CI 0.22 to 1.03; Analysis 1.4; random-effects model; Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 14.24$, df = 6 (P = 0.03); $I^2 = 58\%$). The use of heparin was not associated with a significant reduction in eclampsia (one study; 135 women; RR not estimable; Analysis 1.5). While the use of heparin was associated with a significant difference in mean length of antenatal hospitalisation (one study; 20 women; mean difference (days) (MD) -9.00; 95% CI -15.14 to -2.86; Analysis 1.8), and birth prior to 37 weeks' gestation (five studies; 621 women; RR 0.72; 95% CI 0.58 to 0.90; Analysis 1.10), there were no significant differences in the risk of placental abruption (four studies; 551 women; RR 0.38; 95% CI 0.10 to 1.40; Analysis 1.6).

Infants born to women following heparin administration were significantly less likely to have birthweight below the 10th centile (seven studies; 710 infants; RR 0.41; 95% CI 0.27 to 0.61; Analysis 1.12), and Apgar score of less than seven at five minutes of age (three studies; 519 infants; RR 0.42; 95% CI 0.29 to 0.60; Analysis 1.13). Infants were less likely to require admission to the neonatal intensive care unit (three studies; 416 infants; RR 0.53; 95% CI 0.35 to 0.79), although a high degree of heterogeneity was identified, and when a random-effects model was used, the results were no longer statistically significant (three studies; 416 infants; average RR 0.62; 95% CI 0.25 to 1.53; Analysis 1.14; random-effects model; Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 9.85$, df = 2 (P = 0.007); $I^2 = 80\%$). There were no statistically significant differences identified in risk of either intrauterine fetal death (three studies; 519 women; RR 0.58; 95% CI 0.23 to 1.46; Analysis 1.15), or neonatal death (two studies; 384 infants; RR 0.29; 95% CI 0.06 to 1.36; Analysis 1.16).

Triazolopyrimadine versus placebo

We included a single study involving 160 women at risk of developing pre-eclampsia.

Primary outcomes

None of the pre-specified primary outcomes were reported.

Secondary outcomes

There were no statistically significant differences identified for the outcome pre-eclampsia (one study; 160 women; RR 0.38; 95% CI 0.12 to 1.16; Analysis 2.1).

Unfractionated heparin versus low molecular weight heparin

We included a single study involving 68 women with established fetal growth restriction.

Primary outcomes

There was no available information for the outcome major neurodevelopmental delay at child follow-up (one study; 68 infants; RR not estimable; Analysis 3.1).

Secondary outcomes

There was no available information for the outcomes antepartum haemorrhage or thrombocytopaenia (one study; 68 infants; RR not estimable; Analysis 3.2; Analysis 3.3). There were no statistically significant differences identified for the outcomes preterm birth before 37 weeks' gestation (one study; 68 women; RR 1.26; 95% CI 0.22 to 7.05; Analysis 3.4), or infant birthweight less than the 10th centile (one study; 68 infants; RR 0.84; 95% CI 0.13 to 5.61; Analysis 3.5).

DISCUSSION

Summary of main results

This review identified a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birthweight below the 10th centile for gestational age, when comparing antenatal heparin administration with no treatment for women considered at to be at particularly high risk of adverse outcomes and placental dysfunction.

Overall completeness and applicability of evidence

The findings of this review are based on 10 included randomised studies and 1139 participants. However, for the majority of outcomes, the available meta-analysis involved a smaller number of studies and participants (ranging from 20 to 710). This review identified a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birthweight below the 10th centile for gestational age. The effect of treatment with antithrombotic agents on a woman's risk of pre-eclampsia and eclampsia remain uncertain, with considerable heterogeneity across the identified trials to date, reflecting differences in the included patient populations. There is a lack of reliable information available related to clinically relevant infant health outcomes, which have not been reported to date, including childhood growth and development. Similarly, there is a lack of information available related to maternal side effects from medication, and maternal psychological wellbeing associated with prolonged daily treatment during pregnancy.

The proposed mechanism whereby heparin mediates beneficial effects on maternal and perinatal outcome is based on the assumption that heparin is a placental anticoagulant. However, to date only one trial (Kingdom 2011) has incorporated placental pathology analysis, noting no differences in the prevalence of placental infarction between women exposed to heparin during pregnancy and women who were not. Any subsequent trials evaluating the role of heparin in women with evidence of placental dysfunction are encouraged to incorporate placental pathology assessments blinded to treatment allocation.

Heparin appears to reduce the risk of developing pre-eclampsia. In-vitro, heparin effectively reverses the anti-angiogenic response of placenta villi (Sobel 2011). Severe forms of pre-eclampsia are associated with increased circulating levels of the anti-angiogenic protein sFlt1 and reduced levels of placenta growth factor (PlGF) (Rana 2012). It is of concern therefore that heparin increases placental production of sFlt-1, and thus circulating levels during pregnancy (Drewlo 2011). Further research is therefore required to understand the interactions between heparin and the placenta that mediate a reduction in the risk of developing severe pre-eclampsia.

Quality of the evidence

The overall quality of the included trials was considered fair to good. All trials were stated to be randomised, with six utilising computer-generated random number tables. Two trials utilised a central telephone randomisation service to maintain allocation concealment, while four trials used sealed opaque envelopes. Blinding of outcome assessors was achieved in one trial only, with the remainder either not stating or not achieving blinding of participants or caregivers, increasing the potential for bias. While there did not appear to be evidence of selective reporting or incomplete data, two trials were halted prior to achieving their estimated sample size due to reasons of difficulties with recruitment and futility.

Potential biases in the review process

Methodologically, six of the 10 included trials were considered to be at low risk of bias. However, blinding of outcome assessors was achieved in only one study, and participants and caregivers were aware of treatment allocation in all of the included studies.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment with heparin for women considered at particularly high risk of adverse pregnancy complications secondary to placental insufficiency was associated with a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birthweight below the 10th centile for gestational age, when compared with no treatment. However, important information about infant and long-term childhood growth and development is currently unavailable. Furthermore, the interpretation of these findings and potential clinical use of heparin should be confined to women who are considered to be at particularly high risk of adverse pregnancy outcomes, often based on past pregnancy history.

Implications for research

Further well designed randomised trials that are sufficiently powered to detect differences in important maternal outcomes (including both pre-eclampsia and eclampsia, as well as potential complications from antithrombotic medications), and infant and childhood growth and neurodevelopmental outcomes are required, with standardised reporting of outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Gris 2010

Methods	Trial conducted in France between January 2000 and 2009.
Participants	160 women with placental abruption in a previous pregnancy.
Interventions	Women were randomised to (1) subcutaneous enoxaparin or (2) no treatment.
Outcomes	Perinatal mortality; pre-eclampsia; preterm birth less than 37 and 34 weeks; NICU admission.
Notes	Method of randomisation: computer-generated. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers: no; outcome assessors: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants, caregivers: no.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors: not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears complete.
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	Low risk	No other potential bias identified.

Gris 2011

Methods	Trial conducted in France between January 2000 and 2010.

Gris 2011 *(Continued)*

Participants	224 women with severe pre-eclampsia in a previous pregnancy.
Interventions	Women were randomised to (1) subcutaneous enoxaparin and aspirin or (2) aspirin alone.
Outcomes	Perinatal mortality; pre-eclampsia; preterm birth less than 37 and 34 weeks; NICU admission.
Notes	Method of randomisation: computer-generated. Allocation concealment: sealed opaque envelopes. Blinding of participants, caregivers: no; outcome assessors: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants, caregivers: no.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors: not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears complete.
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	Low risk	No other potential bias identified.

Kincaid-Smith 1995

Methods	Trial conducted in Australia.
Participants	21 women with primary glomerulonephritis or reflux nephropathy who were considered on clinical grounds to be at high risk of developing pre-eclampsia; randomised from 14 weeks' gestation.
Interventions	Women were randomised to (1) subcutaneous heparin and dipyridamole or (2) no treatment.
Outcomes	Perinatal mortality; pre-eclampsia; length of antenatal stay; preterm birth less than 37 weeks; infant birthweight < 2500 g; infant birthweight less than 10th centile for gestational age.
Notes	Method of randomisation: stated "randomized by the envelope method". Allocation concealment: "envelope method". Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Kincaid-Smith 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomized by the envelope method".
Allocation concealment (selection bias)	Low risk	"Envelope method."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears complete.
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	Low risk	No other potential bias identified.

Kingdom 2011

Methods	Trial conducted in Toronto, Canada between March 2007 and May 2010.
Participants	32 women with a singleton pregnancy and negative thrombophilia screen, who had 2 or more of the following: abnormal first or second trimester maternal serum screening (in the absence of a chromosomal fetal anomaly); abnormal placental morphology detected on ultrasound; abnormal maternal uterine artery Doppler waveform prior to 24 weeks' gestation.
Interventions	Women were randomised to (1) subcutaneous heparin 7500 IU twice daily and medical surveillance or (2) medical surveillance only. 8 of 16 women in the control group received low-dose aspirin alone.
Outcomes	Primary outcomes related to feasibility of recruitment and maternal emotional wellbeing.
Notes	Method of randomisation: computer-generated. Allocation concealment: central telephone randomisation. Blinding of participants, caregivers and outcome assessors: no.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation.

Kingdom 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants, caregivers and outcome assessors: no.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of participants, caregivers and outcome assessors: no.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Low risk	No.

Martinelli 2012

Methods	Trial conducted in 8 centres in Italy, between April 2007 and April 2010.
Participants	135 women with a history of pre-eclampsia, eclampsia, HELLP syndrome, previous fetal loss or fetal growth restriction, with gestational age less than 12 weeks' gestation.
Interventions	Women were randomised to (1) low molecular weight heparin and medical surveillance or (2) medical surveillance only.
Outcomes	Pre-eclampsia; eclampsia, HELLP syndrome, placental abruption, fetal growth restriction, or fetal death.
Notes	Method of randomisation: computer-generated random number sequence. Allocation concealment: central telephone randomisation. Blinding of participants and caregivers: no; outcome assessors: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and caregivers: no.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors: not stated.
Incomplete outcome data (attrition bias)	Low risk	135 women randomised; 128 women analysed.

Martinelli 2012 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	High risk	Trial stopped after 135 women randomised due to futility (estimated sample size 266 women).

Mello 2005

Methods	Trial conducted in Italy, between January 2001 and December 2002.
Participants	80 women with a history of pre-eclampsia who were negative on thrombophilia testing; treatment was started as soon as pregnancy was confirmed.
Interventions	Women were randomised to (1) low molecular weight heparin or (2) no treatment.
Outcomes	Pre-eclampsia; infant birthweight less than 10th centile for gestational age.
Notes	Method of randomisation: computer-generated random number sequence. Allocation concealment: not stated. Blinding of participants, caregivers, and outcome assessors: no.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears complete.
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	Low risk	No other potential bias identified.

Nieder 1995

Methods	Trial conducted in Germany.
Participants	160 women at increased risk of developing pre-eclampsia, between 22 and 38 weeks' gestation.
Interventions	Women were randomised to (1) triazolopyrimidine or (2) placebo.
Outcomes	Rate of pre-eclampsia; rate of preterm birth.
Notes	Method of randomisation: not stated. Allocation concealment: not stated. Blinding of participants, caregivers, and outcome assessors: not stated. Study stated to be "randomised, double blind, placebo control".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess.
Selective reporting (reporting bias)	Unclear risk	Unable to assess.
Other bias	Low risk	No other potential bias identified.

Rey 2009

Methods	Trial conducted in Canada between August 2000 and June 2007.
Participants	116 women with past history of severe pre-eclampsia, fetal growth restriction (infant birthweight less than 5th centile), unexplained fetal death or abruption, in the absence of a known thrombophilia; women randomised from 17 weeks' gestation. Original sample size 276 women; trial stopped after an interim analysis due to slow recruitment.
Interventions	Women were randomised to (1) low molecular weight heparin or (2) no treatment.
Outcomes	Primary composite of severe pre-eclampsia, infant birthweight less than 5th centile, abruption requiring birth less than 34 weeks' gestation, or fetal death after 20 weeks.

Rey 2009 *(Continued)*

Notes	Method of randomisation: computer-generated random number table. Allocation concealment: sealed opaque envelopes. Blinding of participants and caregivers: no. Blinding of outcome assessors: yes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants or caregivers.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears complete.
Selective reporting (reporting bias)	Low risk	Appears complete.
Other bias	High risk	Trial stopped early after interim analysis due to slow recruitment.

Yu 2004a

Methods	Trial conducted in China.
Participants	107 women with established fetal growth restriction.
Interventions	Women were randomised to (1) standard heparin infusion, (2) low molecular weight heparin, or (3) dextran infusion.
Outcomes	Major neurodevelopmental handicap at child follow-up; antepartum haemorrhage, thrombocytopaenia, preterm birth less than 37 weeks' gestation, infant birthweight less than 10th centile.
Notes	Method of randomisation: stated "women were randomised into three groups". Allocation concealment: not stated. Blinding of participants, caregivers, and outcome assessors: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation: stated "women were randomised into three groups".

Yu 2004a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess.
Selective reporting (reporting bias)	Unclear risk	Unable to assess.
Other bias	Low risk	No other potential bias identified.

Yu 2010

Methods	Trial conducted in China.
Participants	104 women, 73 with established fetal growth restriction, and 31 with established pre-eclampsia.
Interventions	Women were randomised to (1) standard heparin infusion, or (2) the control group (no details provided as to what this comprised).
Outcomes	Ultrasound and haematological measures; no prespecified review outcomes were reported.
Notes	Method of randomisation: not stated. Allocation concealment: not stated. Blinding of participants, caregivers, and outcome assessors: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Yu 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess.
Selective reporting (reporting bias)	Unclear risk	Unable to assess.
Other bias	Low risk	No other potential bias identified.

HELLP: haemolysis, elevated liver enzymes, low platelet count
IU: international units
NICU: neonatal intensive care unit

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

Study	Reason for exclusion
Airoldi 1988	Not a randomised controlled trial.
Eid 2006	Not a randomised controlled trial.

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

Bonnar 1980

Methods	Study conducted in Ireland.
Participants	40 women at high risk of fetal growth restriction.
Interventions	Treatment with heparin and dipyridamole or no treatment.
Outcomes	Infant growth restriction.
Notes	There is insufficient information presented in the abstract to evaluate study methodology; no data are presented.

Ferrier 2000

Methods	Trial conducted in Switzerland.
Participants	24 women with a history of pre-eclampsia, renal disease, or hypertension.
Interventions	Treatment with heparin and low-dose aspirin or low-dose aspirin alone.
Outcomes	Hypertension, fetal loss, uric acid renal clearance.
Notes	There is insufficient information presented in the abstract to evaluate study methodology.

Yu 2004b

Methods	Trial conducted in China.
Participants	Women with established fetal growth restriction.
Interventions	Women were randomised to (1) standard heparin infusion, (2) low molecular weight heparin, or (3) dextran infusion.
Outcomes	Doppler ultrasound parameters reported.
Notes	Method of randomisation: stated "women were randomised into three groups". Allocation concealment: not stated. Blinding of participants, caregivers, and outcome assessors: not stated. This could be an additional report of Yu 2004a. Awaiting further clarification from authors.

DATA AND ANALYSES

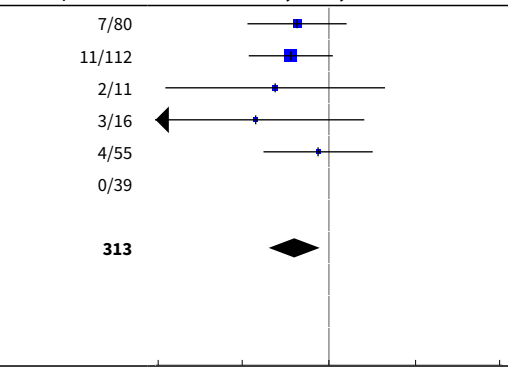
Comparison 1. Heparin (alone or with other medication) versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	6	653	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.20, 0.78]
2 Preterm birth less than 34 weeks' gestation	3	494	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.29, 0.73]
3 Major neurodevelopmental delay at child follow-up	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Pre-eclampsia	7	761	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 1.03]
5 Eclampsia	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Placental abruption	4	551	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.40]
7 Antepartum haemorrhage (after 20 weeks requiring hospitalisation)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mean length of antenatal hospital stay	1	20	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-15.14, -2.86]
9 Thrombocytopaenia	2	242	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Preterm birth less than 37 weeks' gestation	5	621	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.90]
11 Infant birthweight less than 2500 grams	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.37, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Infant birthweight less than 10th centile for gestational age	7	710	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.27, 0.61]
13 Apgar score less than 7 at 5 minutes age	3	519	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.29, 0.60]
14 NICU admission	3	416	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.25, 1.53]
15 Fetal death	3	519	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.23, 1.46]
16 Neonatal death	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.36]

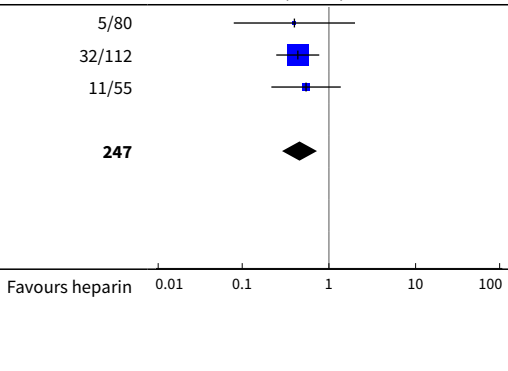
Analysis 1.1. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 1 Perinatal mortality.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gris 2010	3/80	7/80		25.2%	0.43[0.11,1.6]
Gris 2011	4/112	11/112		39.61%	0.36[0.12,1.11]
Kincaid-Smith 1995	0/9	2/11		8.18%	0.24[0.01,4.44]
Kingdom 2011	0/16	3/16		12.6%	0.14[0.01,2.56]
Rey 2009	3/55	4/55		14.4%	0.75[0.18,3.2]
Yu 2004a	0/68	0/39			Not estimable
Total (95% CI)	**340**	**313**		**100%**	**0.4[0.2,0.78]**
Total events: 10 (Heparin), 27 (No treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.37, df=4(P=0.85); I^2=0%					
Test for overall effect: Z=2.66(P=0.01)					



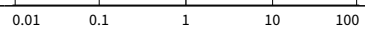
Analysis 1.2. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 2 Preterm birth less than 34 weeks' gestation.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gris 2010	2/80	5/80		10.42%	0.4[0.08,2]
Gris 2011	14/112	32/112		66.67%	0.44[0.25,0.77]
Rey 2009	6/55	11/55		22.92%	0.55[0.22,1.37]
Total (95% CI)	**247**	**247**		**100%**	**0.46[0.29,0.73]**
Total events: 22 (Heparin), 48 (No treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=3.29(P=0)					



Analysis 1.3. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 3 Major neurodevelopmental delay at child follow-up.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/68	0/39			Not estimable
Total (95% CI)	**68**	**39**			**Not estimable**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

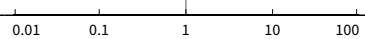


Analysis 1.4. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 4 Pre-eclampsia.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gris 2010	6/80	18/80		20.08%	0.33[0.14,0.8]
Gris 2011	6/112	17/112		19.82%	0.35[0.14,0.86]
Kincaid-Smith 1995	0/9	5/11		6.06%	0.11[0.01,1.74]
Kingdom 2011	6/16	2/16		13.92%	3[0.71,12.69]
Martinelli 2012	5/67	3/68		14.41%	1.69[0.42,6.8]
Mello 2005	3/41	11/39		16.36%	0.26[0.08,0.86]
Rey 2009	1/55	8/55		9.36%	0.13[0.02,0.97]
Total (95% CI)	**380**	**381**		**100%**	**0.47[0.22,1.03]**
Total events: 27 (Heparin), 64 (No treatment)					
Heterogeneity: Tau²=0.58; Chi²=14.24, df=6(P=0.03); I²=57.87%					
Test for overall effect: Z=1.89(P=0.06)					

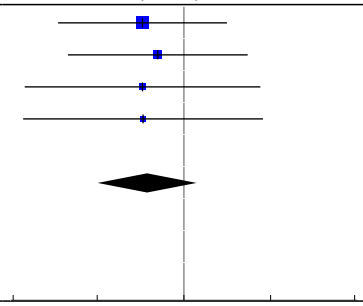
Analysis 1.5. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 5 Eclampsia.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Martinelli 2012	0/67	0/68			Not estimable
Total (95% CI)	**67**	**68**			**Not estimable**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



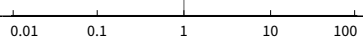
Analysis 1.6. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 6 Placental abruption.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gris 2010	1/80	3/80		37.55%	0.33[0.04,3.14]
Gris 2011	1/112	2/112		25.03%	0.5[0.05,5.44]
Kingdom 2011	0/16	1/16		18.78%	0.33[0.01,7.62]
Martinelli 2012	0/67	1/68		18.64%	0.34[0.01,8.16]
Total (95% CI)	**275**	**276**		**100%**	**0.38[0.1,1.4]**
Total events: 2 (Heparin), 7 (No treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=3(P=0.99); I^2=0%					
Test for overall effect: Z=1.46(P=0.14)					



Analysis 1.7. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 7 Antepartum haemorrhage (after 20 weeks requiring hospitalisation).

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/68	0/39			Not estimable
Total (95% CI)	**68**	**39**			**Not estimable**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

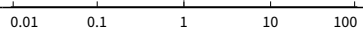


Analysis 1.8. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 8 Mean length of antenatal hospital stay.

Study or subgroup	Heparin N	Heparin Mean(SD)	No treatment N	No treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kincaid-Smith 1995	9	18 (6)	11	27 (8)		100%	-9[-15.14,-2.86]
Total ***	**9**		**11**			**100%**	**-9[-15.14,-2.86]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.87(P=0)							

Analysis 1.9. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 9 Thrombocytopaenia.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Martinelli 2012	0/67	0/68			Not estimable



Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/68	0/39			Not estimable
Total (95% CI)	**135**	**107**			**Not estimable**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours heparin 0.01 0.1 1 10 100 Favours no treatment

Analysis 1.10. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 10 Preterm birth less than 37 weeks' gestation.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gris 2010	34/80	39/80		32.72%	0.87[0.62,1.22]
Gris 2011	30/112	45/112		37.75%	0.67[0.46,0.98]
Kincaid-Smith 1995	2/9	7/11		5.29%	0.35[0.1,1.28]
Rey 2009	16/55	20/55		16.78%	0.8[0.47,1.37]
Yu 2004a	5/68	7/39		7.46%	0.41[0.14,1.2]
Total (95% CI)	**324**	**297**		**100%**	**0.72[0.58,0.9]**
Total events: 87 (Heparin), 118 (No treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.76, df=4(P=0.44); I^2=0%					
Test for overall effect: Z=2.9(P=0)					

Favours heparin 0.01 0.1 1 10 100 Favours no treatment

Analysis 1.11. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 11 Infant birthweight less than 2500 grams.

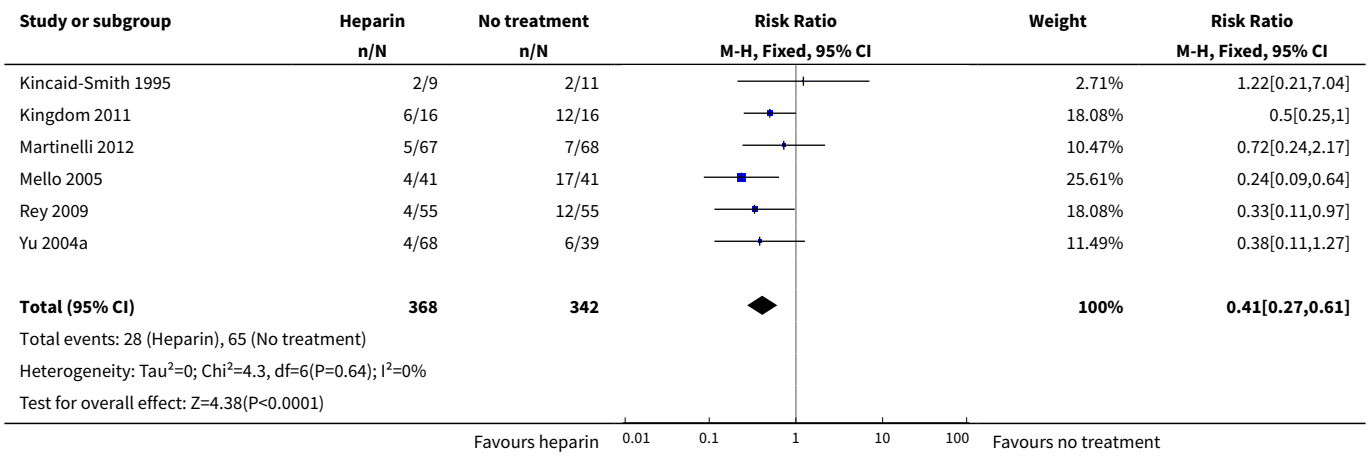
Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rey 2009	9/55	11/55		100%	0.82[0.37,1.82]
Total (95% CI)	**55**	**55**		**100%**	**0.82[0.37,1.82]**
Total events: 9 (Heparin), 11 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					

Favours heparin 0.01 0.1 1 10 100 Favours no treatment

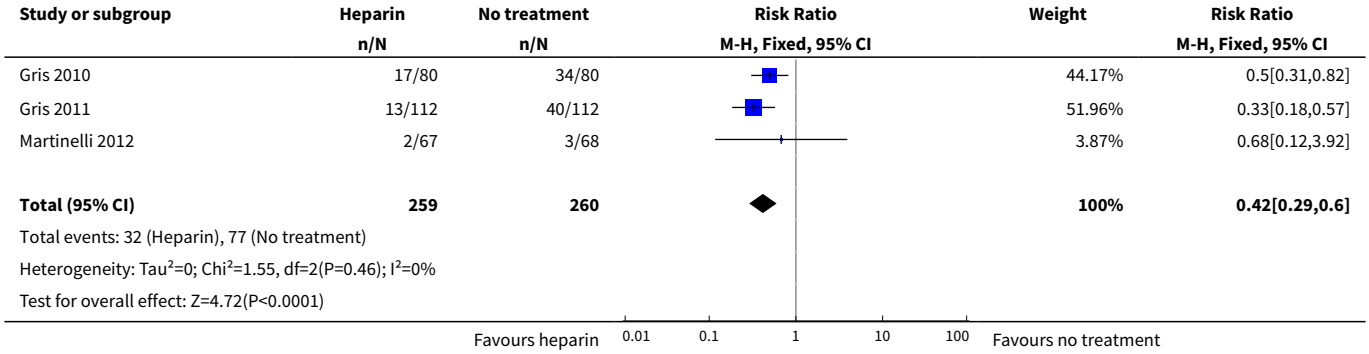
Analysis 1.12. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 12 Infant birthweight less than 10th centile for gestational age.

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gris 2011	3/112	9/112		13.56%	0.33[0.09,1.2]

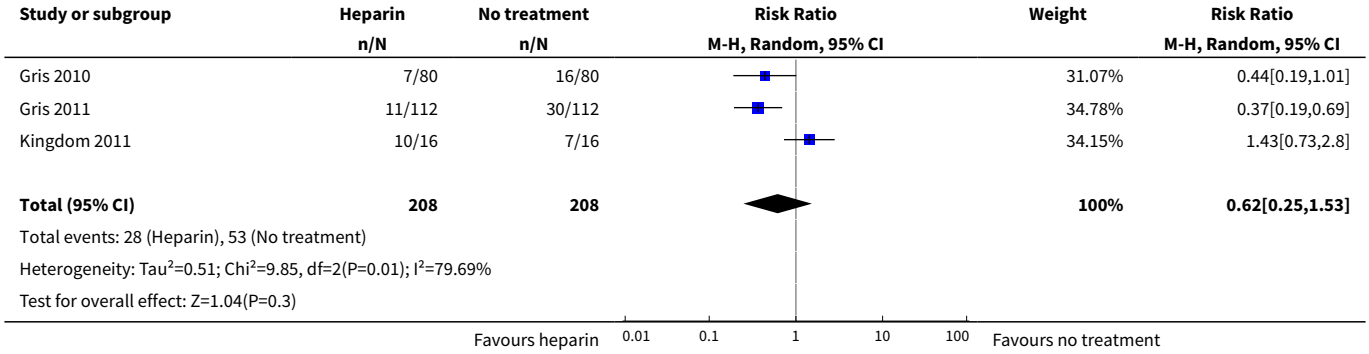
Favours heparin 0.01 0.1 1 10 100 Favours no treatment



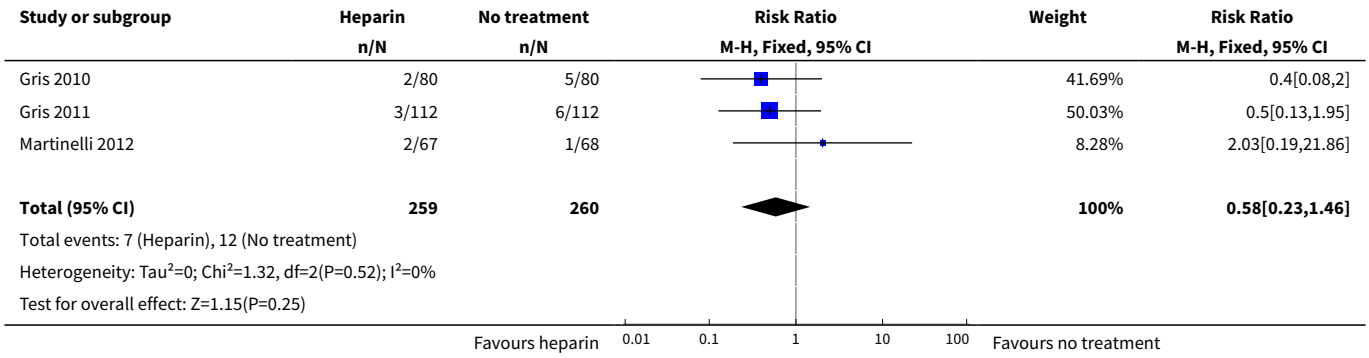
Analysis 1.13. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 13 Apgar score less than 7 at 5 minutes age.



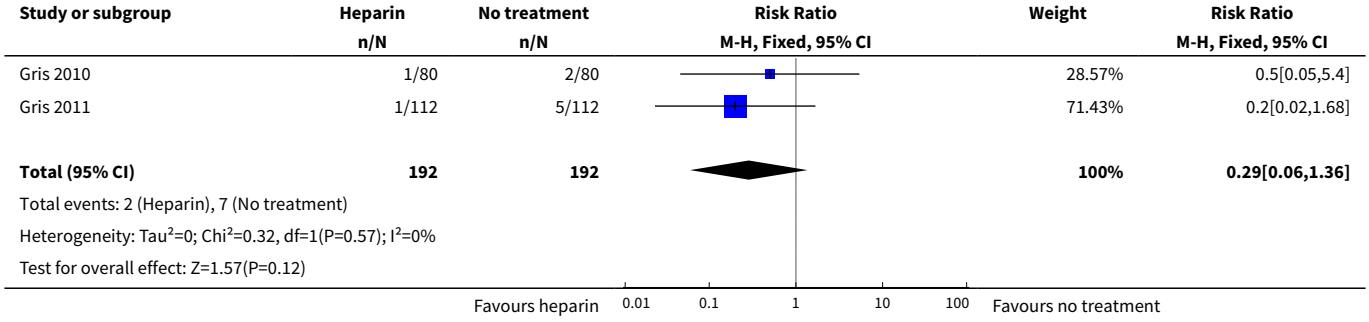
Analysis 1.14. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 14 NICU admission.



Analysis 1.15. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 15 Fetal death.



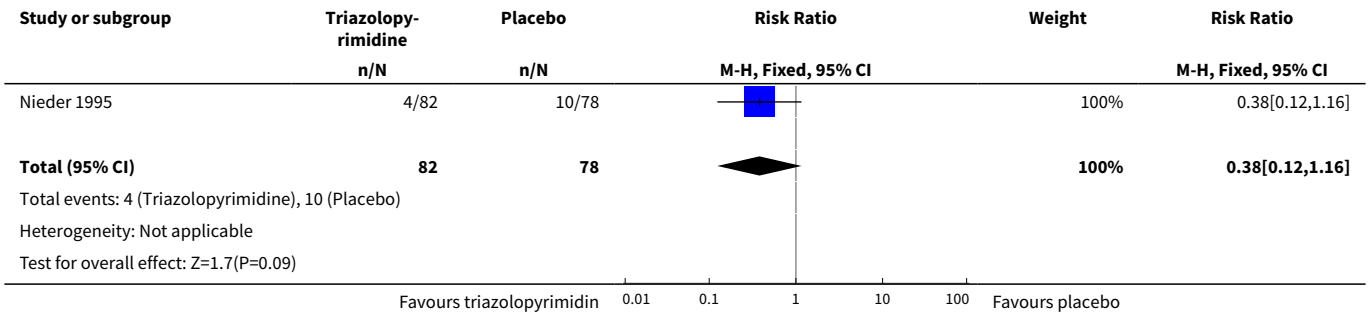
Analysis 1.16. Comparison 1 Heparin (alone or with other medication) versus no treatment, Outcome 16 Neonatal death.



Comparison 2. Triazolopyrimidine (Trapidil) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.12, 1.16]

Analysis 2.1. Comparison 2 Triazolopyrimidine (Trapidil) versus placebo, Outcome 1 Pre-eclampsia.



Comparison 3. Unfractionated heparin versus low molecular weight heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major neurodevelopmental delay at child follow-up	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Antepartum haemorrhage (after 20 weeks and requiring hospitalisation)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Thrombocytopaenia	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Preterm birth prior to 37 weeks' gestation	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.22, 7.05]
5 Infant birthweight less than 10th centile for gestational age	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.13, 5.61]

Analysis 3.1. Comparison 3 Unfractionated heparin versus low molecular weight heparin, Outcome 1 Major neurodevelopmental delay at child follow-up.

Study or subgroup	Unfractionated heparin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/37	0/31			Not estimable
Total (95% CI)	**37**	**31**			**Not estimable**
Total events: 0 (Unfractionated heparin), 0 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 3.2. Comparison 3 Unfractionated heparin versus low molecular weight heparin, Outcome 2 Antepartum haemorrhage (after 20 weeks and requiring hospitalisation).

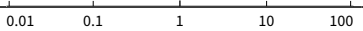
Study or subgroup	Unfractionated heparin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/37	0/31			Not estimable
Total (95% CI)	**37**	**31**			**Not estimable**
Total events: 0 (Unfractionated heparin), 0 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 3.3. Comparison 3 Unfractionated heparin versus low molecular weight heparin, Outcome 3 Thrombocytopaenia.

Study or subgroup	Unfractionated heparin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	0/37	0/31			Not estimable
Total (95% CI)	**37**	**31**			**Not estimable**
Total events: 0 (Unfractionated heparin), 0 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

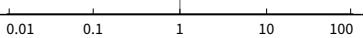
Analysis 3.4. Comparison 3 Unfractionated heparin versus low molecular weight heparin, Outcome 4 Preterm birth prior to 37 weeks' gestation.

Study or subgroup	Unfractionated heparin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	3/37	2/31		100%	1.26[0.22,7.05]
Total (95% CI)	**37**	**31**		**100%**	**1.26[0.22,7.05]**
Total events: 3 (Unfractionated heparin), 2 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					



Analysis 3.5. Comparison 3 Unfractionated heparin versus low molecular weight heparin, Outcome 5 Infant birthweight less than 10th centile for gestational age.

Study or subgroup	Unfractionated heparin n/N	LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2004a	2/37	2/31		100%	0.84[0.13,5.61]
Total (95% CI)	**37**	**31**		**100%**	**0.84[0.13,5.61]**
Total events: 2 (Unfractionated heparin), 2 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					



APPENDICES

Appendix 1. Methods used to assess trials included in previous versions of this review

The following methods were used to assess Kincaid-Smith 1995; Mello 2005; Nieder 1995; Rey 2009; Yu 2004a.

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 person.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors (JD and RW) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2008) and checked for accuracy.

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

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement by discussion or by involving a third assessor.

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we will re-include missing data in the analyses which were undertaken. We considered more than 20% incomplete data to be inadequate. We assessed methods as:

- adequate;
- inadequate:
- unclear.

(5) Selective reporting bias

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

We assessed the methods as:

- adequate (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);
- inadequate (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.

(6) Other sources of bias

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:

- yes;
- no;
- unclear.

(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 2008). 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 analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we have used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any eligible cluster-randomised trials.

Cross-over trials

We did not consider cross-over trials an appropriate study design for the evaluation of this intervention and we have not included them.

Dealing with missing data

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

For all outcomes we have 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. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we had identified substantial heterogeneity (greater than 50%) in a fixed-effect meta-analysis, we would have noted this and repeated the analysis using a random-effects method.

Assessment of reporting biases

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If we had identified clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials we would have used random-effects meta-analysis.

If we had identified substantial heterogeneity in a fixed-effect meta-analysis we would have noted this and repeated the analysis using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We had planned to carry out the following subgroup analyses had we identified substantial heterogeneity:

1. antithrombotic agent administered (unfractionated heparin versus low molecular weight heparin versus other);
2. gestational age treatment commenced (first trimester versus second trimester versus third trimester).

We would have used the primary outcomes in subgroup analysis.

For fixed-effect meta-analyses we conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We did not carry out sensitivity analysis.

WHAT'S NEW

Date	Event	Description
28 August 2012	New search has been performed	Search updated July 2012.
28 August 2012	New citation required and conclusions have changed	The updated review includes an additional five randomised trials which has changed the conclusions of the review. In this 2013 update, there is no evidence of a difference in pre-eclampsia and evidence for a reduction in perinatal mortality and preterm birth before 34 and 37 weeks.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 6, 2010

Date	Event	Description
17 July 2012	Amended	Search updated. Eight reports of seven trials added to Studies awaiting classification (Gris 2010a; Gris 2011a; Kingdom 2011a; Martinelli 2012a; Walker 2011a; Yu 2004b; Yu 2010a).

CONTRIBUTIONS OF AUTHORS

J Dodd prepared this updated review. J Dodd and R Windrim assessed studies for inclusion and conducted data extraction. All review authors reviewed and commented critically on all versions of the updated review and agreed to the final version submitted.

DECLARATIONS OF INTEREST

John Kingdom, Jodie Dodd, Anne McLeod and Rory Windrim are authors of one of the included studies (Kingdom 2011). This trial assessment and data extraction was conducted by an independent assessor, with experience in the conduct of Cochrane systematic reviews.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- Neil Hamilton Fairley Fellowship supported by the NHMRC (ID 399224), Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods updated to current Cochrane Pregnancy and Childbirth Group standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [therapeutic use]; Dipyridamole [therapeutic use]; Eclampsia [prevention & control]; Fibrinolytic Agents [*therapeutic use]; Heparin [therapeutic use]; Infant, Low Birth Weight; Placenta Diseases [*prevention & control]; Pre-Eclampsia [drug therapy] [prevention & control]; Randomized Controlled Trials as Topic; Thrombosis [*prevention & control]; Trapidil [therapeutic use]; Treatment Outcome

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy