Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period (Review)

Tooher R, Gates S, Dowswell T, Davis LJ

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 5

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Rebecca Tooher[1], Simon Gates[2], Therese Dowswell[3], Lucy-Jane Davis[4]

[1]Paediatric Trials Unit, Children,Youth and Women's Health Service, Adelaide, Australia. [2]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK. [3]Cochrane Pregnancy and Childbirth Group, School of Reproductive and Developmental Medicine, Division of Perinatal and Reproductive Medicine, The University of Liverpool, Liverpool, UK. [4]Plymouth, UK

Contact address: Rebecca Tooher, Paediatric Trials Unit, Children,Youth and Women's Health Service, Adelaide, South Australia, 5006, Australia. rebecca.tooher@adelaide.edu.au.

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 5, 2010.
Review content assessed as up-to-date: 26 November 2009.

Citation: Tooher R, Gates S, Dowswell T, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No.: CD001689. DOI: 10.1002/14651858.CD001689.pub2.

ABSTRACT

Background

Venous thromboembolic disease (TED), although rare, is a major cause of maternal mortality and morbidity, hence methods of prophylaxis are often used for women at risk. This may include women delivered by caesarean section, those with a personal or family history of TED and women with inherited or acquired thrombophilias (conditions that predispose people to thrombosis). Many methods of prophylaxis carry a risk of side effects, and as the risk of TED is low, it is possible that the benefits of thromboprophylaxis may be outweighed by harm. Current guidelines for clinical practice are based on expert opinion only, rather than high quality evidence from randomised trials.

Objectives

To determine the effects of thromboprophylaxis in women who are pregnant or have recently delivered and are at increased risk of TED on the incidence of venous TED and side effects of treatment.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (May 2009).

Selection criteria

Randomised trials comparing one method of thromboprophylaxis with placebo or no treatment, and randomised trials comparing two (or more) methods of thromboprophylaxis.

Data collection and analysis

Two review authors extracted data independently and resolved any discrepancies by discussion.

Main results

Sixteen trials met the inclusion criteria but only 13 trials, involving 1774 women, examining a range of methods of thromboprophylaxis, contributed data for the outcomes of interest. Four of them compared methods of antenatal prophylaxis: low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) (two studies), and heparin versus no treatment (two studies). Eight studies assessed postnatal prophylaxis after caesarean section; one compared hydroxyethyl starch with unfractionated heparin; four compared heparin with placebo; and the other three compared UFH with LMWH. One study examined prophylaxis in the postnatal period.

The small number of statistically significant findings in this review are largely derived from trials which are not of high methodological quality. It was not possible to assess the effects of any of these interventions on most outcomes, and especially on rare outcomes such as death, TED and osteoporosis, because of small sample sizes and the small number of trials making the same comparisons.There was some evidence of side effects associated with thromboprophylaxis.

Authors' conclusions

There is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period. Large scale randomised trials of currently-used interventions should be conducted.

PLAIN LANGUAGE SUMMARY

Preventing deep vein clots or thrombosis (DVT) in pregnancy and after the birth

Some women are at risk of forming blood clots in a deep vein during pregnancy, after a caesarean birth, or during the first few weeks after childbirth. If part of the clot breaks off and lodges in a blood vessel in the lungs, it can be life-threatening. Preventive treatments include blood-thinning drugs to prevent clots, support stockings, and exercise soon after the birth to keep circulation moving. However, some drugs might cause problems such as increased blood loss after the birth. Drugs used include heparin, low molecular weight heparin and aspirin. We included 16 randomised controlled studies in the review but only 13 trials with 1774 women contributed data for the outcomes of interest. We did not find enough evidence from the trials to be sure about the effects of these different preventive treatments.This means there is not enough evidence to show which are the best ways to prevent deep vein thrombosis (DVT) during or following pregnancy, or after a caesarean birth.

BACKGROUND

Venous thromboembolic disease (TED) occurs when a blood clot forms in a deep vein, usually in a leg, forming a deep venous thrombosis (DVT), which may cause pain and swelling. This is very rarely fatal, but if part of the clot breaks off it may be carried to the lungs by the circulatory system and block blood vessels there, resulting in a pulmonary embolism. This is more serious, and can cause chest pain, shortness of breath, haemoptysis (coughing blood) and, if large, severe hypoxia (oxygen deprivation) and collapse, which can be fatal. TED is the leading cause of maternal mortality in developed countries (Atrash 1990; Dept of Health 1998; Högberg 1994; Lewis 2004), and most of the maternal deaths caused by it are due to pulmonary embolism. As well as causing maternal death, TED can cause serious long-term maternal morbidity (Lindhagen 1986), including venous insufficiency, often manifesting as a painful and sometimes ulcerating leg, due to the compromised blood flow to the limb.

Alterations to the clotting system during pregnancy increase the risk of a thromboembolic event (DVT or pulmonary embolism); the risk is even greater in the in the early postnatal period especially in those women undergoing caesarean section (CS). A recent case control study reported that compared with non-pregnant women, the risk of venous thromboembolism (VTE) was increased five-fold during pregnancy (especially during the third trimester), and by 60-fold during the first three months after the birth (Pomp 2008).

Although the risk of TED is increased during pregnancy and the immediate postnatal period, it is still relatively rare. One of the best estimates of its incidence is from a Swedish study (Lindqvist 1999), which linked maternity and hospital admission data, and therefore, avoided the problem of earlier studies where the incidence of TED may have been underestimated because some events were not recorded as pregnancy-related. The incidence in this study

was 0.13%, compared with other figures of 0.055% (Rutherford 1991), 0.085% (Andersen 1998), 0.06% (Gherman 1999) and 0.11% (Macklon 1996). In a UK case control study the overall risk of TED was 0.085%, but there was a much higher risk of events in the postnatal period following caesarean delivery. In this study, the risk in the antenatal period was estimated as 0.028% compared with 0.18% following CS (Simpson 2001). All of these figures relate to all pregnancies rather than to any particular group of women at risk. The variability in the estimates is probably due to differences in the reliability of the methods of diagnosis used, as well as differences between the populations in their risk factors and use of thromboprophylaxis. A study examining trends over time suggests that the incidence of TED during pregnancy remained fairly constant between 1966 and 1995, while the incidence in PE during the postnatal period decreased (Heit 2005).

Some groups of women have a higher risk of developing TED in association with pregnancy. Specific risk factors that have been identified include operative delivery; having had one or more previous episodes of TED; a family history of TED; having an inherited or acquired thrombophilia (a condition that predisposes people to developing thromboses); obesity; greater maternal age; higher parity and prolonged immobilisation (Alfirevic 2002; Barbour 1997; Larciprete 2007; Simpson 2001). The size of the increases in risk attributable to these factors has generally been poorly quantified. For thrombophilias the risks of a thromboembolic event in association with pregnancy have been estimated, and range from 5% to 33% depending on the nature of the thrombophilia (Conard 1990; Friederich 1996; Pomp 2008). For women who have had a previous thrombosis in pregnancy, the risk of TED increases considerably in subsequent pregnancies if antenatal thromboprophylaxis is not used (Brill-Edwards 2000; De Stefano 2006).

Women who have particular risk factors for the development of TED are often given thromboprophylaxis during the antenatal or postnatal period or both (Connolly 2003; Dargaud 2005; Taylor 2000). Both pharmacological methods and non-pharmacological methods of thromboprophylaxis have been used. Pharmacological methods use anticoagulant drugs (heparin, warfarin, aspirin and hydroxyethyl starch (HES)) that help to prevent clotting of the blood. Non-pharmacological methods (stockings, pneumatic compression, early mobilisation and surveillance) aim to keep the blood moving in the lower limbs, thus helping to prevent formation of clots.

There has been debate about whether thromboprophylaxis is beneficial and cost effective; routine screening of all pregnant women to identify women with thrombophilias, for example, has not been recommended, and antenatal prophylaxis for all women with known thrombophilias remains controversial (Brenner 2003; Middeldorp 2003; Wu 2005). Pharmacological methods may cause side effects that are sufficiently severe or common to outweigh the benefits of thromboprophylaxis. Warfarin is known to cause congenital abnormalities (Hall 1980) and it is, therefore, rarely used in the first trimester or in the last few weeks of pregnancy. Heparin does not cross the placenta and is safe for the fetus, and therefore, is generally used for antenatal therapy. However, it can cause side effects for the mother (Nelson-Piercy 1997); there is a risk of symptomatic osteoporosis (loss of bone density, leading to fractures), thrombocytopenia (low platelets), bleeding and allergic reactions. When used after caesarean section, heparin may increase the frequency of bleeding and wound complications. Originally, unfractionated heparin (UFH) was used, but this has now been largely superseded, at least for use in pregnancy and postnatally, by low molecular weight heparins (LMWH). These have the advantage that they often need to be given only once daily and laboratory monitoring may not be required rather than needing more complex titration regimens requiring repeated laboratory blood monitoring. In addition, LMWHs are thought to be associated with a lower risk of side effects.

Both heparin and warfarin are used for postnatal thromboprophylaxis and are safe for mothers who are breastfeeding (Letsky 1997; Orme 1977).

Low dose (60 mg to 75 mg) aspirin has been widely used in pregnancy to try to prevent the development of pre-eclampsia (Knight 2001). Aspirin is usually well tolerated and has few side effects, and its use for thromboprophylaxis in orthopaedic surgery (PEP Trial 2000) suggests that it may have a role to play in the prevention of TED in pregnancy.

HES was used for thromboprophylaxis in the past, and is used in one of the trials included in this review, but it is no longer used because of the risk of anaphylaxis (Paull 1987).

The duration of prophylaxis varies depending on the risk factor. Women who have had a previous episode of TED may receive long-term antenatal prophylaxis as well as prolonged postnatal prophylaxis, while women undergoing delivery by CS may receive only postnatal prophylaxis for a few days.

OBJECTIVES

To determine the effects of thromboprophylaxis during pregnancy and the early postnatal period in women at increased risk of venous TED on the incidence of venous TED and side effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any intervention that may prevent TED with placebo or with no treatment, or RCTs comparing any two or more interventions. We did not include quasi-randomised studies (i.e. those that used non-random methods of allocating participants to groups). We did not include studies reported only as abstracts in analyses but as studies awaiting assessment, pending full publication of their results.

Types of participants

Women who were pregnant or had delivered in the previous six weeks and were at increased risk of TED. This includes women who were delivered by caesarean section, had previously had TED, had an acquired or inherited thrombophilia, and other risk factors for TED. We did not include women with artificial heart valves. This is one of a series of Cochrane reviews looking at women at increased risk of adverse outcomes in pregnancy. A related Cochrane review specifically focuses on the role of heparin for pregnant women with known thrombophilias to prevent adverse pregnancy outcomes (Walker 2003). Thromboprophylaxis has also been used to prevent miscarriage in women with recurrent pregnancy loss. Two related Cochrane reviews examine the effects of antenatal thromboprophylaxis on pregnancy loss on women with or without known thrombophilias (Empson 2005; Kaandorp 2009). To avoid duplication, the focus of this review is on the prevention of venous thromboembolic events in pregnancy and the postpartum period, and we have not, therefore, included studies specifically examining the prevention of pre-eclampsia, miscarriage or other adverse pregnancy outcomes.

Types of interventions

We considered RCTs of any intervention that may reduce TED eligible. This included the following:

1. Pharmacological interventions
   - UFH;
   - LMWH;
   - warfarin;
   - aspirin;
   - HES.

2. Non-pharmacological interventions
   - Stockings;
   - pneumatic compression (intermittent compression of the calves during surgery);
   - early mobilisation;
   - surveillance (screening for asymptomatic thromboembolic events to prevent symptomatic deep venous thrombosis or pulmonary embolism).

Types of outcome measures

Primary outcomes

1. Maternal death;
2. symptomatic thromboembolic events;
3. symptomatic pulmonary embolism;
4. symptomatic deep venous thrombosis (DVT).

Secondary outcomes

5. Asymptomatic thromboembolic events (detected by screening);
6. blood transfusion;
7. bleeding episodes;
8. serious wound complications (wound infection requiring antibiotics, dehiscence, resuturing);
9. side effects sufficient to stop treatment;
10. side effects not sufficient to stop treatment;
11. symptomatic osteoporosis (for studies involving the use of antenatal heparin);
12. fetal loss (for studies involving the use of antenatal heparin or aspirin);
13. thrombocytopenia (for studies involving the use of antenatal heparin);
14. fetal anomalies (for studies involving the use of antenatal heparin or aspirin).

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 (May 2009).

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

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

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

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

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified by the search strategy. We resolved disagreement through discussion.

Data extraction and management

Two authors extracted data independently using a data collection form developed for the review. We resolved discrepancies by referring to a third author. We entered data into Review Manager software (RevMan 2008), and checked them for accuracy.

Assessment of risk of bias in included studies

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

(1) Sequence generation

We assessed the methods as:

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

We excluded studies with inadequate random sequence generation (i.e. quasi-randomised).

(2) Allocation concealment

We recorded the method used to conceal the allocation sequence before randomisation for each trial. We assessed methods as adequate if the next allocation in the sequence could not be discovered before randomisation, and could not be changed once allocated.
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

We recorded for each study the methods used, if any, to blind study participants and personnel from knowledge of which intervention each participant received, along with any information relating to whether the intended blinding was effective. Where blinding was not possible, we assessed whether the lack of blinding was likely to have introduced bias.
The methods were assessed as:

- adequate, inadequate, not possible or unclear for participants;
- adequate, inadequate, not possible or unclear for personnel;
- adequate, inadequate, not possible or unclear for outcome assessors.

(4) Incomplete outcome data

We recorded the completeness of outcome data in each study for each main outcome including attrition and exclusions from the analysis.

(5) Other sources of bias

We assessed the possibility of other sources of bias, including selective reporting of outcomes, and reported any evidence of problems.

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). In the absence of heterogeneity we planned to use fixed-effect meta-analysis. For dichotomous data, we have presented results as summary risk ratio with 95% confidence intervals. We used the mean difference for the analysis of continuous outcomes for outcomes measured in the same way between trials, and the standardised mean difference for trials that measured the same outcome using different methods.
We have analysed studies addressing different comparisons separately. We have summarised results under three main headings, each of which included several different comparisons between methods of thromboprophylaxis:

1. antenatal or antenatal + postnatal or antenatal + intrapartum thromboprophylaxis;
2. postnatal or intrapartum + postnatal thromboprophylaxis;
3. thromboprophylaxis given during or after caesarean section.

Unit of analysis issues

We did not identify any cluster-randomised trials. Crossover trials are an inappropriate design and we have not included them.

Dealing with missing data

For all outcomes, we conducted analyses as far as possible on an intention-to-treat basis, i.e. we attempted to include all participants randomised in their allocated group. If participants were omitted or analysed in the incorrect group, we included them in the analyses in the correct group if the report contained sufficient information to allow this. We omitted participants with missing outcome data from the analysis; i.e. we did not impute outcomes for participants with missing data. In all analyses the denominator was the number randomised minus the number with missing data.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 and T^2 statistics. We planned to explore heterogeneity using the pre-specified subgroup analyses, but there were insufficient trials in any comparison to make this feasible. For outcomes where we identified considerable or high levels of heterogeneity ($I^2 > 30\%$) we planned either to carry out a random-effects analysis and to present this result, or not to pool results from studies in meta-analysis. For many outcomes data were available from only a single study and heterogeneity was not an issue.

Subgroup analysis and investigation of heterogeneity

We pre-specified one subgroup analysis: stratifying by risk factors for TED, i.e. previous venous TED; family history of TED; inherited or acquired thrombophilia; emergency or elective caesarean section with or without other risk factors; or other risk factors. However, we were unable to conduct any subgroup analyses due to lack of data. We will include these analyses in future versions of the review if the necessary data become available.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

We considered 38 studies for inclusion (described in 53 reports identified by the search). Of these, we assessed 16 as eligible for inclusion and excluded 16. Four studies are awaiting further assessment because results were reported in abstracts only and we are awaiting publication of the full study report (De Veciana 2001; Dittmer 1991; Hamersley 1998; Kamin 2008). Two studies are ongoing and full results have not yet been published; we hope to include results from these trials in the next update of the review (STOP CLOT; TIPPS).

Two of the studies which were otherwise eligible for inclusion did not report on any of the review's primary or secondary outcomes but focused instead on the laboratory results of blood samples taken from women receiving thromboprophylactic agents (Ellison 2001; Harenberg 1993). More information on these studies is provided in the Characteristics of included studies tables, but these studies have not contributed data to the analyses in the review. One further study, otherwise eligible for inclusion (Cornette 2002) examined the timing of LMW heparin with the first dose administered during versus after caesarean; again we have included details of this study in the Characteristics of included studies tables and have provided a brief summary of results, but we have not included it in any treatment comparisons in the review. In the results section below we will describe findings for those 13 included studies which contributed data to the review.

Included studies

Although 16 studies met the eligibility criteria for inclusion, only 13 studies contributed data for the outcomes of interest.

Eight of the studies evaluated thromboprophylaxis after (or during and after) caesarean section, but there was a range of different comparisons; two studies compared LMWH with placebo (Burrows 2001; Gates 2004a;), one compared UFH with placebo (Hill 1988); one UFH with physiotherapy compared with physiotherapy alone (Welti 1981); three LMWH with UFH (Gibson 1998; Heilmann 2007; Krauss 1994), and one UFH and HES with placebo (Heilmann 1991).

Four studies assessed antenatal, or antenatal and postnatal, thromboprophylaxis. Two studies compared LMWH with UFH (Casele 2006; Pettila 1999); one compared LMWH with placebo (Gates 2004b); and one compared UFH with no treatment in the antenatal period (Howell 1983).

Finally, one study focused on the postnatal period alone, with UFH compared with no treatment (Segal 1975).

Excluded studies

We excluded 16 studies. Several of the studies that may otherwise have been eligible were excluded as their primary focus was, for example, on the prevention of recurrent miscarriage and not on the prevention of TED; they had no information on the review's outcomes relating to TED and, indeed, may have explicitly excluded women known to be at high risk of thromboembolism (Badawy 2008; Brenner 2005; Chistolini 2006; De Vries 2005; Dendrinos 2007; Middeldorp 2005; Rey 2009; Stephenson 2004; Thaler 2004; Tulppala 1997). (Related Cochrane reviews specifically examine the issue of prevention of recurrent miscarriage (Empson 2005; Kaandorp 2009).) We excluded four studies

because they did not use random allocation of women to groups (Blomback 1998; Kutteh 1996a; Kutteh 1996b; Noble 2005).

Risk of bias in included studies

Most of the included studies were not of high methodological quality. Many of the reports did not include information on the methods of randomisation, blinding, baseline characteristics or non-trial treatments received by the groups being compared.

Allocation

Generation of the randomisation sequence was adequate in four trials (Casele 2006; Gates 2004a; Gates 2004b; Pettila 1999) and unclear in 10 trials (Burrows 2001; Cornette 2002; Gibson 1998; Heilmann 2007; Heilmann 1991; Hill 1988; Howell 1983; Krauss 1994; Segal 1975; Welti 1981). Methods of sequence generation reported included: random numbers table in one study (Casele 2006) a central telephone randomisation service in two studies (Gates 2004a; Gates 2004b), and a computer generated list (Pettila 1999). Methods of allocation concealment included using pre-prepared treatment packs dispensed by hospital pharmacy departments in four studies (Burrows 2001; Gates 2004a; Gates 2004b; Hill 1988), and sealed opaque envelopes in two studies (Howell 1983; Pettila 1999).

Blinding

Blinding was poorly reported in many of the included studies, and was either inadequate or unfeasible in the rest. Only three studies reported adequate attempts to blind patients, clinicians and/or outcome assessors.

Only five of the 16 trials included a placebo control (Burrows 2001; Gates 2004a; Gates 2004b; Heilmann 1991; Hill 1988) and one of these (Heilmann 1991) involved the use of HES, an intervention no longer used for thromboprophylaxis (Paull 1987). Most of the trials without a placebo did not blind patients, caregivers or outcomes assessors, and in the remainder blinding was unclear. As the treatments were markedly different for the intervention and control groups in these trials, it can be assumed that there was no blinding of participants and clinicians.

Incomplete outcome data

In 10 trials there were no losses to follow up reported, although two of these trials (Gibson 1998; Krauss 1994) did not specify whether any women were excluded from the analysis. We have assumed that data were recorded for all women randomised, and while two further studies appeared to have no losses to follow up (Segal 1975; Welti 1981) both reported very little methodological detail. Two trials stated that some women who were randomised were excluded from the analysis. In one trial two women were excluded because of withdrawal of consent (Pettila 1999), and no data were available for these individuals. In the other trial (Howell 1983) the number of exclusions varied between the tables in the original paper, but it was possible from the text to establish the outcomes for all randomised women. In one study (Casele 2006) 22 of 120 (18%) women were lost to follow up; however, data were available for some outcomes. As a result, all women were accounted for in some analyses, but not for the main study outcome (bone mass of the proximal femur), and denominators were not always clear.

Other potential sources of bias

In general the sample sizes of the trials were small. The three largest trials recruited 580 women (Welti 1981), 220 women (Segal 1975) and 207 women (Heilmann 1991). Sample sizes of this order are inadequate to detect any difference in the incidence of rare outcomes such as thromboembolic events. This is particularly true for trials comparing two thromboprophylactic regimens, rather than comparing prophylaxis with placebo or no treatment, because the difference expected between two methods of prophylaxis is likely to be much smaller than that between prophylaxis and placebo or no treatment. Meta-analysis could not greatly increase the power of individual comparisons because of the variety of different treatments being compared in different patient populations.

There were too few studies contributing data to allow us to examine possible publication bias.

The assessments of risk of bias in the included studies are set out in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

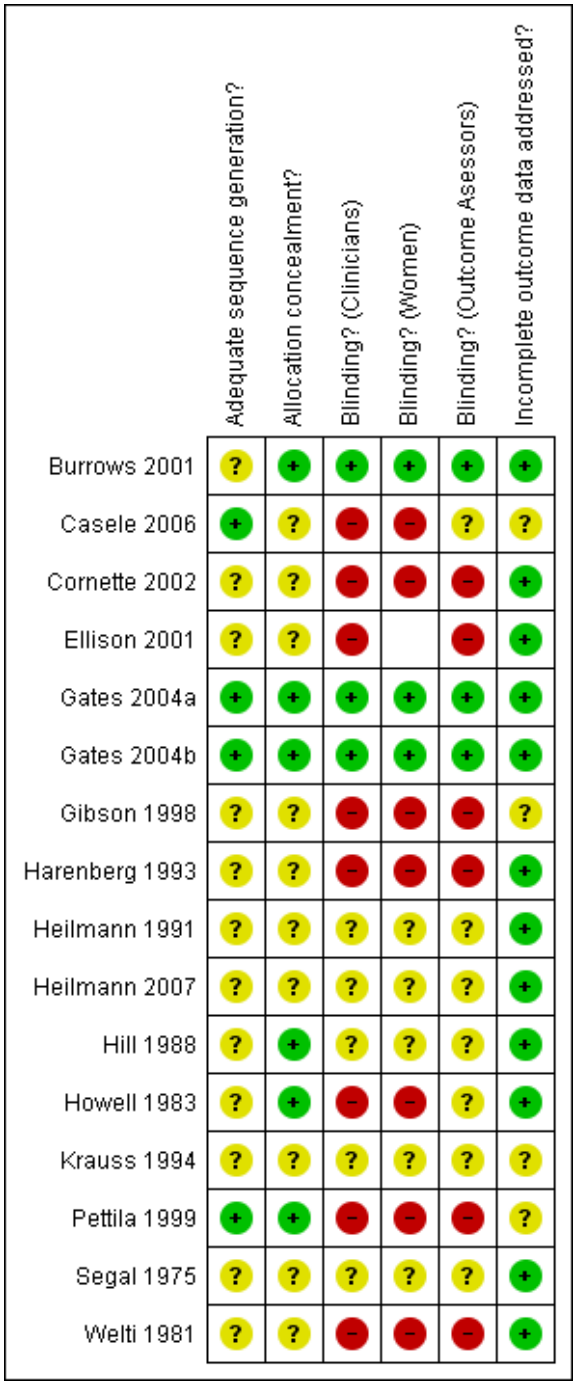
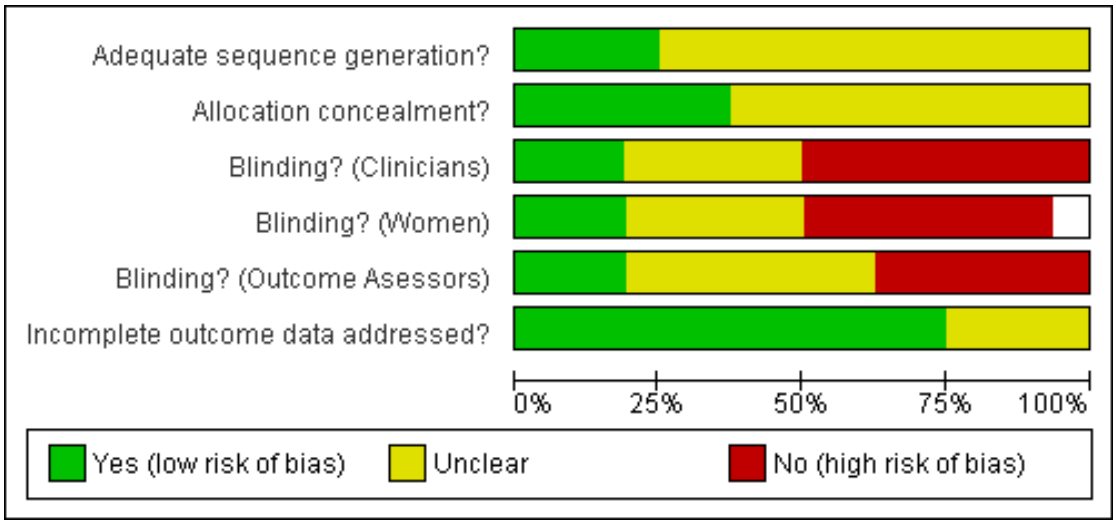


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

Prophylaxis for venous TED: 13 studies with 1774 women

Antenatal prophylaxis

Primary outcomes

LMWH or UFH versus placebo : two studies (Gates 2004b; Howell 1983) with a total of 56 women compared thromboprophylaxis with heparin and placebo, and for most outcomes only one of the studies contributed data to the analyses. Neither study reported whether or not there was any maternal mortality. There was no statistically significant evidence of any difference between groups in the number of symptomatic thromboembolic events; no women in the heparin group had events compared with two in the placebo group (n = 28) (Analysis 1.2; Analysis 1.3; Analysis 1.4).
LMWH versus UFH : two studies (Casele 2006; Pettila 1999) with 178 women examined prophylaxis with LMWH compared with UFH. While there were more symptomatic thromboembolic events in the UFH group, studies did not have sufficient power to detect statistically significant differences between groups (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.09 to 2.49).

Secondary outcomes

LMWH or UFH versus placebo : for several outcomes there were no events reported, and there was no evidence of any significant difference between treatment and control groups for any secondary review outcomes including bleeding episodes, blood transfusion, wound complications, symptomatic osteoporosis, fetal loss or thrombocytopenia (see Analysis 1.5 to Analysis 1.14).
LMWH versus UFH : for antenatal prophylaxis, LMWH may have an advantage over UFH in terms of bleeding episodes; however, data for this outcome were derived from only two studies (Casele 2006; Pettila 1999) and may be at high risk of bias. The rates of bleeding episodes in these two studies were very different, and when we pooled data in meta-analysis there was very high heterogeneity (I^2 = 81%, T^2 = 2.81 and in the Chi^2 test for heterogeneity P = 0.02). In view of such high heterogeneity we decided not to pool data. In the Casele 2006 study, 4/60 in the LMWH and 1/57 in the UFH group were reported to have bleeding episodes (a statistically non-significant difference). In the Pettila 1999 study, the number of women reported to have bleeding episodes was high in both groups (it was not clear what exactly was measured; the authors refer to "bleeding complications" of which only two

were "serious and required blood transfusions"). In this study, 9/50 women in the LMWH group and 35/55 in the UFH group were reported to have bleeding. This difference, favouring LMWH, is statistically significant but needs to be interpreted with caution. This was an unblinded study with what could be considered as an extremely high rate of bleeding episodes. The lack of blinding and knowledge of treatment allocation may have influenced clinicians' judgements about bleeding.

For other secondary outcomes including rates of blood transfusion (Analysis 2.6), side effects sufficient to stop treatment (Analysis 2.9), symptomatic osteoporosis (Analysis 2.11) and thrombocytopenia (Analysis 2.13), there was no evidence of a clinically important difference between groups. Rates of fetal loss were relatively high in the studies included in this comparison, with the loss of 5/110 in the LMWH group and 8/112 in the UFH group; but there was no significant evidence of a difference between treatment groups (RR 0.61, 95% CI 0.21 to 1.77).

Prophylaxis for women undergoing caesarean section

Primary outcomes

LMWH or UFH versus placebo: four studies with 830 women contributed data to this comparison (Burrows 2001; Gates 2004a; Hill 1988; Welti 1981). There was no evidence of a difference between groups for symptomatic thromboembolic events (RR 1.30, 95% CI 0.39 to 4.27) with similar numbers of women in each group experiencing DVT or PE.

LMWH versus UFH : we included three studies with 217 women in this comparison (Gibson 1998; Heilmann 2007; Krauss 1994); overall, there was one symptomatic thromboembolic event (one women with a DVT), and no significant evidence of a difference between groups (RR 0.33, 95% CI 0.01 to 7.99).

HES versus UFH : the study included in this comparison did not report results for symptomatic thromboembolic events (Heilmann 1991).

Secondary outcomes

LMWH or UFH versus placebo: for most secondary review outcomes including blood transfusion (Analysis 3.6), wound complications (Analysis 3.8), and side effects (Analysis 3.9; Analysis 3.10) there was no statistically significant evidence of any differences between groups. There was some evidence that women receiving heparin were more likely to experience bleeding episodes compared to women receiving placebo or no treatment. In all, 46 of the 380 women in the heparin group had bleeding compared with 10 of the 416 controls (RR 5.15, 95% CI 2.64 to 10.05).

LMWH versus UFH: studies included in this comparison did not report results for any of the review's secondary outcomes, except authors of one study reported that there were no bleeding episodes amongst women in either group (Gibson 1998).

HES versus UFH : there was no significant evidence of differences between groups for blood transfusion, bleeding episodes or wound complications (Analysis 5.6; Analysis 5.7; Analysis 5.8); results were not reported for other secondary outcomes.

Postnatal prophylaxis

UFH versus no treatment: one study (Segal 1975) examined postnatal prophylaxis and there was no significant difference between groups for symptomatic VTE events (Analysis 6.1) and no results were reported for any of the review's secondary outcomes.

DISCUSSION

Summary of main results

Overall, few statistically significant differences for any comparison were detected in the included studies. In particular we were unable to detect any statistically significant difference in any of the four primary outcomes of the review.

Maternal deaths were not reported in any of the included studies and symptomatic thromboembolic events were not reported by every included study, so that for many comparisons only one study contributed data to the analyses. As a consequence, given the small number of included studies and their relatively small sample sizes, most analyses lacked the power to detect differences in these rare outcomes even if they did exist.

For secondary outcomes, most of the included studies did not provide data, and where they did, there were few statistically significant findings. Some results appear to show differences between the groups. For antenatal prophylaxis, LMWH seems to be associated with fewer bleeding episodes following treatment compared with UFH. However, results were derived from two small studies; there were high rates of bleeding reported in one of them and the lack of blinding in this study may mean that it is at high risk of bias (Pettila 1999). Further, it is not clear how bleeding was defined in this trial. For prophylaxis for women undergoing caesarean section there was some evidence (from nearly 800 women) that, compared with placebo control, women receiving heparin (either low molecular weight or unfractionated) had more bleeding episodes (RR 5.15, 95% CI 2.64 to 10.05).

Overall, in view of the small number of studies included, the number of different comparisons, and the generally small size of trials, there is insufficient evidence of the benefits or harm associated with thromboprophylaxis.

Overall completeness and applicability of evidence

As already noted, there is a lack of evidence about key indicators of thromboprophylaxis benefit and harm, in particular maternal mortality. However, we cannot assume that because maternal deaths were not reported none occurred. There was a general lack of information about the performance of thromboprophylactic agents in regard to other important secondary outcomes such as asymptomatic thromboembolic events (which may be related to rates of symptomatic events) and bleeding complications.

None of the included studies focused on mechanical methods of prophylaxis (compression stockings or intermittent pneumatic compression devices). Furthermore, many of the studies were quite dated and included thromboprophylaxis methods which are no longer used (such as HES) or are not used as frequently in current thromboprophylactic practice (such as the use of UFH rather than LMWH).

The focus of this review was on the prevention of venous TED in pregnancy and the postpartum period; further evidence on the use of heparin and other thromboprophylactic drugs on the prevention of miscarriage and other pregnancy outcomes are examined in related Cochrane reviews (Empson 2005; Kaandorp 2009; Walker 2003).

Quality of the evidence

The small number of statistically significant findings in this review are largely derived from trials which are not of high methodological quality. Hence, there is a strong possibility that they may be caused by bias or chance. These results need to be confirmed by larger studies before they can be regarded as reliable. Furthermore, these trials were too small to assess the effects of their interventions on other outcomes such as death and thromboembolic events. It is therefore unsafe to conclude that the interventions that appear superior are in fact to be preferred, as they may have important undetected effects on other outcomes.

Agreements and disagreements with other studies or reviews

Related Cochrane reviews examine pharmacological and non-pharmacological means of thromboprophylaxis in a range of patient groups including those with chronic illness or following surgery (e.g. Alikhan 2009; Kakkos 2008; Ramos 2008; Testroote 2008). In a review focusing on thromboprophylaxis in general medical patients, Alikhan 2009 et al suggest that both LMWH and UFH may reduce risk of thromboembolism, but are associated with increased risk of both minor and major bleeding episodes; this increased risk of haemorrhage was less with LMWH. However, reviews which examine outcomes in non-pregnant groups at risk of thromboembolism may not be relevant during pregnancy when the physiological mechanisms controlling blood coagulation are altered, and the risks of TED and the side effects of thromboprophylaxis may be different. Further, during pregnancy the risk to the developing fetus from pharmacological methods of thromboprophylaxis is an important consideration in the choice of method.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence available from RCTs to guide clinical decision-making. In the absence of clear RCT evidence practitioners must rely on consensus derived clinical practice guidelines, such as those produced by the Royal College of Obstetricians and Gynaecologists and the National Institute for Clinical Excellence (NICE) in the UK (NICE 2004; RCOG 2009), and the American College of Chest Physicians (Bates 2008). The RCOG 2009 guidelines recommend that all women should be assessed in early pregnancy for risk of VTE, and those assessed as being at high and persistent risk during pregnancy and after caesarean should be considered for thromboprophylaxis.

Implications for research

There is a clear need for rigorously conducted large scale RCTs with sample sizes sufficiently large to assess the effects of methods of thromboprophylaxis on rare outcomes such as thromboembolic events. Future trials should compare prophylaxis with no prophylaxis and ideally should use a placebo controlled and fully blinded design, to minimise the risk of bias if clinicians become aware of the allocations. No trials have yet assessed non-pharmacological methods of thromboprophylaxis during pregnancy and the postnatal period. The low number of eligible women makes conducting trials of antenatal thromboprophylaxis extremely challenging. To achieve an adequate sample size, a trial would need to be conducted in a very large number of centres, which might require international collaboration. Trials of prophylaxis after caesarean section are much more feasible, even though the incidence of TED is lower and the sample size would therefore need to be even larger (possibly in excess of 10,000). The very high number of caesarean section operations performed means that a trial could be completed within a relatively short time frame and reasonable number of centres. Given the difficulties in recruiting women to trials of prophylaxis for venous TED in pregnancy and the early postnatal period, if all women being considered for prophylaxis could be randomised (with appropriate informed consent), the needed evidence about safety and effectiveness could be obtained most quickly.

ACKNOWLEDGEMENTS

We would like to thank Dr CG Taylor for information about the Hill 1988 trial and additional data for this study, and Prof R Burrows for additional information about the Burrows 2001 trial. Thanks also to Penny Berry for translating the two studies published in German.

REFERENCES

References to studies included in this review

Burrows 2001 *{published data only}*

Burrows RF, Gan ET, Gallus AS, Wallace EM, Burrows EA. A randomised, double blind placebo controlled trial of low molecular weight heparin as prophylaxis in preventing venous thromboembolic events after caesarean section: a pilot study. *BJOG: an international journal of obstetrics and gynaecology* 2001; **108**:835–9.

Casele 2006 *{published data only}*

Casele H. Thrombosis prophylaxis in pregnancy. www.enh.org (accessed 14 June 2005).

Casele H, Haney E, James A, Rosene-Montella K, Carson M. Bone density changes in women receiving thromboprophylaxis in pregnancy [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S14.

* Casele H, Haney EI, James A, Rosene-Montella K, Carson M. Bone density changes in women who receive thromboprophylaxis in pregnancy. *American Journal of Obstetrics and Gynecology* 2006; **195**:1109–13.

Cornette 2002 *{published data only}*

Cornette J, Jacquemyn Y, Vercauteren M, Buytaert P. A randomised trial to compare the effect of pre- or postoperative nandroparin on blood loss during elective caesarean section. *Phlebology* 2002;**17**: 67–9.

Ellison 2001 *{published data only}*

* Ellison J, Thomson AJ, Conkie JA, McCall F, Walker ID, Greer IA. Thromboprophylaxis following caesarean section. A comparison of the antithrombotic properties of three low molecular weight heparins - dalteparin, enoxaparin and tinzaparin. *Thrombosis and Haemostasis* 2001;**86**:1374–8.

Ellison J, Thomson AJ, Walker ID, Greer IA. Comparisons of the anti-factor XA activities of three commonly used low molecular weight heparins following caesarean section. *Scottish Medical Journal* 2000;**45**(3):94–5.

Ellison J, Thomson AJ, Walker ID, Greer IA. Thromboprophylaxis following caesarean section: comparison of the anti-factor Xa activities of dalteparin, enoxaparin and tinzaparin. *BJOG: an international journal of obstetrics and gynaecology* 2000;**107**:823.

Gates 2004a *{published data only}*

Brocklehurst P, Gates S. Randomised controlled trial (PEACH) and meta-analysis of thromboprophylaxis using low-molecular weight heparin (enoxaparin) after caesarean section. *Journal of Obstetrics and Gynaecology* 2002;**22**(2 Suppl):S52.

Brocklehurst P, Thromboprophylaxis in Pregnancy Advisory Group. Thromboprophylaxis in pregnancy trials: apple, plum and peach. *British Journal of Obstetrics and Gynaecology* 1998;**105 Suppl 17**:53.

* Gates S, Brocklehurst P, Ayers S, Bowler U. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low molecular weight heparin. *American Journal of Obstetrics and Gynecology* 2004;**191**:1296–303.

National Perinatal Epidemiology Unit. The PEACH Study. www.npeu.ox.ac.uk/trials/peach.html (accessed 12 January 2001).

Gates 2004b *{published data only}*

Brocklehurst P, Thromboprophylaxis in Pregnancy Advisory Group. Thromboprophylaxis in pregnancy trials: apple, plum and peach. *British Journal of Obstetrics and Gynaecology* 1998;**105 Suppl 17**:53.

* Gates S, Brocklehurst P, Ayers S, Bowler U. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low molecular weight heparin. *American Journal of Obstetrics and Gynecology* 2004;**191**:1296–303.

Gates S, Brocklehurst P, Davis LJ. Antenatal thromboprophylaxis using low molecular weight heparin (enoxaparin) for women at risk of thromboembolic disease: multicentre placebo controlled randomised trial (APPLE) and systematic review. *Journal of Obstetrics and Gynaecology* 2002;**22**(2 Suppl):S44.

National Perinatal Epidemiology Unit. The APPLE Study. www.npeu.ox.ac.uk/trials/apple.html (accessed 12 January 2001).

Gibson 1998 *{published data only}*

Gibson JL, Ekevall K, Walker I, Greer IA. Puerperal thromboprophylaxis: comparison of the anti-Xa activity of enoxaparin and unfractionated heparin. *British Journal of Obstetrics and Gynaecology* 1998;**105**:795–7.

Harenberg 1993 *{published data only}*

Harenberg J, Schneider D, Heilmann L, Wolf H. Lack of anti-factor Xa activity in umbilical cord vein samples after subcutaneous administration of heparin or low molecular mass heparin in pregnant women. *Haemostasis* 1993;**23**:314–20.

Heilmann 1991 *{published data only}*

Heilman L, Heitz R, Koch FU, Ose C. Perioperative thrombosis prophylaxis at the time of caesarean section: results of a randomised prospective comparative study with 6% hydroxyethyl starch 0.62 and low dose heparin [Die perioperative Thromboseprophylaxe beim Kaiserschnitt: Ergebnisse einer randomisierten prospektiven Vergleichsuntersuchung mit 6% Hydroxyathylstarke 0,62 und Low–dose–Heparin]. *Zeitschrift fur Geburtshilfe und Perinatologie* 1991;**195**:10–5.

Heilmann 2007 *{published data only}*

Heilmann L, Rath W, Pollow K, Bick RL. The rheological changes after cesarean section: the influence of low molecular weight or unfractionated heparin on the rheological properties of blood. *Clinical Hemorheology and Microcirculation* 2007;**37**:211–8.

Hill 1988 *{published and unpublished data}*

* Hill NCW, Hill JG, Sargent JM, Taylor CG, Bush PV. Effect of low dose heparin on blood loss at caesarean section. *BMJ* 1988; **296**:505–6.

Hill NCW, Hill JG, Sargent JM, Taylor CG, Bush PV. The effect of low dose heparin on blood loss at caesarean section. 12th FIGO World Congress of Gynecology and Obstetrics; 1988 October 23-28; Brazil. 1988.

Howell 1983 *{published data only}*

Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. *British Journal of Obstetrics and Gynaecology* 1983;**90**:1124–8.

Krauss 1994 *{published data only}*

Krauss T, Rath W, Dittmer U, Kuhn W. Use of LMW heparin (Fragmin) for the prevention of thromboembolism in obstetrics [Thromboembolieprophylaxe mit niedermolekularen Heparin (Fragmin)in der Geburtshilfe]. *Zeitschrift fur Geburtshilfe und Perinatologie* 1994;**198**:120–5.

Pettila 1999 *{published data only}*

* Pettila V, Kaaja R, Leinonen P, Ekblad U, Kataja M, Ikkala E. Thromboprophylaxis with low molecular weight heparin (dalteparin) in pregnancy. *Thrombosis Research* 1999;**96**:275–82.

Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. *Thrombosis and Haemostasis* 2002;**87**(2):182–6.

Segal 1975 *{published data only}*

Segal S, Sadovsky E, Weinstein D, Polishuk WZ. Prevention of postpartum venous thrombosis with low doses of heparin. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1975;**5**:273–6.

Welti 1981 *{published data only}*

Welti H. Prevention of thromboembolism by physiotherapy with and without low dose heparin in gynecology and obstetrics. Results of a controlled, randomized multicenter study [Prophylaxie thrombo–embolique par physiotherapie avec et sans heparine a faibles doses en gynecologie–obstetrique]. *Revue Medicale de la Suisse Romande* 1981;**101**(11):925–34.

References to studies excluded from 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.

Blomback 1998 *{published data only}*

Blomback M, Bremme K, Hellgren M, Lindberg H. A pharmacokinetic study of dalteparin (Fragmin) during late pregnancy. *Blood Coagulation and Fibrinolysis* 1998;**9**:343–50.

Brenner 2005 *{published data only}*

* Brenner B, Bar J, Ellis M, Yarom I, Yohai D, Samueloff A, et al.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 & Sterility* 2005;**84**(3):770–3.

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 [abstract]. *Blood* 2002;**100**(11 Pt 1):702a.

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 [abstract]. *Journal of Thrombosis and Haemostasis* 2003;**1**(Suppl 1):OC084.

Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J, LIVE-ENOX investigators. 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**: 227–9.

Chistolini 2006 *{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.

De Vries 2005 *{published data only}*

De Vries JIP. Low molecular weight heparin (Fragmin (R)) in pregnant women with a history of uteroplacental insufficiency and thombophilia, a randomized trial (FRUIT-study). Netherlands Trial Register (http://www.trialregister.nl) (accessed 1 November 2005).

Dendrinos 2007 *{published data only}*

Dendrinos S, Kalogirou I, Makrakis E, Theodoridis T, Mahmound EA, Christopoulou-Cokkinou V, et al.Safety and effectiveness of tinzaparin sodium in the management of recurrent pregnancy loss. *Clinical and Experimental Obstetrics and Gynecology* 2007;**34**(3): 143–5.

Farquharson 2002 *{published data only}*

Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstetrics & Gynecology* 2002;**100**(3):408–13.

Kutteh 1996a *{published data only}*

Kutteh WH, Ermel LD. A clinical trial for the treatment of antiphospholipid antibody-associated recurrent pregnancy loss with lower dose heparin and aspirin. *American Journal of Reproductive Immunology* 1996;**35**:402–7.

Kutteh 1996b *{published data only}*

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**(5):1584–9.

Middeldorp 2005 *{published data only}*

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).

Noble 2005 ***{published data only}***
Noble LS, Kutteh WS, Lashey N, Franklin RD, Herrada J. Antiphospholipid antibodies associated with recurrent pregnancy loss: prospective, multicenter, controlled pilot study comparing treatment with low-molecular-weight heparin versus unfractionated heparin. *Fertility & Sterility* 2005;**83**(3):684–90.

Rai 1997 ***{published data only}***
Cohen H. Randomized trial of aspirin versus aspirin and heparin in pregnant women with the antiphospholipid syndrome. *Annales de Medicine Interne* 1996;**147 Suppl 1**:44.
* 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.

Rey 2009 ***{published data only}***
Rey E. Dalteparin in prevention of recurrence of severe obstetrical complications in women without thrombophilia. *JOGC: Journal of Obstetrics and Gynaecology Canada* 2007;**29**(6 Suppl 1):S46.
* 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.

Stephenson 2004 ***{published data only}***
Stephenson MD, Ballem PJ, Tsang P, Purkiss S, Ensworth S, Houlihan E, et al.Treatment of antiphospholipid antibody syndrome (aps) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin. *Journal of Obstetrics & Gynaecology Canada: JOGC* 2004;**26**(8):729–34.

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

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

References to studies awaiting assessment

De Veciana 2001 ***{published data only}***
De Veciana M, Trail P, Dattel B, Slotnick RN, Abuhamad A. Dalteparin versus unfractionated heparin for prophylactic anticoagulation during pregnancy [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**185**(6):S182.

Dittmer 1991 ***{published data only}***
Dittmer U, Rath W, Schrader J, Zuchner C, Scheler F, Kuhn W. Prevention of deep vein thrombosis (DVT) in pregnancy, after caesarean section and after gynaecological abdominal surgery. A comparison between low molecular weight heparin (LMW) and standard heparin (UFH) [abstract]. *Annals of Haematology* 1991;**62 Suppl 1**:A40.

Hamersley 1998 ***{published data only}***
Hamersley S, Landy H. Low molecular weight heparin is associated with less peripartum blood loss than unfractionated heparin [abstract]. *American Journal of Obstetrics and Gynecology* 1998;**178** (1 Pt 2):S66.

Kamin 2008 ***{published data only}***
Kamin G, Rogenhofer N, Pildner v. Steinberg S, Neuhoffer A, Seeger S, Schleussner E. 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.

References to ongoing studies

STOP CLOT ***{published data only}***
Rodger M. The STOP CLOT pilot study: study of low molecular weight heparin in high risk postpartum women following cesarean section (ongoing trial). ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 21 March 2006).
Rodgers M. Thrombophilia in pregnancy prophylaxis study (TIPPS). Ottawa Health Research Institute (http://www.ohri.ca) (accessed 17 July 2002).

TIPPS ***{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 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**: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.

Additional references

Alfirevic 2002
Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2002;**101**(1):6–14.

Alikhan 2009

Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD003747.pub2]

Andersen 1998

Andersen BS, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. The cumulative incidence of venous thromboembolism during pregnancy and puerperium - an 11 year Danish population - based study of 63,300 pregnancies. *Acta Obstetricia et Gynecologia Scandinavica* 1998;**77**:170–3.

Atrash 1990

Atrash HK, Koonin LM, Lawson HW, Franks AL, Smith JC. Maternal morbidity in the United States 1979-1986. *Obstetrics & Gynecology* 1990;**76**:1055–60.

Barbour 1997

Barbour LA. Current concepts of anticoagulant therapy in pregnancy. *Obstetrics and Gynecology Clinics of North America* 1997; **24**:499–521.

Bates 2008

Bates S, Greer I, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. *Chest* 2008;**133**:844S–886S.

Brenner 2003

Brenner B. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications--Yes. *Journal of Thrombosis & Haemostasis* 2003;**1**(10):2070–2.

Brill-Edwards 2000

Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C et al for The Recurrence of Clot in This Pregnancy Study Group. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *New England Journal of Medicine* 2000; **343**:1439–44.

Conard 1990

Conard J, Horellou MH, van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies of AT III, Protein C or Protein S: study of 78 women. *Thrombosis and Haemostasis* 1990;**63**:319–20.

Connolly 2003

Connolly T. Thromboembolism prophylaxis and cesarean section: a survey of general obstetricians. *Southern Medical Journal* 2003;**96** (2):146–8.

Dargaud 2005

Dargaud Y, Rugeri L, Ninet J, Negrier C, Trzeciak MC. Management of pregnant women with increased risk of venous thrombosis. *International Journal of Gynecology & Obstetrics* 2005; **90**(3):203–7.

De Stefano 2006

De Stefano V, Martinelli I, Rossi E, Battaglioli T, Za T, Mannuccio MP, et al.The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. *British Journal of Haematology* 2006;**135**(3):386–91.

Dept of Health 1998

Department of Health. Why mothers die. *Report of the Confidential Enquiries into Maternal Deaths 1994-1996*. London: HMSO, 1998.

Empson 2005

Empson MB, Lassere M, Craig JC, Scott JR. 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]

Friederich 1996

Friederich P, Sanson B-J, Simioni P, Zanardi S, Huisman MV, Kindt I, et al.Frequency of pregnancy-related venous thromboembolism in anticoagulant factor deficient women: implications for prophylaxis. *Annals of Internal Medicine* 1996;**125**:955–60.

Gherman 1999

Gherman RB, Goodwin TM, Leung B, Byrne JD, Hethumumi R, Montoro M. Incidence, clinical characteristics and timing of objectively diagnosed venous thromboembolism during pregnancy. *Obstetrics & Gynecology* 1999;**94**:730–4.

Hall 1980

Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *American Journal of Medicine* 1980;**68**:122–40.

Heit 2005

Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Annals of Internal Medicine* 2005;**143**(10): 697–706.

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Högberg 1994

Högberg U, Innala E, Sandstrom A. Maternal mortality in Sweden, 1980-1988. *Obstetrics & Gynecology* 1994;**84**:240–4.

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]

Kakkos 2008

Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD005258.pub2.]

Knight 2001

Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD000492.pub2]

Larciprete 2007

Larciprete G, Gioia S, Angelucci PA, Brosio F, Barbati G, Angelucci GP, et al.Single inherited thrombophilias and adverse pregnancy

outcomes. *Journal of Obstetrics and Gynaecology Research* 2007;**33** (4):423–30.

Letsky 1997
Letsky EA. Peripartum prophylaxis of thrombo-embolism. *Bailliere's Clinical Obstetrics and Gynaecology* 1997;**11**:523–43.

Lewis 2004
Lewis G. *Why mothers die, 2000-2002. The Sixth Report of Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: RCOG Press, 2004.

Lindhagen 1986
Lindhagen A, Bergqvist A, Bergqvist D, Hallbook T. Late venous function in the leg after deep venous thrombosis occurring in relation to pregnancy. *British Journal of Obstetrics and Gynaecology* 1986;**93**:348–52.

Lindqvist 1999
Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. *Obstetrics & Gynecology* 1999;**94**: 595–9.

Macklon 1996
Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. *Scottish Medical Journal* 1996;**41**:83–6.

Middeldorp 2003
Middeldorp S. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications--No. *Journal of Thrombosis & Haemostasis* 2003;**1**(10):2073–4.

Nelson-Piercy 1997
Nelson-Piercy C. Hazards of heparin: allergy, heparin-induced thrombocytopenia and osteoporosis. *Bailliere's Clinical Obstetrics and Gynaecology* 1997;**11**:489–509.

NICE 2004
National Collaborating Centre for Women's and Children's Health. Commissioned by NICE. *Caesarean section*. London: RCOG Press, 2004.

Orme 1977
Orme ML, Lewis PJ, de Swiet M, Serlin MJ, Sibeon R, Baty JD, et al.May mothers given warfarin breast-feed their infants?. *BMJ* 1977;**1**(6076):1564–5.

Paull 1987
Paull J. A prospective study of dextran-induced anaphylactoid reactions in 5745 patients. *Anaesthesia and Intensive Care* 1987;**15**: 163–7.

PEP Trial 2000
PEP Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin. *Lancet* 2000;**355**:1295–302.

Pomp 2008
Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *Journal of Thrombosis & Haemostasis* 2008;**6**(4):632–7.

Ramos 2008
Ramos J, Perrotta C, Badariotti G, Berenstein G. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD005259.pub3]

RCOG 2009
Royal College of Obstetricians and Gynaecologists. *Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37*. London: RCOG, November 2009.

RevMan 2008
The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

Rutherford 1991
Rutherford S, Montoro M, McGehee W, Strong T. Thromboembolic disease associated with pregnancy: an 11 year review. *American Journal of Obstetrics and Gynecology* 1991;**164**: 286.

Simpson 2001
Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. *BJOG: an international journal of obstetrics and gynaecology* 2001; **108**(1):56–60.

Taylor 2000
Taylor GM, McKenzie CA, Mires GJ. Use of a computerised maternity information system to improve clinical effectiveness: thromboprophylaxis at caesarean section. *Postgraduate Medical Journal* 2000;**76**(896):354–6.

Testroote 2008
Testroote M, Stigter WAH, de Visser DC, Janzing HMJ. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD006681.pub2]

Walker 2003
Walker MC, Ferguson FE, Allen VM. Heparin for pregnant women with acquired or inherited thrombophilias. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD003580]

Wu 2005
Wu O, Robertson L, Twaddle S, Lowe G, Clark P, Walker I, et al.Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *British Journal of Haematology* 2005;**131**(1):80–90.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Burrows 2001

Methods	Postnatal prophylaxis after caesarean section. Randomisation after surgery. Randomisation method not stated. Placebo controlled.
Participants	1 centre in Australia. 76 women having elective or emergency caesarean. Exclusions: history of bleeding disorder; anticoagulant therapy; history of TED; heparin sensitivity; recent GI haemorrhage or peptic ulcer; hepatic encephalopathy; renal dysfunction requiring dialysis; uncontrolled hypertension.
Interventions	LMWH (Dalteparin) or matching placebo (saline) once daily for 4-5 days. Started 4-24 hours after caesarean section.
Outcomes	Symptomatic TED. Symptomatic PE. Symptomatic DVT. Blood transfusion. Bleeding episodes. Serious wound complications. Side effects not sufficient to stop treatment.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Yes	Described as "each pack contained prefilled syringes containing either dalteparin or matching placebo".
Blinding? Clinicians	Yes	See above.
Blinding? Women	Yes	See above.
Blinding? Outcome Asessors	Yes	See above.
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up after randomisation.

Casele 2006

Methods	Multi centre RCT in 9 centres in the USA. Individual randomisation in blocks.
Participants	120 women recruited. Inclusion criteria: women requiring thromboprophylaxis in pregnancy (history of blood clot in leg or lung, history of stroke) aged 18 years or more, who could begin therapy at < 24 weeks of gestation. Exclusion criteria: women who were taking heparin because of recurrent pregnancy loss or women with contraindication to anticoagulants.
Interventions	Experimental group (61 women): LMWH (Enoxoparin sodium). Self administered subcutaneous 30 mg twice daily from enrolment until 28 weeks of gestation, then 40 mg twice daily until delivery. Control group (59 women): UFH (heparin sodium). Self administered subcutaneous 7500 units twice daily until 28 weeks, then 10,000 units twice daily until delivery. Baseline bone density test for women in both groups. All women received adjusted dose coudamin for 6-8 weeks after delivery. All women were asked to take prenatal vitamins and were asked to take calcium supplements (500 mg) daily from enrolment until delivery.
Outcomes	Bone mass of the proximal femur (measured at baseline and 4 days after delivery) The power calculation was based on detecting bone mass changes, the original sample estimate required was 240.
Notes	The study was stopped early, the original power calculation had suggested 240 women would be required to detect meaningful changes in loss of bone mass between groups. However, interim analysis suggested that the sample size required would be 1628 and the study was terminated after 120 women had been recruited over 7 years. Women were recruited in 9 centres, no information was provided on recruitment in different centres. It was reported that there was no correlation between bone loss and institution but it is doubtful that with low recruitment that any institution effects on any outcomes would be detected.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table with each site stratified into blocks of 10.
Allocation concealment?	Unclear	Not described.
Blinding? Clinicians	No	Not mentioned.
Blinding? Women	No	Not mentioned.
Blinding? Outcome Asessors	Unclear	It was reported that the radiologists carrying out the bone assessments were blind to group allocation.

Casele 2006 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Some discrepancies in the numbers enrolled and outcomes in the 2 published reports. The main study paper used for outcome data in this review. 120 women randomised. 98 women completed the study (18% attrition) but of the 22 women who were lost to follow up some data were available for some outcomes. It appeared that all women were accounted for in some of the analysis but not for the main study outcome. There were some missing data for main outcomes (bone mass) and denominators were not always clear.

Cornette 2002

Methods	RCT individual randomisation.
Participants	Setting not clear. Study in Antwerp, Belgium. 44 women with full-term singleton pregnancies admitted for elective caesarean section. Exclusion criteria: women with known bleeding or coagulation disorders.
Interventions	Study looking at the TIMING of LMWH comparing pre and post-operative treatment. Experimental group: pre-op, 0.3 ml nandroparin calcium (a LMWH) 12 hours before surgery (n = 22). Control group: 0.3 ml (2850 IU) nandroparin calcium 12 hours after surgery (n = 22). All women received the same fluid regimen before, during and after surgery. Women were allowed to drink freely 6 hours after surgery. It was not clear whether participants received any further doses of LMWH after initial dose.
Outcomes	Haemoglobin and haematocrit concentrations 12 hours before and 48 hours after surgery. The power calculation was based on changes in haemoglobin levels.
Notes	We have not included this study in the analysis as outcomes were not relevant to the the review.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	"randomly divided in two groups."

Cornette 2002 (*Continued*)

Blinding? Clinicians	No	
Blinding? Women	No	
Blinding? Outcome Asessors	No	
Incomplete outcome data addressed? All outcomes	Yes	No loss to follow up apparent.

Ellison 2001

Methods	RCT.
Participants	30 women undergoing caesarean section at risk of thromboembolism.
Interventions	Three arm trial. 1. Dalteparin, 5000 IU once daily (10 women). Enoxaparin 4000 IU once daily (10 women). 3. Tinzaparin 50 IU/kg (based on booking weight) once daily (10 women). Drugs were administered 6 hours following caesarean and were continued for 5 days.
Outcomes	Women were followed up for one day to examine laboratory haemostatic parameters.
Notes	Women in this study had blood samples taken in the first 24 hours after caesarean section. While this study was eligible for inclusion in the review no data relevant to the review's primary or secondary outcomes were reported.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as simple randomisation.
Allocation concealment?	Unclear	Not described.
Blinding? Clinicians	No	Described as single blind.
Blinding? Outcome Asessors	No	
Incomplete outcome data addressed? All outcomes	Yes	All women seem to be accounted for in the analysis

Gates 2004a

Methods	Pilot study. Multi centre RCT with individual randomisation.
Participants	23 hospitals in the UK (women were recruited in only 8 hospitals). 141 women. Women undergoing CS where there was clinical uncertainty that thromboprophylaxis was indicated. Exclusion criteria: women with a known allergy to heparin.
Interventions	Experimental group: once-daily subcutaneous 40 mg enoxoparin (LMWH) in 1ml for up to 14 days following CS. Given by self injection to start no later than 12 hours after caesarean delivery. Control group: once-daily subcutaneous placebo (normal saline 1 ml) for up to 14 days following CS. Trial drugs were packaged identically. Duration of treatment and use of other forms of thromboprophylaxis (eg compression stockings) were at the discretion of attending clinical staff.
Outcomes	Data collection at baseline, at hospital discharge following delivery and at 6 months postpartum. Pilot study: main outcome was the number of women recruited. Clinical outcomes: symptomatic confirmed TED, symptomatic osteoporotic fractures up to 6 months postpartum. Secondary outcomes: DVT, PE, thrombosis during period of prophylaxis, blood transfusion, serious wound complications, bleeding, hospital admission, surgical procedures.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	External randomisation.
Allocation concealment?	Yes	Intervention and identical placebo preparations dispensed by pharmacy.
Blinding? Clinicians	Yes	Identical packaging of trial drugs. Drugs provided to study hospitals. Women, clinical staff and investigators were all described as blind to group allocation.
Blinding? Women	Yes	
Blinding? Outcome Asessors	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Low attrition < 5%. 141 women randomised, data at discharge for 140, and at

Gates 2004a (*Continued*)

		6 months follow up for 132.

Gates 2004b

Methods	Pilot study. Multi centre RCT with individual randomisation.
Participants	23 hospitals in the UK (women were recruited in only 11 hospitals). 16 pregnant women with clinical uncertainty that antenatal thromboprophylaxis was indicated. Recruitment at all gestational ages. Inclusion criteria: women with a history of previous thromboembolic events or women with thrombophilia or another risk factor (all 16 women recruited had had a previous thromboembolic event). Exclusion criteria: women with a known allergy to heparin.
Interventions	Experimental group: self administered once-daily subcutaneous 40 mg enoxoparin (LMWH) in 1 ml from antenatal recruitment until 6 weeks after delivery. Control group: self administered once-daily subcutaneous placebo (normal saline 1 ml) from antenatal recruitment until 6 weeks after delivery.
Outcomes	Data collection at baseline, at hospital discharge following delivery and at 6 months postpartum. Outcomes: pilot study: main outcome was the number of women recruited. Clinical outcomes: symptomatic confirmed TED, symptomatic osteoporotic fractures up to 6 months postpartum. Secondary outcomes: DVT, PE, thrombosis during period of prophylaxis, blood transfusion, serious wound complications, bleeding, hospital admission, surgical procedures, NICU admission for bleeding complications in baby.
Notes	Trial drugs were packaged identically. After delivery some clinicians elected to discontinue study drugs and 3 women in both groups were given heparin postnatally.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Central telephone randomisation service.
Allocation concealment?	Yes	Intervention and identical placebo preparations dispensed by pharmacy.
Blinding? Clinicians	Yes	Identical packaging of trial drugs. Drugs stored in pharmacy and collected by women. Women, clinical staff and pharmacy staff were all described as blind to group allocation.
Blinding? Women	Yes	

Gates 2004b (*Continued*)

Blinding? Outcome Asessors	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Low recruitment to pilot study. All 16 women randomised were followed up until 6 months after delivery. No attrition.

Gibson 1998

Methods	Postnatal prophylaxis after caesarean section. Randomisation methods not stated. No information on blinding - assumed no blinding as drug regimens were different.
Participants	17 women having caesarean section; either emergency or with risk factors for TED.
Interventions	UFH 7500 iu every 12 hours; LMWH (enoxaparin) 20 mg or 40 mg once daily. Intervention started after caesarean section; duration of intervention not stated.
Outcomes	Symptomatic TED. Symptomatic PE. Symptomatic DVT. Bleeding episodes.
Notes	3-way randomisation (UFH/20 mg enoxaparin/40 mg enoxaparin). 2 enoxaparin groups combined for the review.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as 'women were randomised'.
Allocation concealment?	Unclear	Not stated.
Blinding? Clinicians	No	Not feasible.
Blinding? Women	No	Not feasible.
Blinding? Outcome Asessors	No	Not feasible.
Incomplete outcome data addressed? All outcomes	Unclear	No losses to follow up.

Harenberg 1993

Methods	RCT.
Participants	60 pregnant women with no previous indication for thromboprophylaxis.
Interventions	1. UFH, 5000 IU 2 hours prior to delivery (17 women) 2. LMWH 1500 activated partial thromboplastin time units 2 hours before delivery (18 women). 3. No treatment.
Outcomes	Maternal blood and umbilical cord blood samples for prothrombin time and coagulation values.
Notes	While this study was eligible for inclusion in the review, the focus of the study was on blood coagulation parameters and no data relevant to the review's primary or secondary outcomes were reported. Data from this study are not included in the analysis.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	Described as "randomized".
Blinding? Clinicians	No	
Blinding? Women	No	
Blinding? Outcome Asessors	No	
Incomplete outcome data addressed? All outcomes	Yes	No evidence of loss to follow up.

Heilmann 1991

Methods	Intrapartum + postnatal prophylaxis after caesarean section. Method of randomisation not stated. No information on blinding: assumed none as interventions clearly different. All women were screened for thromboses.
Participants	One centre in Germany; 207 women recruited. Eligibility: women delivered by caesarean section.
Interventions	HES 6%, 3 x 500 ml; first 500 ml during the operation, second in the evening of the day of the operation, third in the evening of the first postoperative day. UFH 5000 IU 2 hours before the operation and every 8 hours for 7 days.

Heilmann 1991 (*Continued*)

Outcomes	Asymptomatic TED. Blood transfusion. Bleeding episodes. Serious wound complications.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Unclear	Not stated.
Blinding? Clinicians	Unclear	Not stated.
Blinding? Women	Unclear	Not stated.
Blinding? Outcome Asessors	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up.

Heilmann 2007

Methods	RCT (3 arms).
Participants	100 women undergoing caesarean section in 2 treatment arms (50, 50) and 50 additional matched controls. (Outcome data for the 2 treatment groups only has been included in this review.) "The indication for prophylaxis was the previous diagnosis of a heterozygote factor V-Leiden-mutation." Women with uncomplicated pregnancy and "without risk factors for thrombosis" following elective CS.
Interventions	Experimental groups: (1) 50 women LMWH (Dalteparin 5000 IU/daily for 7 days post op, 1^{st} dose 6 hours post op then every 24 hours). (2) 50 women UFH (Calciparin 5000 IU twice daily, 1^{st} dose 6 hours post op then twice daily). It was not clear if women in either group also received compression stockings. Control group: it was not clear that this group was selected randomly, 50 women received compression stockings but no heparin. Outcome data for this group have not been included in this

Heilmann 2007 (*Continued*)

	review.
Outcomes	DVT.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"The patients were allocated to the treatment group by randomization."
Allocation concealment?	Unclear	Not described.
Blinding? Clinicians	Unclear	Not mentioned.
Blinding? Women	Unclear	Not mentioned.
Blinding? Outcome Asessors	Unclear	Not mentioned.
Incomplete outcome data addressed? All outcomes	Yes	No loss to follow up apparent.

Hill 1988

Methods	Prophylaxis during and after caesarean section. Randomisation by pharmacist not involved in trial. Placebo controlled trial.
Participants	One centre in UK; 50 women. Eligibility: women delivered by caesarean section. Exclusions: complications e.g. multiple pregnancy, APH, previous TED.
Interventions	UFH 1000 units or saline, 1 hour before operation, then twice daily for 5 days.
Outcomes	Symptomatic TED. Symptomatic DVT. Symptomatic PE. Blood transfusion. Serious wound complications.
Notes	

Risk of bias

Item	Authors' judgement	Description

Hill 1988 (*Continued*)

Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Yes	Randomisation by pharmacist not involved in trial.
Blinding? Clinicians	Unclear	Not stated.
Blinding? Women	Unclear	Not stated.
Blinding? Outcome Asessors	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up.

Howell 1983

Methods	Antenatal + intrapartum prophylaxis. Randomisation by sealed envelopes. Recruitment at time of referral to clinic (8-37 weeks' gestational age).
Participants	One centre in UK. 40 women recruited. Eligibility: women who had previously had TED treated with anticoagulants for at least 6 weeks.
Interventions	Calcium heparin antenatally (10000 IU twice daily) and for 6 weeks postpartum (8000 IU twice daily) or for 6 weeks postpartum only.
Outcomes	Symptomatic TED. Bleeding episodes. Symptomatic osteoporosis. Fetal loss.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as "randomised".
Allocation concealment?	Yes	Described as "sealed envelope".
Blinding? Clinicians	No	Not feasible.

Howell 1983 (*Continued*)

Blinding? Women	No	Not feasible.
Blinding? Outcome Asessors	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	Yes	Data could be re-included.

Krauss 1994

Methods	RCT.
Participants	Setting: university hospital, Gottinghen, Germany. 100 women undergoing CS included in the analysis. Exclusion: known heparin allergy, gastro-intestinal ulcers, sever kidney, liver or pancreatic disease or previous cerebral haemorrhage, severe hypertension (RR > 180/120), haemorrhagic diathesis.
Interventions	Experimental group: 50 women. LMWH (fragmin) once daily 2500 to 5000 anti-Xa units. Control group: 50 women 2-3 times daily 5000 units UFH (liquemin) + 500 mL Dextran 60 during caesarean. Treatment for 10 days after surgery.
Outcomes	Thrombosis and side effects.
Notes	Data extraction from translation notes. Original paper in German.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not clear (author confirmed that the allocation to groups was random).
Allocation concealment?	Unclear	Not described.
Blinding? Clinicians	Unclear	Not mentioned.
Blinding? Women	Unclear	Not mentioned.
Blinding? Outcome Asessors	Unclear	Not mentioned.

Krauss 1994 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	No drop-outs or withdrawals.

Pettila 1999

Methods	Antenatal + postnatal prophylaxis. Sealed envelope randomisation. No blinding. 2 women excluded from analysis (withdrawal of consent).
Participants	8 centres in Finland. 107 women recruited. Eligibility: 18 yrs or older, week 0-19 of gestation, any of: (a) previous PE or VTE above knee before current pregnancy; (b) PE or VTE during current pregnancy; (c) previous VTE below knee in association with protein C or protein S deficiency, activated protein C resistance, pregnancy or contraceptive pills.
Interventions	Dalteparin (Fragmin) once daily (starting dose 5000 or 7500 IU, dose adjusted based on anti Xa measurements) or UFH (7500 IU, adjusted according to APTT target values) twice daily. Treatment started before week 20 of gestation and continued for 6 weeks after delivery.
Outcomes	Symptomatic TED. Blood transfusion. Bleeding episodes. Side effects. Symptomatic osteoporosis. Fetal loss.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation "by means of a computer generated procedure".
Allocation concealment?	Yes	"Closed envelope" the randomisation list was kept outside the centres.
Blinding? Clinicians	No	Open design.
Blinding? Women	No	Open design.
Blinding? Outcome Asessors	No	Open design.
Incomplete outcome data addressed? All outcomes	Unclear	2 participants lost to follow up after randomisation.

Segal 1975

Methods	Very little information on study methods. RCT - individual randomisation.
Participants	Setting: 1973, Jerusalem, Israel. 220 randomised (not clear). Women identified with varicose veins before delivery (236). Exclusions: 26 with a history of thrombosis were treated with heparin.
Interventions	Experimental group: 116 women. Heparin 50 mg (5000 IU) subcutaneous heparin every 12 hours for 4-5 days after delivery (time of initial dose varied, for those having vaginal delivery about two-thirds had the first dose in active labour (2-3 cm) and a third after delivery, women having CS the first dose was 2 hrs before). Control group: 94 women. Care in the comparison group was not described**,** there did not seem to be a placebo (routine care/no heparin).
Outcomes	Superficial or deep vein thrombosis. Assessment by clinical signs and symptoms by the investigators (pain, swelling, tenderness, tachycardia, fever). Assessed daily during treatment and at 6 weeks postpartum.
Notes	Very little information on methods was provided. There seemed to be some baseline imbalance between groups with 16/94 in the control group having a caesarean section versus 6/116 in the intervention group.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"divided at random."
Allocation concealment?	Unclear	No information.
Blinding? Clinicians	Unclear	Not stated.
Blinding? Women	Unclear	Not stated.
Blinding? Outcome Asessors	Unclear	Not clear. There did not seem to be any placebo, but it was stated that the outcome assessors were blind to group allocation.
Incomplete outcome data addressed? All outcomes	Yes	All women seem to have been followed up.

Welti 1981

Methods	RCT.
Participants	Setting not clear, authors from university hospital, obstetric and gynaecology department, Lausanne, Switzerland. Study included women undergoing surgery for gynaecological indications. We include in the analysis 580 women undergoing caesarean section (both emergency and elective).
Interventions	Experimental group: 272 women. Physiotherapy and twice daily subcutaneous 5000 IU heparin (UFH). Control group: 308 women. Physiotherapy alone (no heparin).
Outcomes	Thromboembolic events, bleeding complications.
Notes	Data extraction from translation notes and tables in the paper (original paper in French) .

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Unclear	The study was conducted "selon le principle de la randomisation fermee".
Blinding? Clinicians	No	There did not appear to be any placebo.
Blinding? Women	No	
Blinding? Outcome Asessors	No	
Incomplete outcome data addressed? All outcomes	Yes	It appeared that all women were followed up.

APH: antepartum haemorrhage
CS: caesarean section
DVT: deep vein thrombosis
GI: gastrointestinal
IU: international units
LMWH: low molecular weight heparin
NICU: neonatal intensive care unit
PE: pulmonary embolism
RCT: randomised controlled trial
TED: venous thromboembolic disease
UFH: unfractionated heparin
yrs: years

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

Badawy 2008	The primary focus of this study was on fetal loss and pregnancy outcomes which are covered in other related Cochrane reviews (Empson 2005; Kaandorp 2009). Pregnant women at least 8 weeks' gestation with a history of 3 or more consecutive first trimester pregnancy losses with no known cause after investigation were included and the intervention group received thromboprophylaxis. Data on DVT and other thromboembolism and the adverse effects of therapy were also recorded but results were not reported by randomisation group (i.e. for several outcomes results were only reported for the intervention group, and were therefore difficult to interpret) .
Blomback 1998	This was not a randomised trial. The study focused on the pharmacokinetic effects of LMWH in pregnant women that had had a previous thromboembolic event.
Brenner 2005	(The LIVE-ENOX study.) The primary focus of this trial was on recurrent pregnancy loss in women with thrombophilia, and most outcomes relate to pregnancy outcomes (prevention of miscarriage). Women in both arms of the trial received LMWH; the purpose of the study was to compare different dosing regimes (single versus twice daily doses of 40 mg LMWH). Prevention of miscarriage is the focus of related Cochrane reviews (Empson 2005; Kaandorp 2009).
Chistolini 2006	(Abstract.) Study of women with recurrent pregnancy loss.
De Vries 2005	Trial registration/ongoing study examining pregnancy and neonatal outcomes in women with a history of uteroplacental insufficiency (with or without known thrombophilia). Women known to be at high risk of thromboembolism (i.e. that had any previous history of thromboembolism) were explicitly excluded.
Dendrinos 2007	This study focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Farquharson 2002	This study focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Kutteh 1996a	Allocation to this trial was not random; first 25 women allocated to one arm, next 25 to other arm.
Kutteh 1996b	Allocation to this trial was not random; alternate allocation.

(*Continued*)

Middeldorp 2005	This study focused on recurrent miscarriage, not on women at increased risk of thromboembolism; women that had had a previous thromboembolism were explicitly excluded.
Noble 2005	This was not a RCT.
Rai 1997	This study focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Rey 2009	The primary focus of this study was on the prevention of serious obstetric complications (pre-eclampsia and fetal loss). All women recruited had had a serious adverse event in a previous pregnancy (e.g. miscarriage). Women at high risk of thromoboembolism (e.g. with known thrombophilia or that had had a previous thromboembolic event) were specifically excluded and no outcomes for thromboembolism were reported.
Stephenson 2004	This study focused on the prevention of miscarriage; all women recruited to the study had a history of recurrent pregnancy loss and the primary outcome was live birth.
Thaler 2004	(Brief abstract.) Study focusing on placental blood flow and pregnancy outcomes.
Tulppala 1997	This study recruited women after recurrent miscarriage with no known cause, not on women at increased risk of TED.

DVT: deep venous thrombosis
LMWH: low molecular weight heparin
RCT: randomised controlled trial
TED: venous thromboembolic disease

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

De Veciana 2001

Methods	RCT.
Participants	Pregnant women; no further details.
Interventions	Dalteparin (n = 61) versus UFH (n = 60).
Outcomes	No TED occurred.
Notes	Reported as abstract only; awaiting full publication.

Dittmer 1991

Methods	RCT.
Participants	100 women undergoing caesarean section.

Dittmer 1991 (*Continued*)

Interventions	LMWH versus UFH.
Outcomes	DVT, allergic reactions, bleeding.
Notes	Reported as abstract only; awaiting full publication.

Hamersley 1998

Methods	Antenatal prophylaxis. Method of randomisation not stated. No information on blinding; assumed no blinding as interventions have different administration regimens.
Participants	One centre in USA. 61 women recruited. Eligibility: women with antiphospholipid syndrome, protein S or protein C deficiency or idiopathic thrombophilia.
Interventions	LMWH or UFH. Dose adjusted to maintain ani-Xa level between 0.03 and 0.05 IU/ml. Duration of therapy and timing and number of injections not stated. Daily 81 mg aspirin given to both groups.
Outcomes	Symptomatic TED. Thrombocytopenia.
Notes	Assumed to be antenatal prophylaxis - not stated. Published as abstract only - author contacted but no response.

Kamin 2008

Methods	Brief abstract in German. Awaiting translation and publication of full study report.
Participants	
Interventions	
Outcomes	
Notes	

DVT: deep vein thrombosis
IU: international units
LMWH: low molecular weight heparin
RCT: randomised controlled trial
TED: venous thromboembolic disease
UFH: unfractionated heparin

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

STOP CLOT

Trial name or title	STOP CLOT: study of LMWH in high risk postpartum women following caesarean section.
Methods	RCT (randomised, double-blind, placebo-controlled study).
Participants	Women at moderate to high risk for VTE following caesarean section. Aim to recruit 134 women.
Interventions	LMWH (4500 IU tinzaparin sodium) versus placebo once daily for 3-7 days postpartum.
Outcomes	Event rate of DVT (asymptomatic) on day of hospital discharge. Secondary outcomes symptomatic DVT and PE, death, major and minor bleeding in 6 weeks' postpartum.
Starting date	2002
Contact information	Marc Rodger, Ottawa Hospital, Ottawa, Onatrio, Canada.
Notes	Contact author contacted 26.03.09. No response to date.

TIPPS

Trial name or title	TIPPS (Thrombophilia in pregnancy prophylaxis study).
Methods	RCT with a series of add-on studies in different participating centres. Stratified randomisation in permuted blocks prepared by trial statistician. Central randomisation using numbered, sealed, opaque envelopes.
Participants	Women with thrombophilia, placenta-related pregnancy complications or at high risk of thromboembolism. The numbers of women included in different add on studies varied across centres.
Interventions	Intervention: subcutaneous LMWH (Dalteparin sodium) 5000 IU daily until 20 weeks' gestation, then 5000 IU twice daily until the onset of labour (at the discretion of women or clinical staff). Control: no antenatal treatment. Women in both groups received 5000 IU LMWH daily after delivery until 6 weeks postpartum
Outcomes	Range of outcomes in different add-on studies. Including bone density, coagulation activity and pregnancy outcomes.
Starting date	July 2000 (some findings of the study have now been published).
Contact information	Dr Marc Rodger, The Ottawa Hospital, Canada.
Notes	We contacted the lead investigator on 15th June 2009 for more information on the study.

DVT: deep vein thrombosis
IU: international units
LMWH: low molecular weight heparin
PE: pulmonary embolism
RCT: randomised controlled trial
TED: venous thromboembolic disease
VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Symptomatic thromboembolic events	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.99]
2.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
2.2 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
3 Symptomatic pulmonary embolism	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
3.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
4 Symptomatic deep vein thrombosis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
4.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
5 Asymptomatic thromboembolic events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Bleeding episodes	1	40	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 98.00]
7.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 98.00]
7.2 LMWH	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Serious wound complications	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Side effects sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Side effects not sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Symptomatic osteoporosis	2	56	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
11.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
11.2 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Fetal loss	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
12.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
12.2 LMWH	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Thrombocytopenia	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 64.26]
13.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 64.26]
14 Fetal anomalies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Antenatal prophylaxis: LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Symptomatic thromboembolic events	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.49]
3 Symptomatic pulmonary embolism	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Symptomatic deep vein thrombosis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Asymptomatic thromboembolic events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.47]
7 Bleeding episodes	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Serious wound complications	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Side effects sufficient to stop treatment	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.47]
10 Side effects not sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Symptomatic osteoporosis	2	188	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 4.18]
12 Fetal loss	2	222	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.21, 1.77]
13 Thrombocytopenia	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Fetal anomalies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Caesarean section: LMWH or UFH versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Symptomatic thromboembolic events	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.39, 4.27]
2.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.31, 28.03]
2.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.19, 3.76]
3 Symptomatic pulmonary embolism	3	764	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.25, 4.87]
3.1 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.13, 4.48]
3.2 LMWH	1	134	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.51]
4 Symptomatic deep vein thrombosis	3	706	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.23, 13.31]
4.1 LMWH	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.83]
4.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 18.02]
5 Asymptomatic thromboembolic events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	3	266	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.13]
6.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.54]

6.2 UFH	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.97]
7 Bleeding episodes	3	796	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [2.64, 10.05]
7.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	6.17 [0.76, 49.96]
7.2 UFHH	1	580	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [2.49, 10.18]
8 Serious wound complications	3	266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 16.13]
8.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 16.13]
8.2 UFH	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Side effects sufficient to stop treatment	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1 LMWH	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Side effects not sufficient to stop treatment	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.1 LMWH	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 4. Caesarean section: LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Symptomatic thromboembolic events	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
3 Symptomatic pulmonary embolism	1	17	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Symptomatic deep vein thrombosis	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
5 Asymptomatic thromboembolic events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Blood transfusion	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Bleeding episodes	1	17	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Serious wound complications	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Side effects sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Side effects not sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. Caesarean section: HES versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Symptomatic thromboembolic events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Symptomatic pulmonary embolism	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

4 Symptomatic deep vein thrombosis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Asymptomatic thromboembolic events	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.03]
6 Blood transfusion	1	207	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.19, 21.93]
7 Bleeding episodes	1	207	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [0.50, 12.72]
8 Serious wound complications	1	207	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.56, 4.10]
9 Side effects sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Side effects not sufficient to stop treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 6. Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic VTE events	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.36]
2 Pulmonary embolism	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.34]
3 Deep vein thrombosis	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.03, 2.55]

Analysis 1.2. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 2 Symptomatic thromboembolic events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 2 Symptomatic thromboembolic events

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
1 UFH					
Howell 1983	0/20	1/20		50.0 %	0.33 [0.01, 7.72]
Subtotal (95% CI)	**20**	**20**		**50.0 %**	**0.33 [0.01, 7.72]**
Total events: 0 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 LMWH					
Gates 2004b	0/8	1/8		50.0 %	0.33 [0.02, 7.14]
Subtotal (95% CI)	**8**	**8**		**50.0 %**	**0.33 [0.02, 7.14]**
Total events: 0 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
Total (95% CI)	**28**	**28**		**100.0 %**	**0.33 [0.04, 2.99]**
Total events: 0 (Heparin), 2 (No treatment)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.98 (P = 0.33)					

Analysis 1.3. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 3 Symptomatic pulmonary embolism.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 3 Symptomatic pulmonary embolism

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
1 LMWH					
Gates 2004b	0/8	1/8		100.0 %	0.33 [0.02, 7.14]
Total (95% CI)	**8**	**8**		**100.0 %**	**0.33 [0.02, 7.14]**
Total events: 0 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					

Analysis 1.4. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 4 Symptomatic deep vein thrombosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 4 Symptomatic deep vein thrombosis

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
1 UFH					
Howell 1983	0/20	1/20		100.0 %	0.33 [0.01, 7.72]
Total (95% CI)	**20**	**20**		**100.0 %**	**0.33 [0.01, 7.72]**
Total events: 0 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					

Analysis 1.6. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 6 Blood transfusion.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 6 Blood transfusion

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Gates 2004b	0/8	0/8		0.0 [0.0, 0.0]
Total (95% CI)	**8**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (No treatment)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.7. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 7 Bleeding episodes.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 7 Bleeding episodes

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
1 UFH					
Howell 1983	2/20	0/20		100.0 %	5.00 [0.26, 98.00]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**5.00 [0.26, 98.00]**
Total events: 2 (Heparin), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
2 LMWH					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

(*Continued* . . .)

(. . . *Continued*)

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
Total (95% CI)	**20**	**20**		**100.0 %**	**5.00 [0.26, 98.00]**
Total events: 2 (Heparin), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					

Analysis 1.8. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 8 Serious wound complications.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 8 Serious wound complications

Study or subgroup	UF heparin n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Gates 2004b	0/8	0/8		0.0 [0.0, 0.0]
Total (95% CI)	**8**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (UF heparin), 0 (No treatment)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.11. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 11 Symptomatic osteoporosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 11 Symptomatic osteoporosis

Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 UFH				
Howell 1983	1/20	0/20		3.00 [0.13, 69.52]
Subtotal (95% CI)	**20**	**20**		**3.00 [0.13, 69.52]**
Total events: 1 (Heparin), 0 (No treatment)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.69 (P = 0.49)				
2 LMWH				
Gates 2004b	0/8	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**8**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (No treatment)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**28**	**28**		**3.00 [0.13, 69.52]**
Total events: 1 (Heparin), 0 (No treatment)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.69 (P = 0.49)				

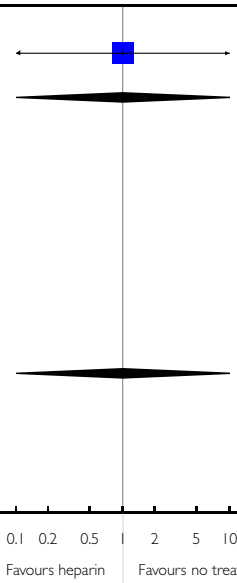
Analysis 1.12. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 12 Fetal loss.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 12 Fetal loss

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
1 UFH					
Howell 1983	1/20	1/20		100.0 %	1.00 [0.07, 14.90]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**1.00 [0.07, 14.90]**
Total events: 1 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 LMWH					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**20**	**20**		**100.0 %**	**1.00 [0.07, 14.90]**
Total events: 1 (Heparin), 1 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					



Analysis 1.13. Comparison 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo, Outcome 13 Thrombocytopenia.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 1 Antenatal prophylaxis: UF or LMW heparin versus no treatment or placebo

Outcome: 13 Thrombocytopenia

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
1 LMWH					
Gates 2004b	1/8	0/8		100.0 %	3.00 [0.14, 64.26]
Total (95% CI)	**8**	**8**		**100.0 %**	**3.00 [0.14, 64.26]**
Total events: 1 (Heparin), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					

Analysis 2.2. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 2 Symptomatic thromboembolic events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 2 Symptomatic thromboembolic events

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Casele 2006	2/60	4/57		0.48 [0.09, 2.49]
Pettila 1999	0/32	0/29		0.0 [0.0, 0.0]
Total (95% CI)	**92**	**86**		**0.48 [0.09, 2.49]**
Total events: 2 (LMW heparin), 4 (UF heparin)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.88 (P = 0.38)				

Analysis 2.6. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 6 Blood transfusion.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 6 Blood transfusion

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pettila 1999	0/50	2/55		100.0 %	0.22 [0.01, 4.47]
Total (95% CI)	**50**	**55**		**100.0 %**	**0.22 [0.01, 4.47]**
Total events: 0 (LMW heparin), 2 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					

Analysis 2.9. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 9 Side effects sufficient to stop treatment.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 9 Side effects sufficient to stop treatment

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pettila 1999	0/50	2/55		100.0 %	0.22 [0.01, 4.47]
Total (95% CI)	**50**	**55**		**100.0 %**	**0.22 [0.01, 4.47]**
Total events: 0 (LMW heparin), 2 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					

Analysis 2.11. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 11 Symptomatic osteoporosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 11 Symptomatic osteoporosis

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Casele 2006	1/43	0/40		17.8 %	2.80 [0.12, 66.70]
Pettila 1999	0/50	2/55		82.2 %	0.22 [0.01, 4.47]
Total (95% CI)	**93**	**95**		**100.0 %**	**0.68 [0.11, 4.18]**

Total events: 1 (LMW heparin), 2 (UF heparin)

Heterogeneity: Chi^2 = 1.30, df = 1 (P = 0.25); I^2 =23%

Test for overall effect: Z = 0.42 (P = 0.68)

Analysis 2.12. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 12 Fetal loss.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 12 Fetal loss

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Casele 2006	4/60	7/57		88.3 %	0.54 [0.17, 1.76]
Pettila 1999	1/50	1/55		11.7 %	1.10 [0.07, 17.12]
Total (95% CI)	**110**	**112**		**100.0 %**	**0.61 [0.21, 1.77]**

Total events: 5 (LMW heparin), 8 (UF heparin)

Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.91 (P = 0.36)

Analysis 2.13. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 13 Thrombocytopenia.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 13 Thrombocytopenia

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Pettila 1999	0/50	0/55		0.0 [0.0, 0.0]
Total (95% CI)	**50**	**55**		**0.0 [0.0, 0.0]**
Total events: 0 (LMW heparin), 0 (UF heparin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 3.2. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 2 Symptomatic thromboembolic events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 2 Symptomatic thromboembolic events

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	1/39	0/37		2.85 [0.12, 67.83]
Gates 2004a	1/66	0/68		3.09 [0.13, 74.51]
Subtotal (95% CI)	**105**	**105**		**2.97 [0.31, 28.03]**
Total events: 2 (Heparin), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%				
Test for overall effect: Z = 0.95 (P = 0.34)				
2 UFH				
Hill 1988	0/25	0/25		0.0 [0.0, 0.0]
Welti 1981	3/272	4/308		0.85 [0.19, 3.76]
Subtotal (95% CI)	**297**	**333**		**0.85 [0.19, 3.76]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total events: 3 (Heparin), 4 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.22 (P = 0.83)				
Total (95% CI)	**402**	**438**		**1.30 [0.39, 4.27]**
Total events: 5 (Heparin), 4 (Placebo)				
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² =0.0%				
Test for overall effect: Z = 0.43 (P = 0.67)				

Analysis 3.3. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 3 Symptomatic pulmonary embolism.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 3 Symptomatic pulmonary embolism

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 UFH				
Hill 1988	0/25	0/25		0.0 [0.0, 0.0]
Welti 1981	2/272	3/308		0.75 [0.13, 4.48]
Subtotal (95% CI)	**297**	**333**		**0.75 [0.13, 4.48]**
Total events: 2 (Heparin), 3 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.31 (P = 0.76)				
2 LMWH				
Gates 2004a	1/66	0/68		3.09 [0.13, 74.51]
Subtotal (95% CI)	**66**	**68**		**3.09 [0.13, 74.51]**
Total events: 1 (Heparin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.69 (P = 0.49)				
Total (95% CI)	**363**	**401**		**1.10 [0.25, 4.87]**
Total events: 3 (Heparin), 3 (Placebo)				
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² =0.0%				
Test for overall effect: Z = 0.13 (P = 0.90)				

Analysis 3.4. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 4 Symptomatic deep vein thrombosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 4 Symptomatic deep vein thrombosis

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	1/39	0/37		2.85 [0.12, 67.83]
Subtotal (95% CI)	**39**	**37**		**2.85 [0.12, 67.83]**
Total events: 1 (Heparin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.65 (P = 0.52)				
2 UFH				
Hill 1988	0/25	0/25		0.0 [0.0, 0.0]
Welti 1981	1/272	1/308		1.13 [0.07, 18.02]
Subtotal (95% CI)	**297**	**333**		**1.13 [0.07, 18.02]**
Total events: 1 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.09 (P = 0.93)				
Total (95% CI)	**336**	**370**		**1.74 [0.23, 13.31]**
Total events: 2 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.67); I^2 =0.0%				
Test for overall effect: Z = 0.53 (P = 0.59)				

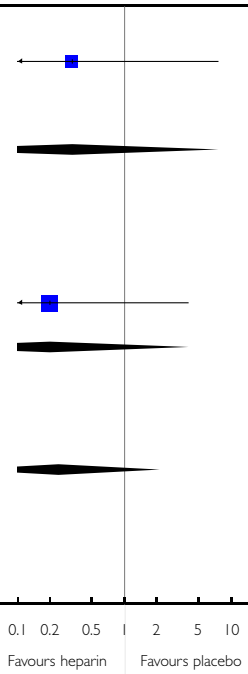
Analysis 3.6. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 6 Blood transfusion.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 6 Blood transfusion

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	0/39	1/37		0.32 [0.01, 7.54]
Gates 2004a	0/69	0/71		0.0 [0.0, 0.0]
Subtotal (95% CI)	**108**	**108**		**0.32 [0.01, 7.54]**
Total events: 0 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.71 (P = 0.48)				
2 UFH				
Hill 1988	0/25	2/25		0.20 [0.01, 3.97]
Subtotal (95% CI)	**25**	**25**		**0.20 [0.01, 3.97]**
Total events: 0 (Heparin), 2 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.06 (P = 0.29)				
Total (95% CI)	**133**	**133**		**0.24 [0.03, 2.13]**
Total events: 0 (Heparin), 3 (Placebo)				
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%				
Test for overall effect: Z = 1.28 (P = 0.20)				



Analysis 3.7. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 7 Bleeding episodes.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 7 Bleeding episodes

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	0/39	0/37		0.0 [0.0, 0.0]
Gates 2004a	6/69	1/71		6.17 [0.76, 49.96]
Subtotal (95% CI)	**108**	**108**		**6.17 [0.76, 49.96]**
Total events: 6 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.71 (P = 0.088)				
2 UFHH				
Welti 1981	40/272	9/308		5.03 [2.49, 10.18]
Subtotal (95% CI)	**272**	**308**		**5.03 [2.49, 10.18]**
Total events: 40 (Heparin), 9 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 4.50 (P < 0.00001)				
Total (95% CI)	**380**	**416**		**5.15 [2.64, 10.05]**
Total events: 46 (Heparin), 10 (Placebo)				
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%				
Test for overall effect: Z = 4.81 (P < 0.00001)				

Analysis 3.8. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 8 Serious wound complications.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 8 Serious wound complications

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	0/39	0/37		0.0 [0.0, 0.0]
Gates 2004a	1/69	1/71		1.03 [0.07, 16.13]
Subtotal (95% CI)	**108**	**108**		**1.03 [0.07, 16.13]**
Total events: 1 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.02 (P = 0.98)				
2 UFH				
Hill 1988	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**25**	**25**		**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**133**	**133**		**1.03 [0.07, 16.13]**
Total events: 1 (Heparin), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.02 (P = 0.98)				

Analysis 3.9. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 9 Side effects sufficient to stop treatment.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 9 Side effects sufficient to stop treatment

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Gates 2004a	0/69	0/71		0.0 [0.0, 0.0]
Total (95% CI)	**69**	**71**		**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

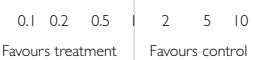
Analysis 3.10. Comparison 3 Caesarean section: LMWH or UFH versus placebo, Outcome 10 Side effects not sufficient to stop treatment.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 3 Caesarean section: LMWH or UFH versus placebo

Outcome: 10 Side effects not sufficient to stop treatment

Study or subgroup	Heparin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 LMWH				
Burrows 2001	0/39	0/37		0.0 [0.0, 0.0]
Total (95% CI)	**39**	**37**		**0.0 [0.0, 0.0]**
Total events: 0 (Heparin), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 4.2. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 2 Symptomatic thromboembolic events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 4 Caesarean section: LMWH versus UFH

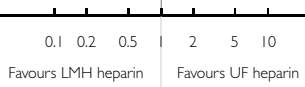
Outcome: 2 Symptomatic thromboembolic events

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6		0.0 [0.0, 0.0]
Heilmann 2007	0/50	1/50		0.33 [0.01, 7.99]
Krauss 1994	0/50	0/50		0.0 [0.0, 0.0]
Total (95% CI)	**111**	**106**		**0.33 [0.01, 7.99]**

Total events: 0 (LMW heparin), 1 (UF heparin)

Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%

Test for overall effect: Z = 0.68 (P = 0.50)



Analysis 4.3. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 3 Symptomatic pulmonary embolism.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 4 Caesarean section: LMWH versus UFH

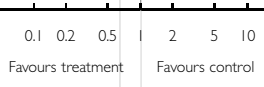
Outcome: 3 Symptomatic pulmonary embolism

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6		0.0 [0.0, 0.0]
Total (95% CI)	**11**	**6**		**0.0 [0.0, 0.0]**

Total events: 0 (LMW heparin), 0 (UF heparin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 4.4. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 4 Symptomatic deep vein thrombosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 4 Caesarean section: LMWH versus UFH

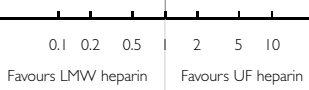
Outcome: 4 Symptomatic deep vein thrombosis

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6		0.0 [0.0, 0.0]
Heilmann 2007	0/50	1/50		0.33 [0.01, 7.99]
Krauss 1994	0/50	0/50		0.0 [0.0, 0.0]
Total (95% CI)	**111**	**106**		**0.33 [0.01, 7.99]**

Total events: 0 (LMW heparin), 1 (UF heparin)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.68 (P = 0.50)



Analysis 4.7. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 7 Bleeding episodes.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 4 Caesarean section: LMWH versus UFH

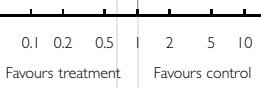
Outcome: 7 Bleeding episodes

Study or subgroup	LMW heparin n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6		0.0 [0.0, 0.0]
Total (95% CI)	**11**	**6**		**0.0 [0.0, 0.0]**

Total events: 0 (LMW heparin), 0 (UF heparin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 5.5. Comparison 5 Caesarean section: HES versus UFH, Outcome 5 Asymptomatic thromboembolic events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 5 Asymptomatic thromboembolic events

Study or subgroup	HES n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	7/103	9/104		100.0 %	0.79 [0.30, 2.03]
Total (95% CI)	**103**	**104**		**100.0 %**	**0.79 [0.30, 2.03]**
Total events: 7 (HES), 9 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					

Analysis 5.6. Comparison 5 Caesarean section: HES versus UFH, Outcome 6 Blood transfusion.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 6 Blood transfusion

Study or subgroup	HES n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	2/103	1/104		100.0 %	2.02 [0.19, 21.93]
Total (95% CI)	**103**	**104**		**100.0 %**	**2.02 [0.19, 21.93]**
Total events: 2 (HES), 1 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					

Analysis 5.7. Comparison 5 Caesarean section: HES versus UFH, Outcome 7 Bleeding episodes.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 7 Bleeding episodes

Study or subgroup	HES n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	5/103	2/104		100.0 %	2.52 [0.50, 12.72]
Total (95% CI)	**103**	**104**		**100.0 %**	**2.52 [0.50, 12.72]**
Total events: 5 (HES), 2 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					

Analysis 5.8. Comparison 5 Caesarean section: HES versus UFH, Outcome 8 Serious wound complications.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 8 Serious wound complications

Study or subgroup	HES n/N	UF heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	9/103	6/104		100.0 %	1.51 [0.56, 4.10]
Total (95% CI)	**103**	**104**		**100.0 %**	**1.51 [0.56, 4.10]**
Total events: 9 (HES), 6 (UF heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.82 (P = 0.41)					

Analysis 6.1. Comparison 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment, Outcome 1 Symptomatic VTE events.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment

Outcome: 1 Symptomatic VTE events

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
Segal 1975	1/116	5/94		100.0 %	0.16 [0.02, 1.36]
Total (95% CI)	**116**	**94**		**100.0 %**	**0.16 [0.02, 1.36]**
Total events: 1 (Heparin), 5 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.094)					

Analysis 6.2. Comparison 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment, Outcome 2 Pulmonary embolism.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment

Outcome: 2 Pulmonary embolism

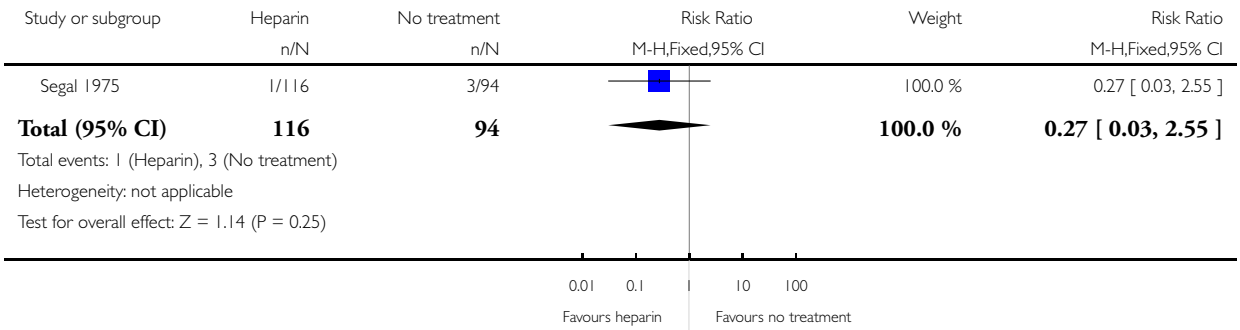
Study or subgroup	Heparin n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Segal 1975	0/116	2/94		100.0 %	0.16 [0.01, 3.34]
Total (95% CI)	**116**	**94**		**100.0 %**	**0.16 [0.01, 3.34]**
Total events: 0 (Heparin), 2 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					

Analysis 6.3. Comparison 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment, Outcome 3 Deep vein thrombosis.

Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 6 Postnatal prophylaxis (including vaginal deliveries and by CS). Heparin versus no treatment

Outcome: 3 Deep vein thrombosis



F E E D B A C K

Cundiff, July 2007

Summary

The guidelines for anticoagulation during pregnancy and post partum by the American College of Chest Physicians [1] and the Royal College of Obstetricians and Gynaecologists[2] are arguably the standard for care in the USA and UK, respectively. Despite the lack of evidence from randomised trials, these opinion-based guidelines recommend anticoagulants in many instances, and they can be referenced in medico-legal cases.

This review appropriately concludes that anticoagulant thromboprophylaxis during pregnancy is not supported by evidence that it is safe and effective. Since anticoagulation carries risks of bleeding, osteoporosis, and fetal deformity, the appropriate implication for practice would be that thromboprophylaxis with anticoagulants should not be used outside of a randomised trial. The implications for research should state that any randomised trial of anticoagulation conducted in pregnant women should be placebo-controlled.

1. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004, 126(3 Suppl):627S-644.

2. Royal College of Obstetricians and Gynaecologists (RCOG). Thromboprophylaxis during pregnancy, labour and after vaginal delivery. London (UK): Royal College of Obstetricians and Gynaecologists; 2004 (Guideline no. 37).

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

Reply

Thanks for these comments. We accept that there remains a need for further randomised trials looking at thromboprophylaxis in pregnant women; as the lack of blinding in previous studies has meant that results are difficult to interpret ideally trials should be placebo-controlled although the use of placebo may not always be practicable or ethical. We acknowledge that anticoagulation carries risk of bleeding, and several related Cochrane reviews provide evidence of this. However, reviews which examine thromboprophylaxis in non-pregnant groups at risk of thromboembolism may not be relevant during pregnancy, as the physiological mechanisms controlling blood coagulation are altered, and the risks of thromboembolic disease and side effects may be different.

In this review, we did not have sufficient evidence from trials to assess the harms and benefits associated with the use of anticoagulants, or with different types of anticoagulant. In the absence of evidence from trials, guidelines based on a range of evidence have been used

to underpin clinical practice. While we do not believe it is appropriate for this review to make recommendations about what such guidelines should say, we note under Implications for research, that if all pregnant women being considered for thromboprophylaxis were entered into randomised trials (with appropriate consent) this would help to obtain the needed evidence about safety and effectiveness as quickly as possible.

Contributors

Reply to feedback prepared by Rebecca Tooher and Therese Dowswell.

WHAT'S NEW

Last assessed as up-to-date: 26 November 2009.

26 June 2009	New search has been performed	Search updated. Data from seven new trials have been included (Casele 2006; Gates 2004a; Gates 2004b; Heilmann 2007; Krauss 1994; Segal 1975; Welti 1981) (including two trials that were ongoing in the previous version of the review). Eleven new studies considered for inclusion have been excluded, and two new trials are still ongoing. One trial which was previously included has now been excluded (Rai 1997). While there is now more evidence on some of the review's outcomes, the main conclusions remain unaltered. The authors have replied to Feedback received from David Cundiff.
26 June 2009	New citation required but conclusions have not changed	New authors prepared this update.

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 2, 2002

3 January 2008	Amended	Converted to new review format.
12 November 2007	Feedback has been incorporated	Feedback from David Cundiff added.

CONTRIBUTIONS OF AUTHORS

In this updated version of the review, all four review authors assessed study eligibility. R Tooher (RT) and T Dowswell (TD) carried out data extraction. TD entered data and RT checked data. All four authors contributed to the text of the review and commented on drafts.

DECLARATIONS OF INTEREST

Simon Gates and Lucy-Jane Davis were involved in the conduct of two studies included in this review (Gates 2004a; Gates 2004b); the other review authors assessed these studies.

SOURCES OF SUPPORT

Internal sources

- The University of Liverpool, UK.

External sources

- National Institute for Health Research, UK.

NIHR NHS Cochrane Collaboration Programme Grant Scheme award for NHS-prioritised centrally-managed, pregnancy and childbirth systematic reviews: CPGS02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this updated version of the review the background and methods section have been updated.

INDEX TERMS

Medical Subject Headings (MeSH)

Postpartum Period; Pregnancy Complications, Hematologic [*prevention & control]; Randomized Controlled Trials as Topic; Venous Thrombosis [*prevention & control]

MeSH check words

Female; Humans; Pregnancy