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

Bain E, Wilson A, Tooher R, Gates S, Davis LJ, Middleton P

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[Intervention Review]

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ABSTRACT

Background

Venous thromboembolism (VTE), although rare, is a major cause of maternal mortality and morbidity, and methods of prophylaxis are therefore often used for women considered to be at risk. This may include women who have given birth by caesarean section, those with a personal or family history of VTE and women with inherited or acquired thrombophilias (conditions that predispose people to thrombosis). Many methods of prophylaxis carry risks of adverse effects, and as the risk of VTE is often low, it is possible that the benefits of thromboprophylaxis may be outweighed by harms. Guidelines for clinical practice have been based on expert opinion rather than high-quality evidence from randomised trials.

Objectives

To assess the effects of thromboprophylaxis in women who are pregnant or have recently given birth and are at increased risk of VTE on the incidence of VTE and adverse effects of treatment.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (27 November 2013).

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

At least two review authors assessed trial eligibility and quality and extracted the data.

Main results

Nineteen trials, at an overall moderate risk of bias, met the inclusion criteria for the review. Only 16 trials, involving 2592 women, assessing a range of methods of thromboprophylaxis, contributed data to the review. Six trials compared methods of antenatal prophylaxis: heparin versus no treatment/placebo (two trials), and low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) (four trials). Nine trials assessed prophylaxis after caesarean section: four compared heparin with placebo; three compared LMWH with UFH; one compared hydroxyethyl starch (HES) with UFH; and one compared five-day versus 10-day LMWH. One study examined prophylaxis with UFH in the postnatal period (including following vaginal births).

For antenatal prophylaxis, none of the included trials reported on maternal mortality, and no differences were detected for the other primary outcomes of symptomatic thromboembolic events, symptomatic pulmonary embolism (PE) and symptomatic deep venous thrombosis (DVT) when LMWH or UFH was compared with no treatment/placebo or when LMWH was compared with UFH. The risk ratios (RR) for symptomatic thromboembolic events were: antenatal LMWH/UFH versus no heparin, RR 0.33; 95% confidence interval (CI) 0.04 to 2.99 (two trials, 56 women); and antenatal LMWH versus UFH, RR 0.47; 95% CI 0.09 to 2.49 (four trials, 404 women). No differences were shown when antenatal LMWH or UFH was compared with no treatment/placebo for any secondary outcomes. Antenatal LMWH was associated with fewer adverse effects sufficient to stop treatment (RR 0.07; 95% CI 0.01 to 0.54; two trials, 226 women), and fewer fetal losses (RR 0.47; 95% CI 0.23 to 0.95; three trials, 343 women) when compared with UFH. In two trials, antenatal LMWH compared with UFH was associated with fewer bleeding episodes (defined in one trial of 121 women as bruises > 1 inch (RR 0.18, 95% CI 0.09 to 0.36); and in one trial of 105 women as injection site haematomas of $\geq$ 2 cm, bleeding during delivery or other bleeding (RR 0.28; 95% CI 0.15 to 0.53)), however in a further trial of 117 women no difference between groups was shown for bleeding at delivery. The results for these secondary outcomes should be interpreted with caution, being derived from small trials that were not of high methodological quality.

For post-caesarean/postnatal prophylaxis, only one trial comparing five-day versus 10-day LMWH after caesarean section reported on maternal mortality, observing no deaths. No differences were seen across any of the comparisons for the other primary outcomes (symptomatic thromboembolic events, symptomatic PE and symptomatic DVT). The RRs for symptomatic thromboembolic events were: post-caesarean LMWH/UFH versus no heparin, RR 1.30; 95% CI 0.39 to 4.27 (four trials, 840 women); post-caesarean LMWH versus UFH, RR 0.33; 95% CI 0.01 to 7.99 (three trials, 217 women); post-caesarean five-day versus 10-day LMWH, RR 0.36; 95% CI 0.01 to 8.78 (one trial, 646 women); postnatal UFH versus no heparin, RR 0.16; 95% CI 0.02 to 1.36 (one trial, 210 women). For prophylaxis after caesarean section, in one trial (of 580 women), women receiving UFH and physiotherapy were more likely to have bleeding complications ('complications hémorragiques') than women receiving physiotherapy alone (RR 5.03; 95% CI 2.49 to 10.18). In two additional trials, that compared LMWH with placebo, no difference between groups in bleeding episodes (major bleeding; major bruising; bleeding/bruising reported at discharge) were detected. No other differences in secondary outcomes were shown when LMWH was compared with UFH post-caesarean, nor when post-caesarean HES was compared with UFH, post-caesarean five-day LMWH was compared with 10-day LMWH, or when UFH was compared to no heparin postnatally.

Authors' conclusions

There is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period, with the small number of differences detected in this review being largely derived from trials that were not of high methodological quality. Large scale, high-quality randomised trials of currently used interventions are warranted.

PLAIN LANGUAGE SUMMARY

Preventing deep vein clots in pregnancy and after the birth

Venous thromboembolism (VTE) 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 blood and block vessels there (this is called a pulmonary embolism (PE)), which can result in death. Normally occurring changes to the clotting system during pregnancy can increase the risk of a thromboembolic event (DVT or PE), and some groups of women have a higher risk of developing VTE (including older and obese women; women with previous VTE; women with thrombophilia (a condition predisposing individuals to developing clots); and women following a caesarean birth). Preventive treatments include drugs to prevent clots, support stockings, and physical activity soon after birth to keep the circulation moving. However, some drugs might cause problems such as increased blood loss after birth. Drugs used include unfractionated heparin, low molecular weight heparin and aspirin.

We included 19 randomised controlled trials in this review but only 16 trials with 2592 women could be included in the analysis. The trials were of a moderate quality, and assessed drugs including unfractionated heparin and low molecular weight heparin in pregnancy and after caesarean birth. We found no evidence to suggest that using heparin in pregnancy or after a caesarean birth reduces the risk of maternal death, DVT or PE, and no differences were shown for these outcomes when different types of heparin were compared. Women who received low molecular weight heparin seemed to be less likely to have bleeding episodes (bruises of more than 1 inch; injection site haematoma (a localised collection of blood outside blood vessels) of at least 2 cm in diameter, bleeding at birth and other bleeding), were less likely to have injection site burning, excess bruising and allergic rashes, and less likely to have a fetal loss, than women who received unfractionated heparin; however, the trials that showed these results were not of high quality.

We did not find enough evidence from the trials to be sure about the effects of these preventive treatments. This means there is not enough evidence to show which are the best ways to prevent VTE (including DVT and PE), during or following pregnancy, including after a caesarean birth.

BACKGROUND

Description of the condition

Venous thromboembolic disease in pregnancy and the early postnatal period

Venous thromboembolism (VTE) is a condition in which the blood clots inappropriately, and which is associated with considerable morbidity and mortality. The term VTE encompasses a continuum, including both deep vein thrombosis (DVT) (the formation of clots in the deep veins of the body - predominately in the legs), and pulmonary embolism (PE) (which occurs when a clot in a deep vein breaks free and is carried to the arteries of the lungs) (Goldhaber 2012). Two of the most common initial symptoms of DVT are pain and swelling in an extremity (such as the lower leg), while symptoms and signs of PE include dyspnoea (shortness of breath), tachypnoea (rapid breathing), chest pain and haemoptysis (coughing up blood). Severe cases of PE can include signs of cyanosis (blue discolouration, particularly of the lips and fingers), and may results in collapse and sudden death (ACOG 2011; Greer 2012).

Pregnancy is associated with a number of physiological and anatomic changes that can increase the risk of VTE (ACOG 2011; Lussana 2012). During pregnancy there is a switch in the global haemostatic balance towards a hypercoagulable state (plasma levels of coagulation factors, fibrinogen, Von Willebrand factor and other markers of thrombin generation are increased in pregnancy) (Andersson 1996); a mechanism which protects the mother against excessive bleeding during birth. Other factors contributing to the higher risk of VTE in pregnancy include increased venous stasis, decreased venous outflow (Gordon 2007; Macklon 1997), compression of the inferior vena cava and pelvic veins by the enlarging uterus, and decreased mobility (Kovacevich 2000).

VTE is one of the most common causes of maternal mortality in high-income countries (Atrash 1990; Bauersachs 2009; CMACE 2011; Dept of Health 1998; Högberg 1994; Lewis 2004; Sultan 2011), with most of the maternal deaths being due to PE. As well as directly causing maternal mortality, VTE can also lead to 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.

Epidemiology

The risk of VTE in women during pregnancy and the immediate postnatal period is substantially higher than in non-pregnant women of the same age. A case-control study (of 285 patients and 857 control participants) reported that compared with non-pregnant women, the risk of VTE was increased five-fold during pregnancy, and by 60-fold during the first three months after birth (Pomp 2008). While the relative risk of VTE is greatly increased for women during pregnancy, the absolute risk remains low, estimated at around one to two in 1000 pregnancies (Arya 2011; Greer 2012; Heit 2005; James 2006; Lindqvist 1999; Lussana 2012). Although much evidence has suggested that the incidence of VTE is roughly similar across the three trimesters, a recent study has suggested that the risk may in fact increase exponentially across the duration of the pregnancy (Virkus 2011).

One of the best estimates of the incidence of VTE is believed to have come from the Lindqvist 1999 study, conducted in Sweden, which linked maternity and hospital admission data, thus avoiding problems of underestimation (of events not recorded as pregnancy-related) faced by earlier studies. The incidence in this study was 0.13% (Lindqvist 1999), compared with other figures of 0.11% (Macklon 1996), 0.09% (Andersen 1998), 0.06%

(Gherman 1999) and 0.06% (Rutherford 1991). Each of these estimates related to all pregnant women rather than to any particular group of women at risk; and much of their variation may be accounted for by differences between populations in their risk factors for VTE, along with differences in use of preventative measures.

In pregnancy, acute DVT is believed to be three to four times more common than acute PE in the antepartum period, with approximately 80% of pregnancy-associated VTE being DVT and 20% to 25% being PE (James 2006; Simpson 2001). The incidence of VTE, especially PE, however is believed to be much higher during the immediate postpartum period (Heit 2005) (strongly associated with caesarean birth) (with between 40% and 60% of all acute PE cases reported to occur postpartum; and an estimated 15-fold increased risk of PE postpartum, compared with antepartum) (Gherman 1999; Heit 2005).

A study examining trends over time suggested that the incidence of VTE during pregnancy remained fairly constant between 1966 and 1995, while the incidence in PE during the postnatal period decreased (Heit 2005). The most recent report from the United Kingdom Centre for Maternal and Child Enquiries (reviewing maternal deaths in the United Kingdom) encouragingly supported a decline overall in deaths associated with VTE in recent years; with a maternal mortality rate (for VTE) of 0.79 per 100,000 pregnancies (CMACE 2011).

Risk factors

Some groups of women have a higher risk of developing VTE. The most important individual risk factor for VTE in pregnancy is a personal history of thrombosis (ACOG 2011). For women who have had a previous thrombosis in pregnancy, the risk of VTE increases considerably in subsequent pregnancies if antenatal thromboprophylaxis is not used (Brill-Edwards 2000; De Stefano 2006), with an estimated increased risk of recurrence of three- to four-fold (Pabinger 2002). Another important individual risk factor for VTE in pregnancy is the presence of an inherited or acquired thrombophilia (a condition that predisposes individuals to developing thromboses) (ACOG 2011; Alfirevic 2002; James 2006; Larciprete 2007; Robertson 2006). The risk of a thromboembolic event occurring during pregnancy has been shown to differ according to the nature of the thrombophilia, with estimates of risk varying from 5% to 33% (Conard 1990; Friederich 1996; Pomp 2008).

Other pregnancy-related factors shown to increase the risk of pregnancy-related VTE include multiple gestation, pre-eclampsia, prolonged labour and caesarean section (especially in the emergency setting). In a case-control study conducted in the United Kingdom, the overall risk of VTE was 0.09%, but there was a much higher risk of events in the postnatal period following caesarean birth. In this study, the risk in the antenatal period was estimated as 0.18% following caesarean section compared with 0.03% without caesarean section (Simpson 2001). Obesity, smoking, advanced maternal age, heart disease, family history of VTE, and prolonged immobilisation are other commonly reported risk factors (James 2006; Knight 2008; Lindqvist 1999; Simpson 2001).

Description of the intervention

Thromboprophyaxis

While the evidence correlating risk factors and the occurrence of pregnancy-related VTE has to date been imprecise, there is currently broad agreement (as shown in one recent review of guidelines from the United States and from other international organisations (Okoroh 2012)) that women should be assessed for VTE risk preconception and again during pregnancy in order to guide VTE thromboprophylaxis (any measures taken in order to prevent thrombosis).

A recent review of international guidelines acknowledged the uncertainties surrounding recommendations for thromboprophylaxis globally (Wu 2013), highlighting differences both within current United Kingdom recommendations (between the recent guidance from the National Institute for Health and Clinical Excellence (NICE) (Hill 2010) and from the Royal College of Obstetricians and Gynaecologists (RCOG) (RCOG 2009), and between the United Kingdom guidelines and a variety of international guidelines. Inconsistencies in international guidelines include advice regarding which groups of women to offer thromboprophylaxis to, and which options should be offered to pregnant women. Recommendations for the duration of prophylaxis also vary. Women who have had a previous episode of VTE may, for example, be recommended long-term antenatal prophylaxis as well as prolonged postnatal prophylaxis, while women undergoing caesarean section may, for example, only be recommended postnatal prophylaxis for a few days.

Options for VTE thromboprophylaxis include both pharmacologic agents and nonpharmacologic methods (NHMRC 2009).

Pharmacologic agents that have been used include:

- unfractionated heparin (UFH) or low molecular weight heparin (LMWH);
- aspirin, a platelet aggregation inhibitor;
- warfarin, a vitamin K antagonist;
- hydroxyethyl starch (HES), a nonionic starch derivative;
- fondaparinux, a selective inhibitor of activated Factor X;
- danaparoid, a heparinoid.

Mechanical methods that have been used include:

- graduated compression stockings;
- intermittent pneumatic compression;
- venous foot pumps;
- early mobilisation;
- surveillance.

How the intervention might work

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

Pharmacological agents, such as heparin, warfarin and aspirin have been used in VTE prevention due to their anticoagulant properties. Thrombin has a key role in haemostasis and thrombosis, and thus anticoagulant strategies to inhibit thrombogenesis focus on either inhibiting thrombin or its generation. UFH, LMWH and coumarin derivatives (such as warfarin) prevent the generation of thrombin through a variety of mechanisms (Ansell 2004). Heparins (such as UFH and LMWH) exert their anticoagulant activity by activating antithrombin, which subsequently inhibits thrombin (and Factor Xa). Coumarin derivatives (such as warfarin) however, produce their anticoagulant effect by interfering with the cyclic conversion of vitamin K (which is required as a co-factor for the 'carboxylation' of vitamin K dependent proteins, which include a number of coagulation factors); by blocking this process, the coagulation factors that are produced have no/little biological activity. Selective inhibitors of activated Factor Xa (such as fondaparinux), exert their antithrombotic activity by neutralisation of Factor Xa, which interrupts the blood coagulation cascade, inhibiting thrombin formation and thrombus development (Ansell 2004).

Non-pharmacological methods, such as graduated compression stockings, intermittent pneumatic compression or venous foot pumps have been used for their ability to reduce venous statis and blood stagnation by promoting venous blood flow through external compression (NHMRC 2009).

The pharmacologic agents and non-pharmacologic methods of thromboprophylaxis discussed above have been used, and have been shown to be effective, in reducing the risk of VTE in a variety of non-pregnant patient groups, such as those with chronic illness and in individuals following surgery. The effectiveness of these agents/methods have been demonstrated in a number of Cochrane reviews, for example: the Alikhan 2010 review supported the use of heparin thromboprophylaxis in medical patients presenting with acute medical illness (with a significant risk reduction in DVT and PE shown); the Testroote 2008 review supported the use of LMWH in outpatients to significantly reduce VTE when immobilisation of the lower leg is required; and the Kakkos 2008 review revealed that compared with compression alone, and compared with pharmacologic prophylaxis, combined prophylactic modalities can significantly decrease the incidence of VTE and DVT respectively.

Despite previously established benefits of these methods of thromboprophylaxis for VTE in non-pregnant patient groups, there is ongoing debate about whether thromboprophylaxis for VTE in pregnancy is cost-effective and beneficial (with particular concern as to whether benefits outweigh the potential harms); routine screening of all pregnant women to identify women with thrombophilias, for example, has not been recommended (Okoroh 2012), and antenatal prophylaxis for all women with known thrombophilias remains controversial (Brenner 2003; Middeldorp 2003; Okoroh 2012; Wu 2005).

Pharmacological methods may cause adverse effects that could be sufficiently severe or common to outweigh the benefits of thromboprophylaxis. Heparin does not cross the placenta and is believed to be safe for the fetus, and therefore, has generally been used for antenatal therapy. However, it can cause adverse effects for the mother (Nelson-Piercy 1997); there is a risk of thrombocytopenia (low platelets), bleeding and allergic reactions and symptomatic osteoporosis (loss of bone density, leading to fractures) in the longer term. When used after caesarean section, heparin may increase the frequency of bleeding and wound complications. Originally, UFH was used, but this now appears to have been largely superseded, at least for use in pregnancy and postnatally, by LMWH. The advantages of LMWH over UFH include a longer half-life (allowing once or twice-daily subcutaneous dosing), high bioavailability, and predictable anticoagulant response; avoiding the need for dose adjustment, or laboratory monitoring in most patients. In addition, LMWHs are thought to be associated with a lower risk of adverse effects (e.g. osteoporosis, and thrombocytopenia) (Bauersachs 2009). Warfarin is known to cause congenital abnormalities (Hall 1980) and it has, therefore, rarely been used in the first trimester or in the last few weeks of pregnancy (Bauersachs 2009). Both heparin and warfarin have been used for postnatal thromboprophylaxis, as they have been considered as safe for mothers who are breastfeeding (Bauersachs 2009; Letsky 1997; Orme 1977).

Low-dose (e.g. 60 mg to 75 mg) aspirin has been widely used in pregnancy in an attempt to prevent the development of pre-eclampsia (Knight 2001). Aspirin is usually well-tolerated and has few adverse 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 VTE in pregnancy (Bauersachs 2009). Hydroxyethyl starch (HES) has been used for thromboprophylaxis in the past however, it is believed to be no longer in use because of the risk of anaphylaxis (Paull 1987).

Why it is important to do this review

This review updates a previously published Cochrane review on interventions for the prophylaxis of VTE in pregnancy and the early postnatal period (Tooher 2010), which concluded that there was insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period, and that large scale randomised trials of currently-used interventions should be conducted.

Thromboembolic disease, although rare, is a major cause of maternal mortality and morbidity; hence methods of prophylaxis are often used for women at risk. Many methods of prophylaxis carry a risk of adverse effects, and as the risk of VTE is low, it is pos-

sible that the benefits of thromboprophylaxis may be outweighed by harm. Current guidelines for clinical practice are based largely on expert opinion, rather than high-quality evidence from randomised trials.

It is therefore important to examine the use of thromboprophylaxis in women who are pregnant or have recently given birth and are at increased risk of VTE, exploring both the incidence of VTE and adverse effects of treatment.

OBJECTIVES

To assess the effects of thromboprophylaxis during pregnancy and the early postnatal period in women at increased risk of VTE on the incidence of venous thromboembolic disease and adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing any intervention that may prevent VTE versus placebo or no treatment, or randomised controlled trials comparing two or more interventions for the prevention of VTE. We excluded quasi-randomised studies (i.e. those that used non-random methods of allocating participants to groups) and cross-over trials and planned to include cluster-randomised trials. We have included studies reported only as abstracts in the analyses where it was possible to extract relevant data from the text. When this was not possible, we included the studies as awaiting assessment, pending further publication of their results.

Types of participants

Women who were pregnant or had given birth in the previous six weeks and were at increased risk of VTE. This includes women who had a caesarean section, had previously had VTE, had an acquired or inherited thrombophilia, and other risk factors for VTE (discussed above). 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). A further Cochrane review assesses the role of antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction (Dodd 2010). To avoid duplication, the focus of this review is on the prevention of VTE 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 randomised controlled trials of any intervention that may reduce VTE to be eligible. This included the following.

1. Pharmacological interventions
   - Unfractionated heparin (UFH);
   - low molecular weight (LMWH);
   - aspirin;
   - warfarin;
   - hydroxyethyl starch (HES);
   - other.

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

Types of outcome measures

Primary outcomes

1. Maternal death;
2. symptomatic thromboembolic events;
3. symptomatic PE;
4. symptomatic 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. adverse effects sufficient to stop treatment;
10. adverse 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 (27 November 2013).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and Embase and 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

At least two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and where necessary, by involving a third review author.

Data extraction and management

We designed a form to extract data (based on the data extraction template of the Cochrane Pregnancy and Childbirth Group). For eligible studies, two review authors extracted the data using the agreed form. We resolved any discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager software (RevMan 2012) and checked for accuracy.
When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

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

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

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

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

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

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

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

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

We described for each included study, the methods, if any, used to blind study participants and personnel from knowledge of which intervention a participant received. We considered studies to be

at a low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

We assessed the methods as:

- low risk of bias (e.g. where there was no missing data or where reasons for missing data were balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting bias (checking for reporting bias)

We described for each included study how the possibility of selective outcome reporting bias was examined by us and what we found.

We assessed the methods as:

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

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

We described for each included study any important concerns we had about other possible sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias:

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

(7) Overall risk of bias

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

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. We would have adjusted their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we had used ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we

had identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We would have considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.
We would have acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

We considered cross-over designs inappropriate for this research question.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.
In future updates of this review, if we include any studies where women were recruited preconception, for outcomes relating to pregnancy, we plan to take a pragmatic approach and include in the denominators only those women known to have become pregnant.

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Had there been clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or where substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We would have treated the random-effects summary as the average range of possible treatment effects and we would have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not considered clinically meaningful, we would not have combined trials.
If we had used random-effects analyses, we would have presented the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.
We analysed studies addressing different interventions separately, in seven comparisons. We summarised results under three main headings, each of which included different comparisons between methods of thromboprophylaxis:

- antenatal or antenatal + postnatal or antenatal + intrapartum thromboprophylaxis;
- thromboprophylaxis given during or after caesarean section;
- postnatal or intrapartum + postnatal thromboprophylaxis.

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses based on:

- risk factors for VTE (i.e. previous VTE versus family history of VTE versus inherited or acquired thrombophilia versus emergency or elective caesarean section, with or without other risk factors versus other risk factors).

We planned to restrict subgroup analyses to primary outcomes.
We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2012). We planned to report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.
However, we were unable to conduct subgroup analyses in this update due to lack of data. We will include these analyses in future versions of the review if the necessary data become available.

Sensitivity analysis

We carried out sensitivity analyses to explore the effects of trial quality by allocation concealment and sequence generation, by omitting studies rated as 'high' or 'unclear risk of bias' for these components. We restricted sensitivity analyses to the primary outcomes.

RESULTS

Description of studies

Results of the search

For this update, the search of the Cochrane Pregnancy and Childbirth Group's Trials Register identified 20 reports, relating to 14 new studies. Of these 14 new studies identified, we included two trials (Cruz 2011; O'Riordan 2008), and excluded five studies (Gris 2010; Gris 2011; Pyregov 2012; Ratiu 2009; Visser 2011). We have classified six trials as ongoing (NCT00878826; NCT01019655; NCT01068795; NCT01274637; NCT01793194; NCT01828697). One trial has been listed as 'awaiting classification', pending further contact from the trialists or full publication of the study (Nagornaya 2012). Of the studies that were 'awaiting classification' in the previous version of this review, we have included two (De Veciana 2001; Hamersley 1998), and have excluded one (Kamin 2008). One trial remains awaiting classification (Dittmer 1991). We have also excluded one study that was included in the previous version of this review (Harenberg 1993).

Overall, we have considered a total of 52 studies for inclusion in this review (described in 72 reports identified by the searches). Of these, we have assessed 19 as eligible for inclusion and we have excluded 23. Two studies are awaiting further assessment because results were reported in abstracts only and we are awaiting publication of the full study reports or contact from the study authors to enable inclusion (Dittmer 1991; Nagornaya 2012). Eight studies are ongoing and full results have not yet been published. We hope to include results from these trials in a future update of this review if the trials become eligible for inclusion (NCT00225108; NCT00878826; NCT00967382; NCT01019655; NCT01068795; NCT01274637; NCT01793194; NCT01828697).

Three of the included studies do not contribute data to this review. One of the studies focused on the laboratory results of blood samples taken from women receiving thromboprophylactic agents (Ellison 2001). One further study (Cornette 2002) examined the timing of low molecular weight heparin (LMWH) with the first dose administered during versus after caesarean, however, it did not contribute results to any comparisons in the review. The third study (O'Riordan 2008) compared two LMWHs (tinzaparin and enoxaparin) following caesarean section; however only data relating to the pharmokinetics of these drugs were reported. More information on the 19 included trials is provided in the Characteristics of included studies tables.

In the results section below we therefore describe findings for those 16 included studies, involving 2592 women, which contributed data to the review.

Included studies

Although 19 studies met the eligibility criteria for inclusion, only 16 studies contributed data for the outcomes of interest.

Of those studies that reported data on the review's pre-specified outcomes, six studies assessed antenatal, or antenatal and postnatal, thromboprophylaxis. Four studies compared LMWH with unfractionated heparin (UFH) (Casele 2006; De Veciana 2001; Hamersley 1998; Pettila 1999); one compared LMWH with placebo (Gates 2004b); and one compared UFH with no treatment in the antenatal period (Howell 1983).

Nine of the studies evaluated thromboprophylaxis after (or during and after) caesarean section, and 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 compared UFH with physiotherapy compared with physiotherapy alone (Welti 1981); three compared LMWH with UFH (Gibson 1998; Heilmann 2007; Krauss 1994); one compared UFH with hydroxyethyl starch (HES) (Heilmann 1991); and one compared a 10-day bemiparin (LMWH) regimen with a five-day regimen (Cruz 2011).

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

For further details, see Characteristics of included studies.

Excluded studies

We excluded 23 studies. Several of the studies were excluded as their primary focus was, for example, on the prevention of recurrent miscarriage and not on the prevention of venous thromboembolism (VTE) (Badawy 2008; Brenner 2005; Giancotti 2012; Dendrinos 2007; Farquharson 2002; Kamin 2008; Kaandorp 2010; Rai 1997; Stephenson 2004; Thaler 2004; Tulppala 1997; Visser 2011), or they explicitly excluded women at high risk of VTE (de Vries 2005; Rey 2009). The prevention of recurrent miscarriage is examined in two other related Cochrane reviews (Empson 2005; Kaandorp 2009). Two further trials were excluded as they assessed the secondary prevention of placental vascular complications in women with severe pre-eclampsia or placental abruption and specifically excluded women at high risk of VTE (Gris 2010; Gris 2011); these trials are awaiting assessment in a related Cochrane review (Dodd 2010).

See Table 1 for a summary of the data regarding thromboembolic events reported in these excluded studies (data have only been summarised if thromboembolic events were reported in the study (including where it was specified that no events occurred)).

One trial was excluded as it did not include women at risk of VTE (i.e. included healthy pregnant women and assessed pharmacokinetics) (Harenberg 1993), and a further trial was excluded as it assessed interventions for the treatment (not prevention) of deep vein thrombosis (DVT) in pregnant women (Ratiu 2009).

Five studies were excluded as they were not randomised trials (Blomback 1998; Kutteh 1996a; Kutteh 1996b; Noble 2005;

Pyregov 2012).
For further details, see Characteristics of excluded studies.

Risk of bias in included studies

Most of the included studies were not of high methodological quality and for many studies, a number of the risk of bias items have been judged as 'unclear'. 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. Overall, the trials were judged to be of a moderate risk of bias.
The assessments of the risk of bias across the included studies are set out in Figure 1 and Figure 2.

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

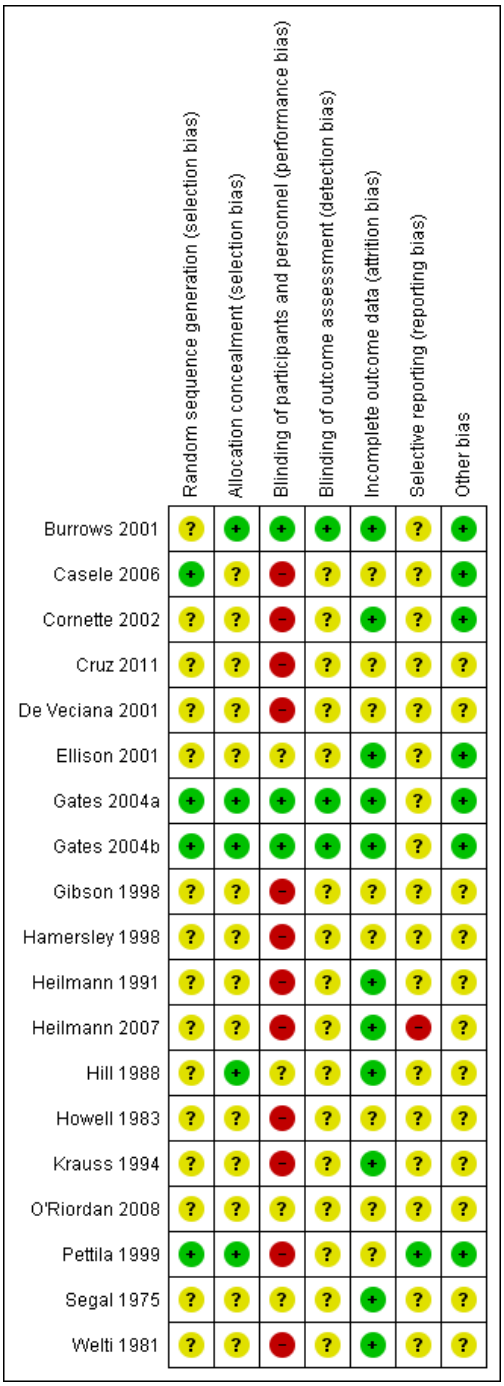
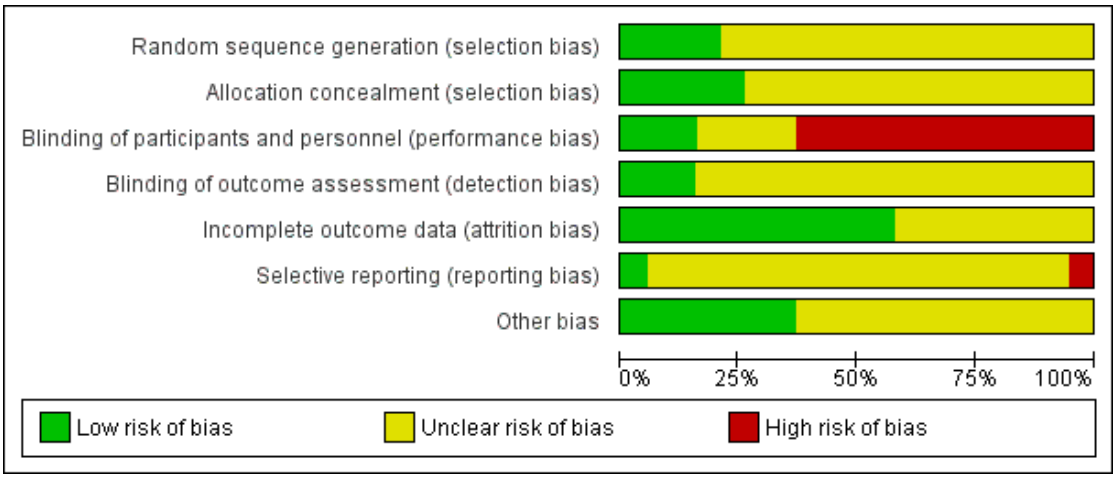


Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Generation of the randomisation sequence was considered adequate in four trials (Casele 2006; Gates 2004a; Gates 2004b; Pettila 1999) and unclear in 15 trials (Burrows 2001; Cornette 2002; Cruz 2011; De Veciana 2001; Ellison 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981). Adequate methods of sequence generation reported included: use of a random number table in one study (Casele 2006); use of a central telephone randomisation service in two studies (Gates 2004a; Gates 2004b); and use of a computer-generated list in one study (Pettila 1999).

Methods of allocation concealment were judged as adequate in only five of the studies, and included use of 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 one study (Pettila 1999). For the remaining 14 studies, the risk of selection bias due to inadequate concealment of allocation was judged to be unclear (Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; Ellison 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981).

Blinding

Blinding was poorly reported in many of the included studies, and was judged as inadequate or unfeasible (particularly for women and study personnel) in a number of studies also. Only three studies reported adequate attempts to blind patients, clinicians and outcome assessors (Burrows 2001; Gates 2004a; Gates 2004b).

Only four of the 19 trials included a placebo control (Burrows 2001; Gates 2004a; Gates 2004b; Hill 1988). For most of the trials without a placebo, we have judged the risk of performance bias (due to a lack of blinding of women and study personnel) as high, as we considered it unfeasible due to the differing interventions and comparisons. For the majority of studies, the risk of detection bias due to inadequate blinding of outcome assessment has been judged as unclear, with no specific details provided in the trial reports.

Incomplete outcome data

Eleven trials were judged to be at a low risk of attrition bias, with very few or no losses to follow-up or exclusions post-randomisation reported (Burrows 2001; Cornette 2002; Ellison 2001; Gates 2004a; Gates 2004b; Heilmann 1991; Heilmann 2007; Hill 1988; Krauss 1994; Segal 1975; Welti 1981). While two of these studies appeared to have no losses to follow-up (Segal 1975; Welti 1981), it is important to note that both reported very little methodological detail.

Five studies did not specify whether any losses or exclusions oc-

curred, and have thus been judged at an unclear risk of attrition bias (Cruz 2011; De Veciana 2001; Gibson 1998; Hamersley 1998; O'Riordan 2008). Three further trials were judged at an unclear risk of attrition bias. 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.

Selective reporting

Almost all of the 19 trials were judged to be at an unclear risk of reporting bias (Burrows 2001; Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; Ellison 2001; Gates 2004a; Gates 2004b; Gibson 1998; Hamersley 1998; Heilmann 1991; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981). In each case, the review authors were not able to access a trial protocol, and could not confidently assess the risk of selective reporting.

Pettila 1999 was judged to be at a low risk of reporting bias, as it reported all pre-specified and many expected outcomes, including relevant clinical data. Heilmann 2007, however, was judged to be at a high risk of reporting bias, as for a number of clinical outcomes, the data were incompletely reported; for example, groups "showed no differences in the blood loss...and thrombocytopenia or Osteopenia".

Other potential sources of bias

Seven of the trials were judged at a low risk of other potential bias, with no other obvious sources of bias identified (Burrows 2001; Casele 2006; Cornette 2002; Ellison 2001; Gates 2004a; Gates 2004b; Pettila 1999).

The remaining 12 trials were judged at an unclear risk of other potential bias, largely due to a lack of methodological detail provided in the trial reports (Cruz 2011; De Veciana 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981).

Effects of interventions

Prophylaxis for venous thromboembolic disease: 16 studies with 2592 women

Antenatal prophylaxis

Comparison 1: LMWH or UFH versus no treatment or placebo

Two studies (Gates 2004b; Howell 1983) with a total of 56 women compared thromboprophylaxis with heparin (LMWH or UFH) with placebo or no treatment; for most outcomes only one of the trials contributed data to the analysis.

Primary outcomes

Neither study reported whether or not there was any maternal mortality. No differences between groups were detected for the outcomes: symptomatic thromboembolic events (risk ratio (RR) 0.33; 95% confidence interval (CI) 0.04 to 2.99; two trials, 56 women) (Analysis 1.1), symptomatic pulmonary embolism (PE) (RR 0.33; 95% CI 0.02 to 7.14; one trial, 16 women) (Analysis 1.2), or symptomatic DVT (RR 0.33; 95% CI 0.01 to 7.72; one trial, 40 women) (Analysis 1.3). For each outcome, however, there was considerable uncertainty about the treatment effect, which may reflect lack of power of the included trials to detect differences (with small sample sizes), and the low event rates that were observed for each of these outcomes.

Secondary outcomes

There were no reported blood transfusions in the Gates 2004b trial (Analysis 1.4), or any serious wound complications (Analysis 1.6). No differences were observed for the other reported secondary outcomes including symptomatic osteoporosis (RR 3.00; 95% CI 0.13 to 69.52; two trials, 56 women) (Analysis 1.7), fetal loss (RR 1.00; 95% CI 0.07 to 14.90; one trial, 40 women) (Analysis 1.8) and thrombocytopenia (RR 3.00; 95% CI 0.14 to 64.26; one trial, 16 women) (Analysis 1.9). Considering bleeding episodes, Gates 2004b reported that two women had antenatal vaginal bleeding in the UFH group and two in the no treatment group (in the UFH group, one woman had a placental abruption at 34 weeks followed by labour, and one woman had vaginal bleeding followed by a complete abortion at 24 weeks; in the no treatment group, one woman had vaginal bleeding and a threatened abortion, and one woman had vaginal bleeding and an incomplete abortion at 13 weeks of an embryonic pregnancy) (RR 1.00; 95% CI 0.16 to 6.42; one trial, 40 women) (Analysis 1.5). For each secondary outcome, small numbers of women and low event rates resulted in wide CIs and imprecise estimates of effect.

Comparison 2: LMWH versus UFH

Four studies (Casele 2006; De Veciana 2001; Hamersley 1998; Pettila 1999) involving 404 women compared prophylaxis with LMWH or UFH.

Primary outcomes

While there were more symptomatic thromboembolic events in the UFH group compared with in the LMWH group, the difference between groups was not statistically significant, and all events occurred in the two groups of one of the four trials (Casele 2006). There was considerable uncertainty about the treatment effect, suggesting that the studies may have lacked power to detect a difference between groups for this outcome (RR 0.47; 95% CI 0.09 to 2.49; four trials, 404 women) (Analysis 2.1). There were no observed cases of symptomatic PE or symptomatic DVT in the two trials that reported these outcomes separately (Analysis 2.2; Analysis 2.3).

Secondary outcomes

Considering the need for blood transfusions, there was no difference observed between the antenatal LMWH and UFH groups in one trial of 105 women (Pettila 1999) (RR 0.22; 95% CI 0.01 to 4.47) (Analysis 2.4). As the definitions for "bleeding episodes" across the three trials reporting on this outcome varied and/or were unclear, we did not combine results from the individual trials. In Casele 2006, no difference between the two groups was shown for "bleeding at delivery", with four of the 60 women in the LMWH experiencing bleeding at delivery compared with one of the 57 women in the UFH group (RR 3.80; 95% CI 0.44 to 32.99; 117 women). In both the De Veciana 2001 and Pettila 1999 trials there were more cases of bleeding in the UFH group, compared with the LMWH group. In De Veciana 2001, reporting on "Bruises > 1 inch", there were 39 events among the 60 women in the UFH group, compared with seven events among the 61 women in the LMWH group (RR 0.18; 95% CI 0.09 to 0.36; 121 women); in Pettila 1999, measuring "bleeding complications" (which included injection-site haematomas (≥ 2 cm in diameter), bleeding during delivery and other bleeding), 35 of the 55 women in the UFH group experienced complications compared with nine of the 50 women in the LMWH group (RR 0.28; 95% CI 0.15 to 0.53; 105 women) (Analysis 2.5). Caution should be taken when interpreting these results, with both Pettila 1999 and De Veciana 2001 being at a high risk of performance bias, and unclear risk of detection bias.

Significantly fewer adverse effects sufficient to stop treatment (including excess bruising/allergic rashes), were observed for LMWH compared with UFH (RR 0.07; 95% CI 0.01 to 0.54; two trials, 226 women) (Analysis 2.6), however no difference was observed in the De Veciana 2001 trial of 121 women in regards to adverse effects not sufficient to stop treatment (injection burning) (RR 0.79; 95% CI 0.53 to 1.18) (Analysis 2.7).

Fewer fetal losses occurred for women who received LMWH as compared with UFH (RR 0.47; 95% CI 0.23 to 0.95; three trials, 343 women) (Analysis 2.9). While there was no observed statistical heterogeneity for this outcome, the trials that contributed data to this outcome were not of high quality, and the De Veciana 2001 trial (with over 60% of the weight in the meta-analysis), has been published in abstract form only, and thus the risk of bias in this trial has largely been judged as unclear (with inadequate information detailed regarding trial methods). This result should thus be interpreted with caution.

No differences were detected between the two groups for the outcomes symptomatic osteoporosis (RR 0.68; 95% CI 0.11 to 4.18; two trials, 188 women) (Analysis 2.8) and thrombocytopenia (RR 0.18; 95% CI 0.01 to 3.64; three trials, 287 women) (Analysis 2.10). However, for both outcomes there was considerable uncertainty about the treatment effects.

Prophylaxis for women undergoing caesarean section

Comparison 3: LMWH or UFH versus no treatment or placebo

Four studies with 840 women contributed data to this comparison (Burrows 2001; Gates 2004a; Hill 1988; Welti 1981).

Primary outcomes

There was no difference between groups detected for symptomatic thromboembolic events (RR 1.30, 95% CI 0.39 to 4.27; four trials, 840 women) (Analysis 3.1) with similar numbers of women in each group experiencing PE (RR 1.10; 95% CI 0.25 to 4.87; four trials, 840 women) (Analysis 3.2) and DVT (RR 1.74; 95% CI 0.23 to 13.31; four trials; 840 women) (Analysis 3.3).

Secondary outcomes

For most secondary review outcomes there was substantial uncertainty about the treatment effect and no differences between groups were detected, including for blood transfusion (RR 0.24; 95% CI 0.03 to 2.13; three trials, 266 women) (Analysis 3.4), wound complications (RR 1.03; 95% CI 0.07 to 16.13; three trials, 266 women) (Analysis 3.6), and adverse effects (no adverse effects sufficient to stop treatment were observed in Gates 2004a; and no adverse effects were observed in Burrows 2001) (Analysis 3.7; Analysis 3.8). As the definitions for "bleeding episodes" across these trials varied and/or were unclear, we did not combine results from the individual trials. In Burrows 2001, no cases of major bleeding occurred in either the 39 women in the LMWH group or the 37 women in the placebo group (defined as either a 20 g/L fall in haemoglobin, the need for a blood transfusion of more than two units of blood, a retroperitoneal, intraocular or intracranial bleed); similarly, no cases of major bruising were observed in either group in this trial. In Gates 2004a, there were more cases of bleeding/bruising reported at discharge for women in the LMWH (six cases) compared with women in the placebo group (one case); this difference did not reach statistical significance (RR 6.17; 95%

CI 0.76 to 49.96; 140 women). Finally, in Welti 1981, a difference in the risk of "complications hémorragiques" was detected between groups, with more events occurring in the combined UFH and physiotherapy group compared with the physiotherapy alone group (RR 5.03; 95% CI 2.49 to 10.18; 580 women) (Analysis 3.5).

Comparison 4: LMWH versus UFH

We included three studies with 217 women in this comparison (Gibson 1998; Heilmann 2007; Krauss 1994).

Primary outcomes

Overall, there was only one symptomatic thromboembolic event in this comparison (one woman with a DVT in the UFH group of the Heilmann 2007 trial) (RR 0.33, 95% CI 0.01 to 7.99; three trials, 217 women) (Analysis 4.1; Analysis 4.2; Analysis 4.3).

Secondary outcomes

Studies included in this comparison did not report results for any of the review's secondary outcomes, except the authors of Gibson 1998 reported that "no woman suffered any...haemorrhagic events" (Gibson 1998) (Analysis 4.4).

Comparison 5: HES versus UFH

One trial, involving 207 women was included in this comparison (Heilmann 1991).

Primary outcomes

The one included trial did not report results for symptomatic thromboembolic events (Heilmann 1991).

Secondary outcomes

There was no difference between groups detected for asymptomatic thromboembolic events (RR 0.79; 95% CI 0.30 to 2.03) (Analysis 5.1), and similarly no differences between groups were detected for the outcomes: blood transfusion (RR 0.50; 95% CI 0.05 to 5.48) (Analysis 5.2), bleeding episodes (RR 0.40; 95% CI 0.08 to 2.03) (Analysis 5.3) or wound complications (RR 0.67; 95% CI 0.25 to 1.82) (Analysis 5.4); results were not reported for other secondary outcomes.

Comparison 6: five-day LMWH versus 10-day LMWH

One trial (Cruz 2011) involving 646 women was included in this comparison, and assessed five-day versus 10-day LMWH for women undergoing a caesarean section.

Primary outcomes

There were no maternal deaths reported in this trial (Analysis 6.1). There was only one case of symptomatic PE observed in the trial, and this occurred in the 10-day LMWH group (RR 0.36; 95% CI 0.01 to 8.78) (Analysis 6.2; Analysis 6.3); no other symptomatic VTE events (including DVTs) occurred in either group (Analysis 6.4).

Secondary outcomes

There was no difference between groups observed for the outcome post-caesarean infection (RR 1.13; 95% CI 0.63 to 2.05) (Analysis 6.5). This trial did not report of any of the review's other secondary outcomes.

Postnatal prophylaxis

Comparison 7: UFH versus no treatment

One study (Segal 1975), involving 210 women was included in this comparison assessing postnatal UFH after birth (including after caesarean section and vaginal birth).

Primary outcomes

The one included trial examined postnatal prophylaxis and did not detect any differences between UFH and no treatment for symptomatic thromboembolic events (RR 0.16; 95% CI 0.02 to 1.36) (Analysis 7.1), symptomatic PE (RR 0.16; 95% CI 0.01 to 3.34) (Analysis 7.2), and symptomatic DVT (RR 0.27; 95% CI 0.03 to 2.55) (Analysis 7.3).

Secondary outcomes

No results were reported for any of the review's secondary outcomes in this trial.

LMWH versus UFH, placebo, no treatment (high-quality trials only)

When the pre-specified sensitivity analysis was undertaken to examine the influence of study quality, we included only three trials, which were judged to be at a low risk of bias for both sequence generation and allocation concealment (Gates 2004a; Gates 2004b; Pettila 1999). These three trials were included in three different comparisons in the review, comparing different interventions, and thus their results could not be pooled.

When antenatal LMWH was compared to placebo in Gates 2004b, no difference was detected for symptomatic thromboembolic events (RR 0.33; 95% CI 0.02 to 7.14; 16 women), as in the main analysis (of two trials).

In Pettila 1999 no symptomatic thromboembolic events were observed when antenatal LMWH was compared to UFH, and thus similar to in the main meta-analysis (of four trials), no difference between the two treatments was shown.

When LMWH was compared to placebo for prophylaxis following caesarean section in Gates 2004a, no differences in symptomatic thromboembolic events or symptomatic PE were shown (for both, the RR was 3.09; 95% CI 0.13 to 74.51; 134 women); similar to in the main analysis of four trials. In Gates 2004a, no DVT was observed in either group.

500 women that, compared with placebo control, women receiving UFH had more "complications hémorragiques" (Welti 1981). A difference in bleeding episodes (major bleeding/major bruising (Burrows 2001) or bleeding/bruising reported at discharge (Gates 2004a)) between groups was not however detected in the other two trials that compared LMWH with placebo for women undergoing caesarean section.

Overall, in view of the small number of studies included, the number of different comparisons, and the generally small sizes of the included trials, there is insufficient evidence of the benefits or harms associated with interventions for thromboprophylaxis in pregnancy.

DISCUSSION

Summary of main results

Overall, few differences in any of the seven comparisons were detected from the 16 included studies that contributed data to this review. In particular, we were unable to detect differences in any of the four primary outcomes of the review (maternal death; symptomatic thromboembolic events; symptomatic pulmonary embolism (PE); symptomatic deep vein thrombosis (DVT)).

Maternal deaths were reported in only one of the included studies (and no deaths occurred in this trial) (Cruz 2011), and symptomatic thromboembolic events, including PE and DVT, were not reported by every included study, so that for many comparisons only one or two studies contributed data to the analyses. As a consequence, given the small number of included studies in each comparison and their relatively small sample sizes, most analyses lacked power to detect differences in these rare outcomes.

For secondary outcomes, many of the included studies did not provide data, and where they did, mostly we did not detect differences between groups. Due to differences in the terminology and definitions used, some comparisons between studies were also difficult. Some results did appear to show differences between the groups. For antenatal prophylaxis, low molecular weight heparin (LMWH) compared with unfractionated heparin (UFH) seemed to be associated with fewer adverse effects sufficient to stop treatment (including excess bruising/allergic rashes), and fewer fetal losses; and in two trials, LMWH seemed to be associated with fewer bleeding episodes. However, results for these three outcomes were derived from three small studies, and while high rates of bleeding for women receiving UFH were reported in two trials, definitions of bleeding episodes were unclear and varied ("Bruises > 1 inch" (De Veciana 2001); injection-site haematomas ($\geq$ 2 cm), bleeding during delivery and other bleeding (Pettila 1999)). Further, the lack of blinding (or unclear blinding) in these studies means that the potential for bias cannot be excluded (De Veciana 2001; Pettila 1999). For prophylaxis for women undergoing caesarean section there was some evidence, from one trial of over

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 largely not reported, that 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; and unclear definitions made some comparisons between studies difficult.

None of the included studies focused on mechanical methods of prophylaxis (graduated 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 hydroxyethyl starch (Paull 1987)), or are not used as frequently in current thromboprophylactic practice (such as the use of UFH rather than LMWH).

In general the sample sizes of the trials were small. The three largest trials recruited 646 women (Cruz 2011), 580 women (Welti 1981), and 210 women (Segal 1975). Sample sizes of this order are generally inadequate to detect any differences in the incidences 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 (as 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 populations of women.

The focus of this review was on the prevention of VTE 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 differences detected in this review are largely derived from small 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.

Potential biases in the review process

The evidence for this review has been derived from trials identified through a detailed search process. It is possible (but unlikely) that additional trials assessing prophylaxis for VTE in pregnancy have been published but not identified. It is also possible that other studies have been conducted but not published. Should such studies be identified we will include them in future updates of this review.

We attempted to reduce bias wherever possible by having at least two review authors independently working on study selection, data extraction and quality assessment.

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 2010; Kakkos 2008; Ramos 2008; Testroote 2008). In a review focusing on thromboprophylaxis in general medical patients, Alikhan 2010 et al suggested that both LMWH and UFH may reduce risk of thromboembolism, but are associated with increased risks of both minor and major bleeding episodes; this increased risk of haemorrhage was less with LMWH.

However, reviews that examine outcomes in non-pregnant groups at risk of VTE may not be relevant during pregnancy when the physiological mechanisms controlling blood coagulation are altered, and the risks of VTE and the adverse effects of thromboprophylaxis may be different. Further, during pregnancy the risk to the developing fetus from pharmacologic agents is an important consideration in the choice of method.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence available from the randomised controlled trials included in this review to guide clinical decision-making. In the absence of clear randomised controlled trial evidence practitioners must rely on consensus-derived clinical practice guidelines or recommendations, such as those produced or endorsed by the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute for Health and Care Excellence (NICE) in the United Kingdom (Hill 2010; RCOG 2009), the American College of Chest Physicians (Bates 2008), the Australian National Medical Research Council (NHMRC 2009), the Society of Obstetric Medicine of Australia and New Zealand and the Australasian Society of Thrombosis and Haemostasis (McLintock 2012) and other international bodies (Okoroh 2012).

In a review of guidelines for the prevention of VTE in pregnancy from the United States and other international bodies, eight of the nine guidelines assessed recommended that all women should undergo risk factor assessment for VTE either in pregnancy or preconception; seven of the nine guidelines recommended that pregnant women with more than one additional known VTE risk factor should be considered for thromboprophylaxis (Okoroh 2012. The guidelines assessed included those from the American College of Chest Physicians (ACCP); European Genetics Foundation (EGF); Queensland Maternity and Neonatal Clinical Guidelines Program (QMNC); RCOG; NICE; the French Society of Anesthesiology and Intensive Care (SFAR); Scottish Intercollegiate Guidelines Network (SIGN); Society for Obstetricians and Gynaecologists of Canada (SOGC); and the Italian Society for Haemostasis and Thrombosis (SISET)).

This review also showed variation in regards to recommendations for preventing VTE after caesarean section, for example, with the ACCP recommending against the use of specific thromboprophylaxis (other than early mobilisation) in women with no additional risk factors; NICE recommending combined (pharmacologic and mechanical) prophylaxis; and a number of other organisations (ACCP; RCOG; SIGN; SOGC) recommending initiating thromboprophylaxis for women undergoing caesarean section if additional risk factors are present (Okoroh 2012).

Implications for research

There is a clear need for rigorously conducted large scale randomised controlled trials with sample sizes sufficiently large to assess the effects of methods of thromboprophylaxis on rare outcomes such as thromboembolic events (Barbour 1997; Wu 2013). Future trials should first compare prophylaxis with no prophylaxis and ideally should use a placebo controlled and fully blinded design, to minimise the risk of bias, which may be substantial if clinicians are aware of the allocations. The low number of eligible women makes conducting trials of antenatal thromboprophylaxis extremely challenging. To achieve an adequate sample size, a

trial may need to be conducted in a very large number of centres, which might require international collaboration. Trials of prophylaxis after caesarean section may be more feasible, even though the incidence of VTE is lower and the sample size would therefore need to be even larger (Barbour 1997). The very high number of caesarean section operations performed means that a trial could be completed within a relatively short time frame and in a reasonable number of centres. Given the difficulties in recruiting women to trials of prophylaxis for VTE in pregnancy and the early postnatal period, if all women being considered for prophylaxis could be randomised (with appropriate informed consent), the required evidence about safety and effectiveness could be obtained.

A number of placebo (or no treatment) controlled trials are currently ongoing (see Characteristics of ongoing studies) including one assessing LMWH in women considered at high risk of VTE (NCT01274637); one assessing LMWH for prophylaxis in women at moderate to high risk of VTE following caesarean section (NCT00225108); and two assessing LMWH for prophylaxis in women with thrombophilia (NCT00967382; NCT01019655). Three other ongoing trials are comparing doses of LMWH: in women at high risk of VTE (NCT00878826); for the prevention of recurrent VTE in women with a previous history of VTE (NCT01828697); and in women with a thrombophilia (NCT01068795).

While no completed trials have yet assessed non-pharmacological methods of thromboprophylaxis during pregnancy and the postnatal period, one such pilot study is underway (NCT01793194).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Burrows 2001

Methods	Randomised controlled trial.
Participants	76 women were recruited. Setting: tertiary obstetric centre in Australia from June to November 1999 Inclusion criteria: women having an elective or emergency caesarean section Exclusion criteria: history of bleeding disorder; anticoagulant therapy; history of VTE; heparin sensitivity; recent GI haemorrhage or peptic ulcer; hepatic encephalopathy; renal dysfunction requiring dialysis; uncontrolled hypertension
Interventions	Intervention (n = 39) LMWH (Dalteparin), 2500 IU. Control (n = 37) Matching placebo (saline) once daily for 4 to 5 days. Treatment was started 4 to 24 hours after caesarean section. Each pack contained enough syringes for 5 days of treatment. The injections, 4 or 5, depending on hospital stay, were given either in the thigh or abdomen, depending on patient preference and the site rotated each day
Outcomes	Symptomatic thromboembolic disease; symptomatic PE; symptomatic DVT; blood transfusion; bleeding episodes (major bleeding: 20 g/L fall in haemoglobin, the need for a blood transfusion, a retroperitoneal, intraocular or intracranial bleed); serious wound complications (wound infections, wound disruption (minor and major requiring surgical repair)); side effects not sufficient to stop treatment
Notes	A pilot protocol for a national multi-centre randomised trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods not detailed.
Allocation concealment (selection bias)	Low risk	Described as "each pack contained pre-filled syringes containing either dalteparin or matching placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as double-blind, with the use of an identical placebo; quote "each pack contained pre-filled syringes containing either dalteparin or matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above - not explicitly stated but considered probably done

Burrows 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All primary analyses were based on patient group allocation at randomisation (intention-to-treat). No losses to follow-up after randomisation. Follow-up to 6 weeks was achieved in all women who were recruited
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Low risk	More women in the placebo arm had general anaesthesia, but otherwise the 2 groups had similar characteristics at randomisation. No other obvious risk of bias identified

Casele 2006

Methods	Multi-centre randomised controlled trial.
Participants	120 women were recruited. Setting: 9 centres in the United States from September 1998 until December 2005 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 less than 24 weeks of gestation Exclusion criteria: women who were taking heparin because of recurrent pregnancy loss or women with contraindication to anticoagulants
Interventions	Intervention (n = 61) LMWH (enoxaparin sodium). Self-administered subcutaneous 30 mg twice daily from enrolment until 28 weeks of gestation, then 40 mg twice daily until delivery Comparison (n = 59) 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 coumadin for 6 to 8 weeks after delivery All women were asked to take antenatal 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); gestational age at delivery; infant birthweight; rate of early treatment withdrawal; rate of complications (spontaneous abortion, bleeding, recurrent thrombosis)
Notes	The power calculation was based on detecting bone mass changes, the original sample estimate required was 240. 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, and thus the study was terminated early

Risk of bias

Casele 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table with each site stratified into blocks of 10
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned, and considered unlikely in view of the differing interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was reported that the radiologists carrying out the bone assessments were blind to group allocation; it is unclear as to whether this was successfully achieved. Not mentioned for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Low risk	The groups were comparable with regards to maternal age, race, and parity. No other obvious risk of bias

Cornette 2002

Methods	Randomised controlled trial (somewhat unclear).
Participants	44 women were randomised. Setting: Antwerp, Belgium. Inclusion criteria: women with full-term singleton pregnancies admitted for elective caesarean section Exclusion criteria: women with known bleeding or coagulation disorders

Cornette 2002 (*Continued*)

Interventions	Study looking at the TIMING of LMWH comparing pre and post-operative treatment Intervention (n = 22) Pre-operative, 0.3 mL nadroparin calcium (LMWH) 12 hours before surgery Comparison (n = 22) Post-operative, 0.3 mL (2850 IU) nadroparin calcium 12 hours after surgery 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
Notes	We have not included this study in the analysis as outcomes were not relevant to the review. The power calculation was based on changes in haemoglobin levels

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described, quote: "randomly divided in two groups".
Allocation concealment (selection bias)	Unclear risk	As above.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up apparent.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting, furthermore, no relevant outcome data were reported
Other bias	Low risk	No other obvious risk of bias identified.

Cruz 2011

Methods	Randomised controlled trial.
Participants	646 women were randomised. Setting: hospital (San Cecilio University Hospital, Granada, Spain), over a 1-year period Inclusion criteria: women who had undergone a caesarean section who had not required prophylaxis or treatment with any type of LMWH during pregnancy (low risk of VTE during pregnancy), with absence of allergy to heparin or derivatives Exclusion criteria: women who did not fulfil the duration of proposed prevention were excluded
Interventions	Intervention (n = 335) Women received a 10-day bemiparin regimen (3500 IU once daily) as post-caesarean section prophylaxis Comparison (n = 311) Women received a 5-day bemiparin regimen (3500 IU once daily) as post-caesarean section prophylaxis
Outcomes	The number of DVT and PE episodes and venous thromboembolic-related maternal death up to 3 months following caesarean section. Variables assessed as possible risk factors for a thromboembolic event included age; smoking; obesity; hypertension; parity; multiple pregnancy; diabetes; week of delivery; type of caesarean section; type of anaesthesia; blood loss; immobility. Post-caesarean section risk factors that were measured included post-caesarean section hypertension, infection and anaemia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: women were assigned "in a randomly systematic way".
Allocation concealment (selection bias)	Unclear risk	Quote: women were assigned "in a randomly systematic way".
Blinding of participants and personnel (performance bias) All outcomes	High risk	No detail of blinding and considered unfeasible for the participants and personnel in view of the intervention (i.e. 5 days versus 10 days of prophylaxis)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detail of any losses to follow-up or exclusions post-randomisation. The uneven group numbers suggest that there may have been post-randomisation exclusions (quote "96 women who underwent a caesarean section were excluded because they did not fulfil the exclusion

Cruz 2011 (*Continued*)

		criteria"), and this may have been possible considering that "women who did not fulfil the duration of proposed prevention were excluded"
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting; further important outcomes such as side effects and bleeding episodes were not reported
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

De Veciana 2001

Methods	Randomised controlled trial.
Participants	121 women were randomised. Setting: Eastern Virginia Medical School, Obstetrics and Gynecology, Norfolk, Virginia, United States Inclusion criteria: women with an indication for prophylactic anticoagulation in pregnancy: antiphospholipid syndrome, a history of DVT/embolus, protein C/protein S deficiency, Factor V Leiden mutation, or obesity Exclusion criteria: women with renal/liver disease, bleeding diathesis, pork/heparin sensitivity were excluded
Interventions	Intervention (n = 61) Dalteparin (LMWH): initial dosing was 2500 IU (5000 IU if > 176 lbs) subcutaneously once daily; increased to a maximum of 10,000 IU/day to maintain alpha-Factor Xa levels at 0.1 to 0.3 IU/mL Comparison (n = 60) UFH: dosed with the standard 5000 U (8000 U if > 171lbs) subcutaneously twice daily
Outcomes	Bleeding complications including excess bruising and injection burning; pregnancy complications including stillbirths at less than 20 weeks; estimated gestational age at delivery; thrombosis/embolism; thrombocytopenia; anaesthesia complications
Notes	Published as abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Prospective randomized controlled trial".
Allocation concealment (selection bias)	Unclear risk	Quote: "Prospective randomized controlled trial".

De Veciana 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not detailed, however considered unfeasible in view of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up or exclusions detailed, however insufficient detail to confidently assess attrition bias
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess selective reporting.
Other bias	Unclear risk	Maternal demographics and anticoagulation indicators "were similar". Insufficient information to assess other potential sources of bias

Ellison 2001

Methods	Randomised controlled trial.
Participants	30 women were recruited. Inclusion criteria: women undergoing caesarean section, with an additional risk factor for thromboembolism (including: obesity, immobility, maternal age older than 35 year, parity of more than 4, labour for more than 4 hours, gross varicose veins, current infection, pre-eclampsia, major current illness, caesarean section performed as an emergency)
Interventions	3-arm trial. Intervention (n = 10) Women received dalteparin (LMWH) 5000 IU once daily. Comparison 1 (n = 10) Women received enoxaparin (LMWH) 4000 IU once daily. Comparison 2 (n = 10) Women received tinzaparin (LMWH) 50 IU/kg (based on booking weight) once daily Drugs were administered 6 hours following caesarean section and were continued for 5 days
Outcomes	Women were followed up for 1 day to examine laboratory haemostatic parameters. The study also reported that on "thrombotic and haemorrhagic events", skin reactions and excessive bruising
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, it was unclear as to whether the "No woman suffered any thrombotic or haemorrhagic events" referred to the women antenatally or postnatally (following treatment); thus these data were not included in a meta-analysis

Risk of bias

Ellison 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "simple randomisation".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "single blind"; no further detail provided regarding how blinding was achieved, or exactly who was blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women seem to be accounted for in the analysis.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Low risk	No other obvious risk of bias identified.

Gates 2004a

Methods	Multi-centre randomised controlled trial.
Participants	141 women were recruited from November 1998 to June 2000. Setting: 23 hospitals in the United Kingdom (women were recruited in only 8 hospitals) Inclusion criteria: women undergoing caesarean section where there was clinical uncertainty that thromboprophylaxis was indicated, including women with a history of previous thromboembolic events, women with a known congenital thrombophilia, and women with other accepted risk factors for which clinicians would consider the use of antenatal heparin Exclusion criteria: women with a known allergy to heparin.
Interventions	Intervention (n = 70) Once-daily self-injected subcutaneous 40 mg enoxaparin (LMWH) in 1 mL Control (n = 71) Once-daily self-injected subcutaneous placebo (normal saline 1 mL) All trial drugs were packaged identically in packs that contained 14 prefilled syringes. The drug was given by once daily subcutaneous injection, from study entry for a maximum of 14 days. Treatment with the study drug began within 12 hours of the caesarean section, and its duration was determined by the attending clinician. All other clinical treatment, including other forms of thromboprophylaxis during or after the caesarean section (such as stockings or inflatable boots), was left to the discretion of the responsible clinician

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 thromboembolic disease; 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	Pilot study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	External randomisation, with a "a prerandomized sequence".
Allocation concealment (selection bias)	Low risk	Quote: "The packs that were supplied to participating hospitals were numbered in a prerandomized sequence. Hospitals were instructed to use the packs in numeric order, which automatically would ensure random allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants, care givers, and investigators were blind to the allocation. An identical placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition of less than 5%. 141 women randomised, data at discharge for 140, and at 6 months, follow-up for 132
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Low risk	No other obvious risk of bias identified.

Gates 2004b

Methods	Multi-centre randomised controlled trial.
Participants	16 women were recruited from April 1998 to February 2000. Setting: 23 hospitals in the United Kingdom (women were recruited in only 11 hospitals) Inclusion criteria: pregnant women with clinical uncertainty that antenatal thromboprophylaxis was indicated. Recruitment at all gestational ages Women with a history of previous thromboembolic events or women with thrombophilia or another risk factor were eligible (all 16 women recruited had had a previous thromboembolic event) Exclusion criteria: women with a known allergy to heparin.
Interventions	Intervention (n = 8) Self-administered once-daily subcutaneous 40 mg enoxaparin (LMWH) in 1 mL from antenatal recruitment until a maximum of 6 weeks after delivery Control (n = 8) Self-administered once-daily subcutaneous placebo (normal saline 1 mL) from antenatal recruitment until 6 a maximum of weeks after delivery All trial drugs were packaged identically in packs that contained 7 prefilled syringes, which was enough drug for 1 week. Drugs were stored in the hospital pharmacy, and at each antenatal visit, women who were taking part in the study were given enough packs of the study drug to last until their next visit
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 thromboembolic disease; 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	Pilot study. After delivery some clinicians elected to discontinue study drugs and 3 women in both groups were given heparin postnatally

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central telephone randomisation service.
Allocation concealment (selection bias)	Low risk	A central telephone randomisation service based at the study office was used. Quote: "Each woman was allocated a unique study number that was recorded on the woman's prescription chart. For the first few women who were recruited, the number corresponded to a numbered treatment pack that contained enough study drug for the treatment of a woman throughout pregnancy

Gates 2004b (*Continued*)

		and for 6 weeks after delivery. Subsequently, pharmacists at each participating hospital were provided with 2 large bins of study drug (labelled A and B): 1 bin containing LMWH, and the other placebo, together with a list of the study numbers that corresponded to each allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical packaging of trial drugs. Women, clinical staff and investigators were all described as blind to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above - blinding of all involved in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low recruitment to pilot study. All 16 women randomised were followed up until 6 months after delivery. No attrition
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Low risk	6 women (3 women in each group) were given open-label heparin after delivery. No other obvious risk of bias identified

Gibson 1998

Methods	Randomised controlled trial.
Participants	17 women were recruited. Inclusion criteria: women undergoing a caesarean section; either an emergency caesarean section or with other risk factors for VTE
Interventions	Intervention 1 (n = 6) LMWH (enoxaparin) 20 mg once daily. Intervention 2 (n = 5) LMWH (enoxaparin) 40 mg once daily. Control (n = 6) UFH 7500 IU every 12 hours. Intervention started after caesarean section; duration of intervention not stated
Outcomes	Symptomatic thromboembolic disease; symptomatic PE; symptomatic DVT; bleeding episodes
Notes	3-way randomisation (UFH/20 mg enoxaparin/40 mg enoxaparin). 2 enoxaparin groups combined for the review

Gibson 1998 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "women were randomised".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up stated; no detail regarding exclusions
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting; furthermore data for many relevant clinical outcomes was not reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Hamersley 1998

Methods	Randomised controlled trial.
Participants	61 women were recruited. Setting: the George Washington University Medical Centre, Washington, DC, United States Inclusion criteria: pregnant women with an underlying diagnosis of either antiphospholipid syndrome, protein S or C deficiency, or idiopathic thrombophilia Exclusion criteria: none detailed.
Interventions	Intervention (n = 32) LMWH. Comparison (n = 29) UFH. For all women, the dose was adjusted to maintain an anti-Xa (heparin assay) level between 0.03 to 0.05 U/mL. A daily baby aspirin (81 mg) was also prescribed
Outcomes	Thrombocytopenia; thromboembolism; epidural-related complications; blood loss; post-delivery haematocrit

Hamersley 1998 (*Continued*)

Notes	Published as an abstract only; authors contacted with no response	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote "patients...were randomized...".
Allocation concealment (selection bias)	Unclear risk	Quote "patients...were randomized...".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unfeasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not detailed.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

Heilmann 1991

Methods	Randomised controlled trial.
Participants	207 women were recruited. Setting: 1 centre in Germany. Inclusion criteria: women delivered by caesarean section.
Interventions	Intervention (n = 103) HES 6%, 3 x 500 mL; first 500 mL during the operation (caesarean section) (the first 500 mL), second in the evening of the day of the operation, third in the evening of the first postoperative day Control (n = 104) UFH 5000 IU 2 hours after the operation and every 8 hours for 7 days The treatment was given by injection, either in the outer thigh or upper arm
Outcomes	Asymptomatic thromboembolic disease; blood transfusion; bleeding episodes; serious wound complications. A number of laboratory measurements were also taken (relating to blood clotting factors)

Heilmann 1991 (*Continued*)

Notes	Information obtained from a translation of the manuscript.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Trial described as randomised but no further detail on generation of the randomisation sequence provided
Allocation concealment (selection bias)	Unclear risk	The women were divided into 2 groups (no further detail).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting; furthermore data for many relevant clinical outcomes were not reported
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

Heilmann 2007

Methods	Randomised controlled trial (3 arms).
Participants	100 women were randomised. Inclusion criteria: women with uncomplicated pregnancy following elective caesarean section."The indication for prophylaxis was the previous diagnosis of a heterozygote factor V-Leiden-mutation."
Interventions	Intervention (n = 50) LMWH (Dalteparin 5000 IU/daily for 7 days post operatively, with the first dose 6 hours following caesarean section and then at 24-hourly intervals) Comparison (n = 50) UFH (Calciparin 2 x 5000 IU daily, with the first dose 6 hours following caesarean section, and then at 8-hour intervals) There was a further control group (n = 50), who received no pharmacological prophylaxis but compressions stockings according to the guidelines of RCOG (Controls) during hospital days. Outcome data for this non-randomised group, was not included in this

Heilmann 2007 (*Continued*)

	review
Outcomes	DVT; blood loss; thrombocytopenia. A number of outcomes relating to the rheological properties of blood were also assessed
Notes	50 additional matched controls were assessed in the manuscript (Outcome data for the 2 treatment groups only has been included in this review.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were allocated to the treatment group by randomization"
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned, considered unfeasible in view of the interventions being assessed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up apparent.
Selective reporting (reporting bias)	High risk	Clinical outcome data were incompletely reported, with statements such as "showed no differences in the blood loss...and thrombocytopenia or Osteopenia", and "The women with Calciparin prophylaxis showed multiple thrombi in the calf and proximal veins..." with no values of the number of events per group reported
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

Hill 1988

Methods	Randomised controlled trial.
Participants	50 women were randomised. Setting: 1 centre in the United Kingdom. Inclusion criteria: women delivered by caesarean section. Exclusion criteria: complications, e.g. multiple pregnancy, APH, previous thromboembolic disease

Hill 1988 (*Continued*)

Interventions	Intervention (n = 25) UFH 1000 units, 1 hour before operation, then twice daily for 5 days Control (n = 25) Saline, 1 hour before operation, then twice daily for 5 days
Outcomes	Symptomatic VTE; symptomatic DVT; symptomatic PE; blood transfusion; serious wound complications
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Randomisation by pharmacist not involved in trial.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	While saline was administered to the control group by the same regimen, blinding was not detailed, and it was therefore unclear as to whether women and study personnel were aware of treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting; furthermore this was a short-report only
Other bias	Unclear risk	There were no significant differences in age, parity, blood pressure, height, weight, and gestation between the 2 groups. Insufficient information to assess other potential sources of bias

Howell 1983

Methods	Randomised controlled trial.
Participants	40 women were recruited. Setting: 1 centre in United Kingdom. Inclusion criteria: women who had previously had thromboembolic disease treated with anticoagulants for at least 6 weeks. Recruitment at time of referral to clinic (8 to 37

Howell 1983 (*Continued*)

	weeks' gestational age)
Interventions	Intervention (n = 20) Subcutaneous calcium heparin antenatally (10,000 IU twice daily) and for 6 weeks postpartum (8000 IU twice daily) Comparison (n = 20) Calcium heparin or for 6 weeks postpartum only.
Outcomes	Symptomatic thromboembolic disease; bleeding episodes; symptomatic osteoporosis; fetal loss
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomised".
Allocation concealment (selection bias)	Unclear risk	Described as "sealed envelope".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 patients refused any treatment either antenatally or postnatally once the trial had been explained to them. They were not included in the overall analysis, but none developed thromboembolism either before or after delivery. 1 patient initially allocated to the control group developed a DVT at 28 weeks and was subsequently treated by intravenous, followed by subcutaneous heparin. She was omitted from any further analyses. Data could be re-included for the review
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

Krauss 1994

Methods	Randomised controlled trial.
Participants	100 women were recruited. Setting: University Hospital, Gottinghen, Germany. Inclusion criteria: women undergoing caesarean section. Exclusion criteria: known heparin allergy, GI ulcers, sever kidney, liver or pancreatic disease or previous cerebral haemorrhage, severe hypertension (RR > 180/120), haemorrhagic diathesis
Interventions	Intervention (n = 50) LMWH (fragmin) once daily 2500 to 5000 anti-Xa units. Comparison (n = 50) 2 to 3 times daily 5000 units UFH (Liquemin) + 500 mL Dextran 60 during caesarean section Treatment for 10 days after surgery.
Outcomes	Thrombosis and side effects.
Notes	Data extraction from translation notes. Original paper in German. An additional 30 women undergoing tocolysis were randomised to the intervention and comparison groups; data regarding adverse effects were reported for 75 women in the intervention group and 75 women in the comparison group, and thus we could not include these data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not clear (author confirmed that the allocation to groups was random)
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned; considered unfeasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs or withdrawals.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

O'Riordan 2008

Methods	Randomised controlled trial.
Participants	20 women were recruited. Setting: University College Cork, Ireland. Inclusion criteria: women undergoing a caesarean section. Exclusion criteria: none detailed.
Interventions	Intervention Enoxaprin 40 mg once daily subcutaneously. The first dose of LMWH was administered 4 to 6 hours following the caesarean section Control Tinazaprin 4500 units once daily subcutaneously. The first dose of LMWH was administered 4 to 6 hours following the caesarean section
Outcomes	Venous blood samples were taken for: APTT, Factor Xa, Factor II, vWF, platelet count, volume and granularity
Notes	This trial assessed the pharmacokinetics of LMWHs in the postpartum period, and did not report data relating to any of our review's pre-specified outcomes. Published as abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote "The patients were randomised".
Allocation concealment (selection bias)	Unclear risk	Quote "The patients were randomised".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detail provided; considered unfeasible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine risk of attrition bias
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting; furthermore no relevant clinical outcomes were reported
Other bias	Unclear risk	"There was no significant difference in characteristics (including BMI) between the two groups." Insufficient information to assess other potential sources of bias

Pettila 1999

Methods	Randomised controlled trial.
Participants	107 women were recruited. Setting: 8 centres in Finland from February 1994 to February 1997 Inclusion criteria: 18 years or older, week 0 to 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	Intervention (n = 51) Subcutaneous dalteparin (Fragmin) once daily (starting dose 5000 or 7500 IU, dose adjusted based on anti Xa measurements) Comparison (n = 56) Subcutaneous 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 VTE; blood transfusion; bleeding episodes; side effects; symptomatic osteoporosis; fetal loss. Further data for clinical outcomes, including birthweight and Apgar score were reported)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation "by means of a computer generated procedure".
Allocation concealment (selection bias)	Low risk	"Closed envelope" the randomisation list was kept outside the centres
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open design (not feasible).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 randomised patients (1 from each group) received no prophylactic treatment before discontinuation of the study because of withdrawal of consent and were excluded from the analysis. Thus 105 patients, 50 patients from the dalteparin and 55 from the heparin group, were included in the intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No clear evidence of selective reporting; expected and pre-specified outcomes reported

Pettila 1999 (*Continued*)

Other bias	Low risk	No other obvious risk of bias identified.

Segal 1975

Methods	Randomised controlled trial.
Participants	210 randomised (not clear). Setting: 1973, Jerusalem, Israel. Inclusion criteria: women identified with varicose veins before delivery Exclusion criteria: a history of thrombosis, and thus treatment with heparin
Interventions	Intervention (n = 116) UFH 50 mg (5000 IU) subcutaneous UFH every 12 hours for 4 to 5 days after delivery (time of initial dose varied, for those having a vaginal birth about two-thirds had the first dose in active labour (2 to 3 cm) and a third after delivery, women having a caesarean section the first dose was 2 hours before) Control group (n = 94) Care in the comparison group was not described, there did not seem to be a placebo (routine care/no heparin)
Outcomes	Superficial or DVT. 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote, "divided at random".
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear. There did not seem to be any placebo, but it was stated that the outcome assessors were blind to group allocation, quote "the daily clinical evaluation for signs of deep or superficial thrombosis was done by two of us without knowing the mentioned distribution"

Segal 1975 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All women seem to have been followed up.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Unclear risk	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. Insufficient information to assess other potential sources of bias

Welti 1981

Methods	Randomised controlled trial.
Participants	580 women were included. Setting: not clear, authors from University Hospital, Obstetric and Gynaecology Department, Lausanne, Switzerland Inclusion criteria: women undergoing surgery for gynaecological indications. We included in the analysis 580 women undergoing caesarean section (both emergency and elective)
Interventions	Intervention (n = 272) Physiotherapy and twice daily subcutaneous 5000 IU heparin (UFH) Control (n = 308) 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	The study was conducted "selon le principle de la randomisation fermee"
Blinding of participants and personnel (performance bias) All outcomes	High risk	There did not appear to be any placebo.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - no detail of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared that all women were followed up.
Selective reporting (reporting bias)	Unclear risk	With no access to a trial protocol it is not possible to confidently assess selective reporting
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias

APH: antepartum haemorrhage
APTT: activated partial thromboplastin time
DVT: deep vein thrombosis
GI: gastrointestinal
HES: hydroxyethyl starch
IU: international units
LMWH: low molecular weight heparin
NICU: neonatal intensive care unit
PE: pulmonary embolism
RR: risk ratio
UFH: unfractionated heparin
VTE: venous thromboembolism
vWF: von Willebrand factor

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

Study	Reason for exclusion
Badawy 2008	The primary focus of this trial was on fetal loss and pregnancy outcomes which are covered in other related Cochrane reviews (Empson 2005; Kaandorp 2009). Pregnant women of 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
Blomback 1998	This was not a randomised trial. The study focused on the pharmacokinetic effects of LMWH in pregnant women who 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 (prevention of miscarriage). Women in both arms of the trial received LMWH; the purpose of the study was to compare different dosing regimens (single versus twice daily doses of 40 mg LMWH). Prevention of miscarriage is the focus of related Cochrane reviews (Empson 2005; Kaandorp 2009).

(*Continued*)

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 VTE (i.e. who had any previous history of VTE) were explicitly excluded
Dendrinos 2007	This trial focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Farquharson 2002	This trial focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Giancotti 2012	This trial focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Gris 2010	This trial focuses on the secondary prevention of placental vascular complications in women with abruptio placentae, and is awaiting assessment for including in a related Cochrane review (Dodd 2010). Women known to be at high risk of VTE (i.e. who had previous DVT or antiphospholipid antibodies) were explicitly excluded
Gris 2011	This trial focuses on the secondary prevention of placental vascular complications in women with severe pre-eclampsia, and is awaiting assessment for including in a related Cochrane review (Dodd 2010). Women known to be at high risk of VTE (i.e. that had a previous DVT or antiphospholipid antibodies) were explicitly excluded
Harenberg 1993	This randomised trial included healthy pregnant women; not those at a high risk of VTE
Kaandorp 2010	This trial focused on recurrent miscarriage, not on women at increased risk of VTE; women who had had a previous VTE were explicitly excluded
Kamin 2008	(The ETHiG II Study). This trial 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; the first 25 women were allocated to 1 arm, and the next 25 to other arm
Kutteh 1996b	Allocation to this trial was not random; allocation was by alternation
Noble 2005	This was not a randomised controlled trial.
Pyregov 2012	This trial was quasi-randomised, allocating women according to the day of the week to either daily natrium enoxaparin or no treatment after caesarean delivery, to assess endotoxin concentrations
Rai 1997	This trial focuses on recurrent pregnancy loss which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).
Ratiu 2009	This trial compares compression and early mobilisation with compression and bed rest for the treatment of acute stage proximal DVT in pregnant women. This study does not assess prophylaxis for VTE in pregnancy
Rey 2009	The primary focus of this trial 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 VTE (e.g. with known thrombophilia or who had had a previous thromboembolic event) were

(*Continued*)

	specifically excluded and no outcomes for VTE were reported
Stephenson 2004	This trial 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 assessing the efficacy on enoxaparin for improving pregnancy outcomes and uteroplacental blood flow in women with thrombophilia and recurrent pregnancy loss
Tulppala 1997	This trial recruited women after recurrent miscarriage with no known cause, not women at increased risk of VTE
Visser 2011	This trial focuses on recurrent pregnancy loss in women with or without thrombophilia which is covered in related Cochrane reviews (Empson 2005; Kaandorp 2009).

DVT: deep venous thrombosis
LMWH: low molecular weight heparin
VTE: venous thromboembolism

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

Dittmer 1991

Methods	Randomised controlled trial.
Participants	100 women undergoing caesarean section.
Interventions	LMWH versus UFH.
Outcomes	DVT, allergic reactions, bleeding.
Notes	Reported as abstract only and includes 30 pregnant patients with premature labor (at "low risk" to develop a DVT), and 100 patients undergoing gynaecological surgery; awaiting full publication or a response from the author regarding data for pregnant women undergoing caesarean section only

Nagornaya 2012

Methods	Unclear. The abstract states in the methods that the "study was prospective and randomized" but this was not clear
Participants	"500 pregnant women were examined in 39-40 weeks of pregnancy...97 patients were examined after caesarean section."
Interventions	Thromboprophylaxis was conducted with bemiparin-sodium (with the dose dependant on the woman's weight and risk)
Outcomes	Risk factors for VTE; "thrombohaemorrhagic complications during 6 months of follow-up"

Notes	Reported as abstract only. Unclear if this truly was a randomised trial, as the results report on risk factors in a cohort of women. Have attempted to contact trial authors; will await contact or full publication

DVT: deep vein thrombosis
LMWH: low molecular weight heparin
UFH: unfractionated heparin
VTE: venous thromboembolism

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

NCT00225108

Trial name or title	NCT00225108: Study of LMWH in high-risk postpartum women following caesarean section
Methods	Randomised controlled trial.
Participants	Women at moderate to high risk for VTE following caesarean section. Estimated enrolment: 134 women
Interventions	Intervention: LMWH (4500 IU tinzaparin sodium). Control: placebo once daily for 3 to 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 at 6 weeks postpartum
Starting date	2002.
Contact information	Marc Rodger, Ottawa Hospital, Ottawa, Onatrio, Canada.
Notes	

NCT00878826

Trial name or title	NCT00878826: Prophylactic Enoxaparin Dosing for Prevention of Venous Thromboembolism in Pregnancy
Methods	Randomised controlled trial (open-label). Estimated enrolment: 64 women
Participants	Women at more than 18 years, where prophylaxis against VTE in pregnancy is warranted (according to the American College of Obstetrics and Gynecology Practice Bulletin 2000); history of idiopathic thrombosis; history of thrombosis related to pregnancy or oral contraceptive use; history of thrombosis accompanied by an underlying thrombophilia (other than homozygous for the factor V Leiden mutation, heterozygous for both the factor V Leiden and the prothrombin G20210A mutation or AT-II deficiency; known thrombophilia (expect those listed above, with a history of adverse pregnancy outcome). Exclusions: need for therapeutic level anticoagulation as determined by physician; renal disease; weight > 90 kg; allergy to enoxaparin

NCT00878826 (*Continued*)

Interventions	Intervention: enoxaparin 40 mg once daily. Active control: enoxaparin 1 mg/kg daily. Active control 2: enoxaparin current dose as prescribed from first prenatal visit
Outcomes	Proportion of women in each arm who have anti-XA levels within appropriate range; correlation of anti-XA levels with renal function; adverse outcomes (bleeding events, thromboembolic events, side effects, tolerability)
Starting date	May 2009.
Contact information	Deirdre Judith Lyell, Standord University.
Notes	

NCT00967382

Trial name or title	NCT00967382: Thrombophilia in pregnancy prophylaxis study.
Methods	Randomised controlled trial, 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 varies 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 receive 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.
Contact information	Dr Marc Rodger, The Ottawa Hospital, Canada.
Notes	

NCT01019655

Trial name or title	NCT01019655: Heparin for pregnant women with thrombophilia.
Methods	Randomised controlled trial (open-label).
Participants	Pregnant women with thrombophilia. Estimated enrolment: 300 women

NCT01019655 (*Continued*)

Interventions	Intervention: nadroparin calcium 0.3 mL daily during pregnancy and 6 weeks postpartum Control: no intervention other than usual care at the study site
Outcomes	Primary outcome: composite endpoint: pregnancy-associated VTE; miscarriage; pre-eclampsia; intrauterine growth retardation
Starting date	January 2010.
Contact information	Dr Clemens B Tempfer, University of Vienna, Austria.
Notes	

NCT01068795

Trial name or title	NCT01068795: Dose Adjusting Enoxaparin Thromboprophylaxis Dosage According to Anti-factor Xa Plasma Levels Improve Pregnancy Outcomes
Methods	Randomised controlled trial (open-label).
Participants	Women with a singleton pregnancy; with a history of fetal demise, fetal growth restriction, placental abruption, pre-eclampsia, recurrent abortions or maternal thromboembolic event; acquired or congential thrombophilia treated with LMWH. Exclusions: women treated empirically with LMWH; women with a history of pre-gestational diabetes; significant polyhydramnios or oligohydramnios; major fetal structural, genetic or chromosomal malformations
Interventions	Intervention: enoxaparin adjusted according to anti-factor Xa plasma levels Control: enoxaparin fixed dosage.
Outcomes	Placental syndrome or thromboembolic event; enoxaparin side effects
Starting date	July 2009.
Contact information	Dr Raed Salim, HaEmek Medical Centre, Israel.
Notes	

NCT01274637

Trial name or title	NCT01274637: PROSPER: postpartum prophylaxis for PE randomized control trial pilot
Methods	Randomised controlled trial (open-label).
Participants	Women must be at high risk for VTE for 1 of the following reasons: known low risk thrombophilia, immobilisation; OR any 2 of the following reasons: postpartum infection, postpartum haemorrhage, pre-pregnancy BMI > 25 kg/m^2, emergency caesarean birth, smoking > 5 cigarettes per day prior to pregnancy, pre-eclampsia, infant birthweight (adjusted for sex and gestational age) < 3rd percentile (i.e. small-for-gestational age). Estimated enrolment: 384 women

NCT01274637 (*Continued*)

Interventions	Intervention: LMWH. Prophylactic-dose (5000 IU/0.2 mL) LMWH, administered subcutaneously once daily in pre-filled glass syringes for 10 days (+/- 3 days) for a total of 10 (+/-3) study drug injections Control: no treatment control group.
Outcomes	Primary outcome: feasibility of recruitment and trial operations. Secondary outcomes: VTE in the early postpartum period; late symptomatic VTE; death from VTE; major bleeding or clinically relevant non-major bleeding; heparin-induced thrombocytopenia
Starting date	March 2011.
Contact information	Dr Marc A Rodger, Ottawa Hospital Research Institute, Canada
Notes	

NCT01793194

Trial name or title	NCT01793194: Preventing the Development of Venous Insufficiency in Pregnant Women Through Use of Compression Stockings: A Randomized Pilot Study
Methods	Randomised controlled trial (no blinding).
Participants	Women must be pregnant, between 18-45 years of age; between 8 and 20 weeks' gestation; seeking care for pregnant at 1 of the study locations; able to give informed consent. Exclusions: inability to wear compression stockings; women prescribed to wear compression stockings; chromic dermatological condition; chronic DVT/phlebitis. Estimated enrolment: 80 women
Interventions	Intervention: compression stocking use. Control: no stocking use.
Outcomes	Primary outcomes: incidence of varicose veins; incidence of superficial thrombophlebitis and DVT. Secondary outcomes: incidence of venous insufficiency
Starting date	February 2012.
Contact information	Assistant Professor Jennifer Heller, John Hopkins University
Notes	

NCT01828697

Trial name or title	NCT01828697: Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolisms in Pregnancy
Methods	Randomised controlled trial (open-label).

NCT01828697 (*Continued*)

Participants	Inclusion criteria: women at 18 years or older; at less than 14 weeks' gestational age; previously objective confirmed VTE (unprovoked, in the presence of use of oral contraceptives or oestrogen/progestogen, or related to pregnancy or the postpartum period, or minor risk factors). Exclusions: previous VTE related to a major provoking risk factor or indication for treatment with therapeutic dose anticoagulant therapy, or contraindications. Estimated enrolment: 1000 women
Interventions	Intervention: low-dose LMWH. Comparator: intermediate dose LMWH.
Outcomes	Symptomatic DVT; symptomatic PE; major bleeding; composite of major bleeding and clinically relevant non-major bleeding; early postpartum haemorrhage; late postpartum haemorrhage; blood transfusion < 24 hours postpartum and < 6 weeks after birth; mortality; minor bleeding; skin complications; easy bruising; necessity to switch to other LMWH; thrombocytopenia; congenital anomalies or birth defects
Starting date	April 2013.
Contact information	Dr S Middeldorp, Acadmic Mecial Centre, Amsterdam.
Notes	

AT-II: antithrombin II
BMI: body mass index
DVT: deep vein thrombosis
IU: international units
LMWH: low molecular weight heparin
PE: pulmonary embolism
VTE: venus thromboembolism

DATA AND ANALYSES

Comparison 1. Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic thromboembolic events	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.99]
1.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
1.2 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
2 Symptomatic pulmonary embolism	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
2.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
3 Symptomatic deep vein thrombosis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
3.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
4 Blood transfusion	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Bleeding episodes (antenatal vaginal bleeding)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.42]
5.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.42]
6 Serious wound complications	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Symptomatic osteoporosis	2	56	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
7.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
8 Fetal loss	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
8.1 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
9 Thrombocytopenia	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 64.26]
9.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 64.26]

Comparison 2. Antenatal prophylaxis: LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic thromboembolic events	4	404	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.49]
2 Symptomatic pulmonary embolism	2	182	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Symptomatic deep vein thrombosis	2	182	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Blood transfusion	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.47]
5 Bleeding episodes (variously defined)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Bleeding at delivery	1	117	Risk Ratio (M-H, Fixed, 95% CI)	3.8 [0.44, 32.99]

5.2 Bruises > 1 inch	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.09, 0.36]
5.3 Bleeding complications	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.53]
6 Adverse effects sufficient to stop treatment	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
7 Adverse effects not sufficient to stop treatment (injection burning)	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.53, 1.18]
8 Symptomatic osteoporosis	2	188	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 4.18]
9 Fetal loss	3	343	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.95]
10 Thrombocytopenia	3	287	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.64]

Comparison 3. Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic thromboembolic events	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.39, 4.27]
1.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.31, 28.03]
1.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.19, 3.76]
2 Symptomatic pulmonary embolism	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.25, 4.87]
2.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.51]
2.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.13, 4.48]
3 Symptomatic deep vein thrombosis	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.23, 13.31]
3.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.83]
3.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 18.02]
4 Blood transfusion	3	266	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.13]
4.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.54]
4.2 UFH	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.97]
5 Bleeding episodes (variously defined)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Major bleeding	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Major bruising	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Bleeding/bruising reported at discharge	1	140	Risk Ratio (M-H, Fixed, 95% CI)	6.17 [0.76, 49.96]
5.4 "Complications hémorragiques"	1	580	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [2.49, 10.18]
6 Serious wound complications	3	266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 16.13]
6.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 16.13]
6.2 UFH	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Adverse effects sufficient to stop treatment	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 LMWH	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Adverse effects not sufficient to stop treatment	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 LMWH	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Caesarean section: LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic thromboembolic events	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
2 Symptomatic pulmonary embolism	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Symptomatic deep vein thrombosis	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
4 Bleeding episodes ("haemorrhagic events")	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Caesarean section: HES versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asymptomatic thromboembolic events	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.03]
2 Blood transfusion	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.48]
3 Bleeding episodes	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.03]
4 Serious wound complications	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.82]

Comparison 6. Caesarean section: five-day LMWH versus 10-day LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Symptomatic thromboembolic events	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
3 Symptomatic pulmonary embolism	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
4 Symptomatic deep vein thrombosis	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Post-caesarean infection	1	646	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.05]

Comparison 7. Postnatal (including after vaginal deliveries): UFH versus no treatment

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

Analysis 1.1. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 1 Symptomatic thromboembolic events.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 1 Symptomatic thromboembolic events

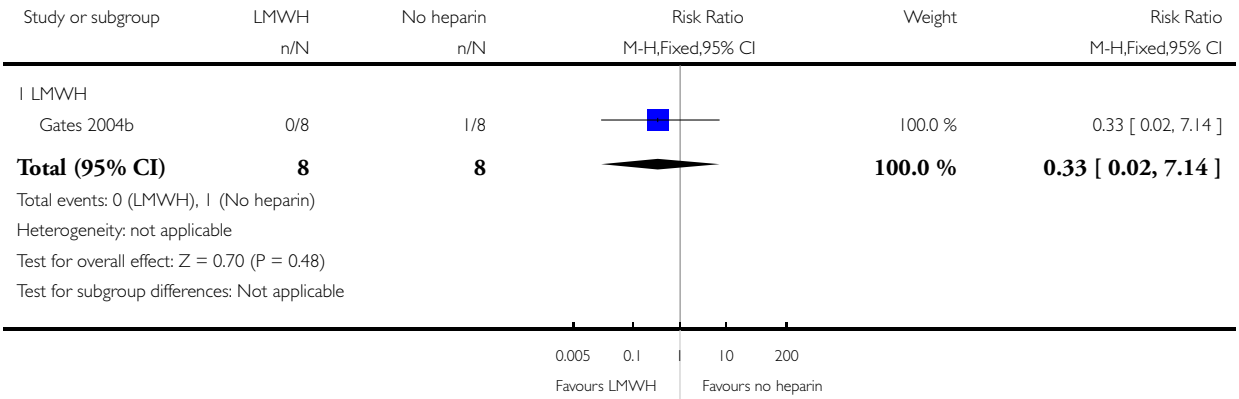
Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Gates 2004b	0/8	1/8		50.0 %	0.33 [0.02, 7.14]
Subtotal (95% CI)	**8**	**8**		**50.0 %**	**0.33 [0.02, 7.14]**
Total events: 0 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
2 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 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Total (95% CI)	**28**	**28**		**100.0 %**	**0.33 [0.04, 2.99]**
Total events: 0 (UFH/LMWH), 2 (No heparin)					
Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Chi² = 0.0, df = 1 (P = 1.00), I² =0.0%					

Analysis 1.2. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 2 Symptomatic pulmonary embolism.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 2 Symptomatic pulmonary embolism

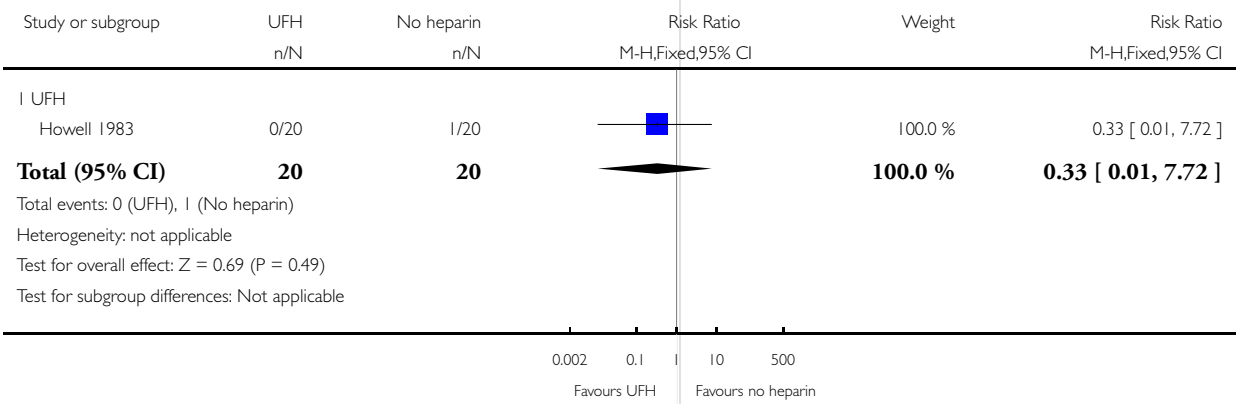


Analysis 1.3. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 3 Symptomatic deep vein thrombosis.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 3 Symptomatic deep vein thrombosis



Analysis 1.4. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 4 Blood transfusion.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 4 Blood transfusion

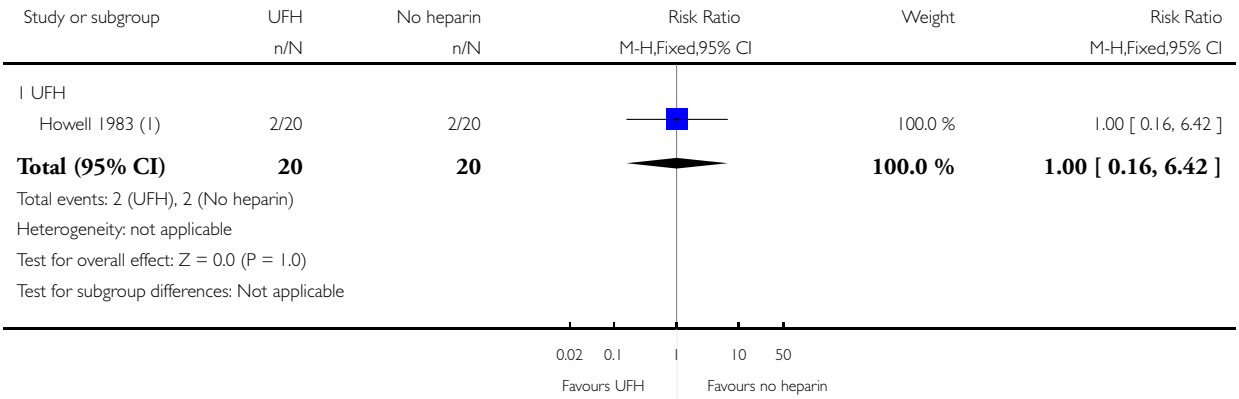
Study or subgroup	LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Gates 2004b	0/8	0/8			Not estimable
Total (95% CI)	**8**	**8**			**Not estimable**
Total events: 0 (LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

Analysis 1.5. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 5 Bleeding episodes (antenatal vaginal bleeding).

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 5 Bleeding episodes (antenatal vaginal bleeding)



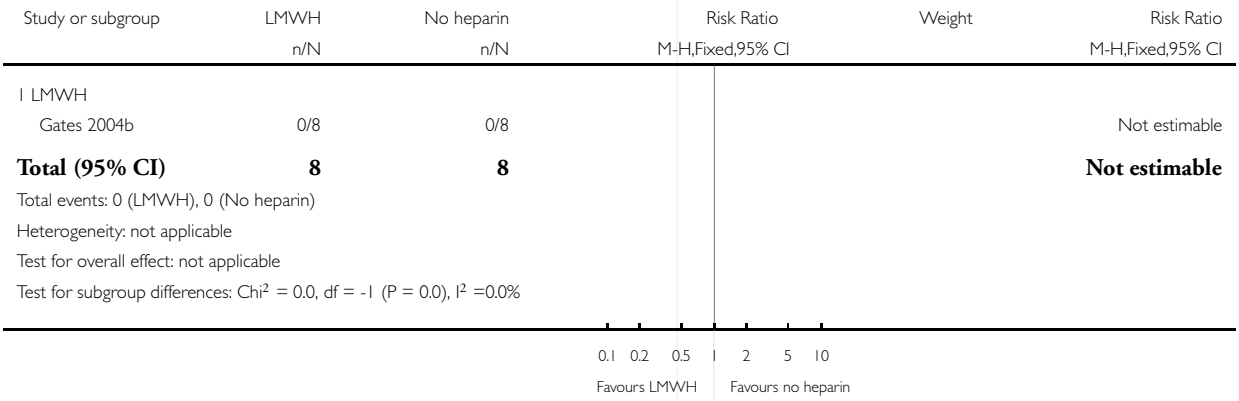
(1) Bleeding episode: antenatal vaginal bleeding

Analysis 1.6. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 6 Serious wound complications.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 6 Serious wound complications



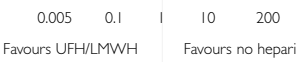
Analysis 1.7. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 7 Symptomatic osteoporosis.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 7 Symptomatic osteoporosis

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Gates 2004b	0/8	0/8			Not estimable
Subtotal (95% CI)	**8**	**8**			**Not estimable**
Total events: 0 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 UFH					
Howell 1983	1/20	0/20		100.0 %	3.00 [0.13, 69.52]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**3.00 [0.13, 69.52]**
Total events: 1 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Total (95% CI)	**28**	**28**		**100.0 %**	**3.00 [0.13, 69.52]**
Total events: 1 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

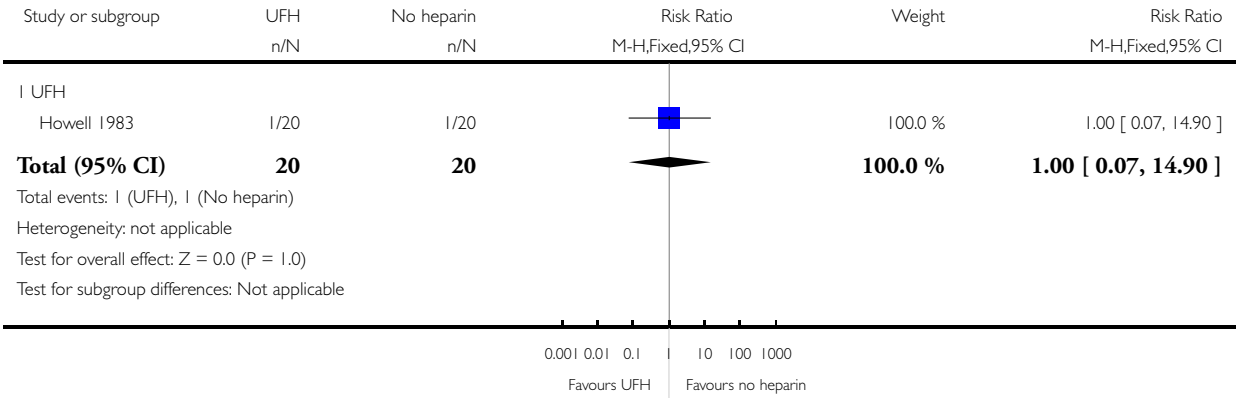


Analysis 1.8. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 8 Fetal loss.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 8 Fetal loss

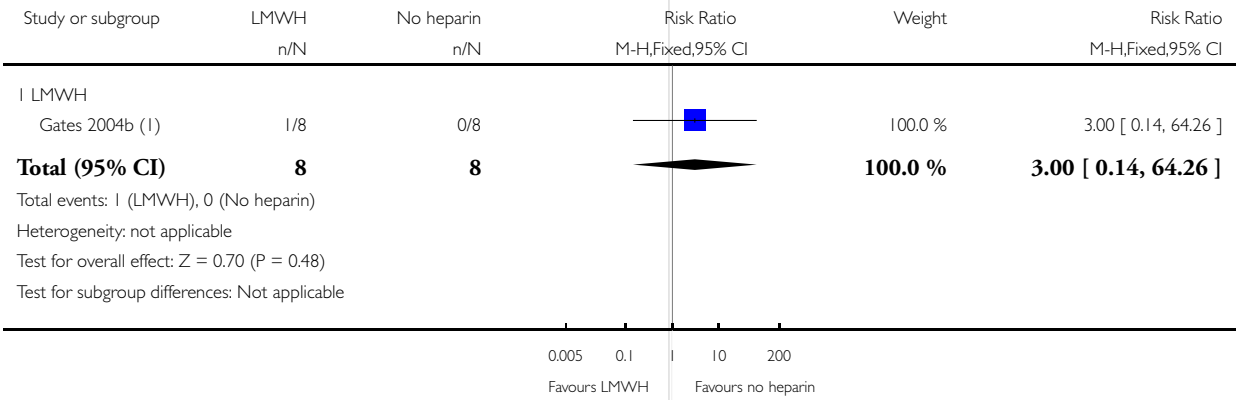


Analysis 1.9. Comparison 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo, Outcome 9 Thrombocytopenia.

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

Comparison: 1 Antenatal prophylaxis: LMWH or UFH versus no treatment or placebo

Outcome: 9 Thrombocytopenia



(1) Described as mild thrombocytopenia

Analysis 2.1. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 1 Symptomatic thromboembolic events.

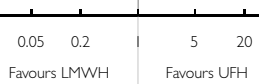
Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 1 Symptomatic thromboembolic events

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Casele 2006 (1)	2/60	4/57		100.0 %	0.48 [0.09, 2.49]
De Veciana 2001	0/61	0/60			Not estimable
Hamersley 1998	0/32	0/29			Not estimable
Pettila 1999	0/50	0/55			Not estimable
Total (95% CI)	**203**	**201**		**100.0 %**	**0.48 [0.09, 2.49]**

Total events: 2 (LMWH), 4 (UFH)
Heterogeneity: not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



(1) Not clear if events were symptomatic, described as "recurrent thrombosis".

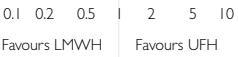
Analysis 2.2. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 2 Symptomatic pulmonary embolism.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 2 Symptomatic pulmonary embolism

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Veciana 2001	0/61	0/60			Not estimable
Hamersley 1998	0/32	0/29			Not estimable
Total (95% CI)	**93**	**89**			**Not estimable**
Total events: 0 (LMWH), 0 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 2.3. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 3 Symptomatic deep vein thrombosis.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 3 Symptomatic deep vein thrombosis

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Veciana 2001	0/61	0/60			Not estimable
Hamersley 1998	0/32	0/29			Not estimable
Total (95% CI)	**93**	**89**			**Not estimable**
Total events: 0 (LMWH), 0 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

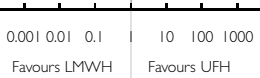
Analysis 2.4. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 4 Blood transfusion.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 4 Blood transfusion

Study or subgroup	LMWH n/N	UFH 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 (LMWH), 2 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Not applicable					



Analysis 2.5. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 5 Bleeding episodes (variously defined).

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 5 Bleeding episodes (variously defined)

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Bleeding at delivery					
Casele 2006	4/60	1/57		100.0 %	3.80 [0.44, 32.99]
Subtotal (95% CI)	**60**	**57**		**100.0 %**	**3.80 [0.44, 32.99]**
Total events: 4 (LMWH), 1 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.23)					
2 Bruises > 1 inch					
De Veciana 2001	7/61	39/60		100.0 %	0.18 [0.09, 0.36]
Subtotal (95% CI)	**61**	**60**		**100.0 %**	**0.18 [0.09, 0.36]**
Total events: 7 (LMWH), 39 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.71 (P < 0.00001)					
3 Bleeding complications					
Pettila 1999 (1)	9/50	35/55		100.0 %	0.28 [0.15, 0.53]
Subtotal (95% CI)	**50**	**55**		**100.0 %**	**0.28 [0.15, 0.53]**
Total events: 9 (LMWH), 35 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.96 (P = 0.000074)					
Test for subgroup differences: Chi^2 = 7.09, df = 2 (P = 0.03), I^2 =72%					

(1) Bleeding complications: injection-site haematoma (≥ 2 cm), bleeding during delivery and other bleeding

Analysis 2.6. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 6 Adverse 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: 6 Adverse effects sufficient to stop treatment

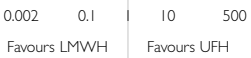
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Veciana 2001	0/61	11/60		82.9 %	0.04 [0.00, 0.71]
Pettila 1999	0/50	2/55		17.1 %	0.22 [0.01, 4.47]
Total (95% CI)	**111**	**115**		**100.0 %**	**0.07 [0.01, 0.54]**

Total events: 0 (LMWH), 13 (UFH)

Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² =0.0%

Test for overall effect: Z = 2.57 (P = 0.010)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 7 Adverse effects not sufficient to stop treatment (injection burning).

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 7 Adverse effects not sufficient to stop treatment (injection burning)

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Veciana 2001	24/61	30/60		100.0 %	0.79 [0.53, 1.18]
Total (95% CI)	**61**	**60**		**100.0 %**	**0.79 [0.53, 1.18]**

Total events: 24 (LMWH), 30 (UFH)

Heterogeneity: not applicable

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 8 Symptomatic osteoporosis.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 8 Symptomatic osteoporosis

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Casele 2006 (1)	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 (LMWH), 2 (UFH)

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

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

Test for subgroup differences: Not applicable

(1) Clinically significant bone loss (total femur)

Analysis 2.9. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 9 Fetal loss.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 9 Fetal loss

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Casele 2006 (1)	4/60	7/57		33.8 %	0.54 [0.17, 1.76]
De Veciana 2001 (2)	5/61	13/60		61.7 %	0.38 [0.14, 1.00]
Pettila 1999	1/50	1/55		4.5 %	1.10 [0.07, 17.12]
Total (95% CI)	**171**	**172**		**100.0 %**	**0.47 [0.23, 0.95]**

Total events: 10 (LMWH), 21 (UFH)

Heterogeneity: Chi^2 = 0.62, df = 2 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable

(1) Spontaneous abortion

(2) This included stillbirths at < 20 weeks

Analysis 2.10. Comparison 2 Antenatal prophylaxis: LMWH versus UFH, Outcome 10 Thrombocytopenia.

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

Comparison: 2 Antenatal prophylaxis: LMWH versus UFH

Outcome: 10 Thrombocytopenia

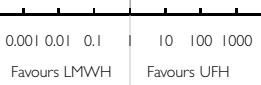
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Veciana 2001	0/61	0/60			Not estimable
Hamersley 1998	0/32	2/29		100.0 %	0.18 [0.01, 3.64]
Pettila 1999	0/50	0/55			Not estimable
Total (95% CI)	**143**	**144**		**100.0 %**	**0.18 [0.01, 3.64]**

Total events: 0 (LMWH), 2 (UFH)

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable



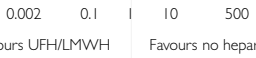
Analysis 3.1. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 1 Symptomatic thromboembolic events.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 1 Symptomatic thromboembolic events

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	1/39	0/37		10.8 %	2.85 [0.12, 67.83]
Gates 2004a	1/66	0/68		10.4 %	3.09 [0.13, 74.51]
Subtotal (95% CI)	**105**	**105**		**21.1 %**	**2.97 [0.31, 28.03]**
Total events: 2 (UFH/LMWH), 0 (No heparin)					
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			Not estimable
Welti 1981 (1)	3/272	4/308		78.9 %	0.85 [0.19, 3.76]
Subtotal (95% CI)	**297**	**333**		**78.9 %**	**0.85 [0.19, 3.76]**
Total events: 3 (UFH/LMWH), 4 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					
Total (95% CI)	**402**	**438**		**100.0 %**	**1.30 [0.39, 4.27]**
Total events: 5 (UFH/LMWH), 4 (No heparin)					
Heterogeneity: Chi^2 = 0.83, df = 2 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Chi^2 = 0.83, df = 1 (P = 0.36), I^2 =0.0%					



(1) Not clear whether symptomatic. All thromboses and embolisms.

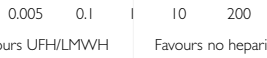
Analysis 3.2. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 2 Symptomatic pulmonary embolism.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 2 Symptomatic pulmonary embolism

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	0/39	0/37			Not estimable
Gates 2004a	1/66	0/68		14.9 %	3.09 [0.13, 74.51]
Subtotal (95% CI)	**105**	**105**		**14.9 %**	**3.09 [0.13, 74.51]**
Total events: 1 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 UFH					
Hill 1988	0/25	0/25			Not estimable
Welti 1981	2/272	3/308		85.1 %	0.75 [0.13, 4.48]
Subtotal (95% CI)	**297**	**333**		**85.1 %**	**0.75 [0.13, 4.48]**
Total events: 2 (UFH/LMWH), 3 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
Total (95% CI)	**402**	**438**		**100.0 %**	**1.10 [0.25, 4.87]**
Total events: 3 (UFH/LMWH), 3 (No heparin)					
Heterogeneity: Chi^2 = 0.58, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.13 (P = 0.90)					
Test for subgroup differences: Chi^2 = 0.57, df = 1 (P = 0.45), I^2 =0.0%					



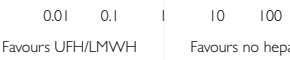
Analysis 3.3. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 3 Symptomatic deep vein thrombosis.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 3 Symptomatic deep vein thrombosis

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	1/39	0/37		35.3 %	2.85 [0.12, 67.83]
Gates 2004a	0/66	0/68			Not estimable
Subtotal (95% CI)	**105**	**105**		**35.3 %**	**2.85 [0.12, 67.83]**
Total events: 1 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
2 UFH					
Hill 1988	0/25	0/25			Not estimable
Welti 1981	1/272	1/308		64.7 %	1.13 [0.07, 18.02]
Subtotal (95% CI)	**297**	**333**		**64.7 %**	**1.13 [0.07, 18.02]**
Total events: 1 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
Total (95% CI)	**402**	**438**		**100.0 %**	**1.74 [0.23, 13.31]**
Total events: 2 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.53 (P = 0.59)					
Test for subgroup differences: Chi^2 = 0.18, df = 1 (P = 0.67), I^2 =0.0%					



Analysis 3.4. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 4 Blood transfusion.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 4 Blood transfusion

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	0/39	1/37		38.1 %	0.32 [0.01, 7.54]
Gates 2004a	0/69	0/71			Not estimable
Subtotal (95% CI)	**108**	**108**		**38.1 %**	**0.32 [0.01, 7.54]**
Total events: 0 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 UFH					
Hill 1988	0/25	2/25		61.9 %	0.20 [0.01, 3.97]
Subtotal (95% CI)	**25**	**25**		**61.9 %**	**0.20 [0.01, 3.97]**
Total events: 0 (UFH/LMWH), 2 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**133**	**133**		**100.0 %**	**0.24 [0.03, 2.13]**
Total events: 0 (UFH/LMWH), 3 (No heparin)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%					

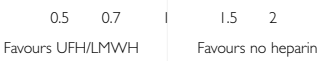
Analysis 3.5. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 5 Bleeding episodes (variously defined).

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 5 Bleeding episodes (variously defined)

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Major bleeding					
Burrows 2001	0/39	0/37			Not estimable
Subtotal (95% CI)	**39**	**37**			**Not estimable**
Total events: 0 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Major bruising					
Burrows 2001	0/39	0/37			Not estimable
Subtotal (95% CI)	**39**	**37**			**Not estimable**
Total events: 0 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Bleeding/bruising reported at discharge					
Gates 2004a	6/69	1/71		100.0 %	6.17 [0.76, 49.96]
Subtotal (95% CI)	**69**	**71**		**100.0 %**	**6.17 [0.76, 49.96]**
Total events: 6 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.088)					
4 "Complications h morragiques"					
Welti 1981	40/272	9/308		100.0 %	5.03 [2.49, 10.18]
Subtotal (95% CI)	**272**	**308**		**100.0 %**	**5.03 [2.49, 10.18]**
Total events: 40 (UFH/LMWH), 9 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.50 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 =0.0%					



Analysis 3.6. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 6 Serious wound complications.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 6 Serious wound complications

Study or subgroup	UFH/LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	0/39	0/37			Not estimable
Gates 2004a	1/69	1/71		100.0 %	1.03 [0.07, 16.13]
Subtotal (95% CI)	**108**	**108**		**100.0 %**	**1.03 [0.07, 16.13]**
Total events: 1 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
2 UFH					
Hill 1988	0/25	0/25			Not estimable
Subtotal (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (UFH/LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**133**	**133**		**100.0 %**	**1.03 [0.07, 16.13]**
Total events: 1 (UFH/LMWH), 1 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
Test for subgroup differences: Not applicable					

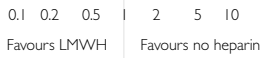
Analysis 3.7. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 7 Adverse effects sufficient to stop treatment.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 7 Adverse effects sufficient to stop treatment

Study or subgroup	LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Gates 2004a	0/69	0/71			Not estimable
Total (95% CI)	**69**	**71**			**Not estimable**
Total events: 0 (LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					



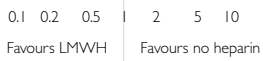
Analysis 3.8. Comparison 3 Caesarean section: LMWH or UFH versus no treatment or placebo, Outcome 8 Adverse effects not sufficient to stop treatment.

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

Comparison: 3 Caesarean section: LMWH or UFH versus no treatment or placebo

Outcome: 8 Adverse effects not sufficient to stop treatment

Study or subgroup	LMWH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 LMWH					
Burrows 2001	0/39	0/37			Not estimable
Total (95% CI)	**39**	**37**			**Not estimable**
Total events: 0 (LMWH), 0 (No heparin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					



Analysis 4.1. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 1 Symptomatic thromboembolic events.

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

Comparison: 4 Caesarean section: LMWH versus UFH

Outcome: 1 Symptomatic thromboembolic events

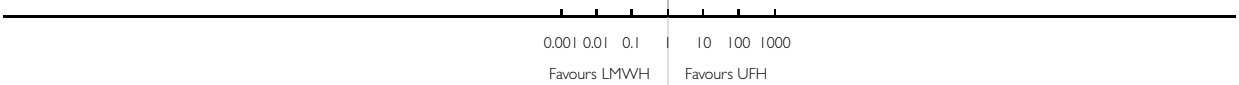
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6			Not estimable
Heilmann 2007 (1)	0/50	1/50		100.0 %	0.33 [0.01, 7.99]
Krauss 1994 (2)	0/50	0/50			Not estimable
Total (95% CI)	**111**	**106**		**100.0 %**	**0.33 [0.01, 7.99]**

Total events: 0 (LMWH), 1 (UFH)

Heterogeneity: not applicable

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

Test for subgroup differences: Not applicable



(1) Not clear whether symptomatic

(2) Not clear whether events were symptomatic

Analysis 4.2. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 2 Symptomatic pulmonary embolism.

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

Comparison: 4 Caesarean section: LMWH versus UFH

Outcome: 2 Symptomatic pulmonary embolism

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6			Not estimable
Total (95% CI)	**11**	**6**			**Not estimable**
Total events: 0 (LMWH), 0 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

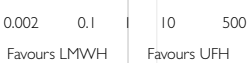
Analysis 4.3. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 3 Symptomatic deep vein thrombosis.

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

Comparison: 4 Caesarean section: LMWH versus UFH

Outcome: 3 Symptomatic deep vein thrombosis

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6			Not estimable
Heilmann 2007 (1)	0/50	1/50		100.0 %	0.33 [0.01, 7.99]
Krauss 1994 (2)	0/50	0/50			Not estimable
Total (95% CI)	**111**	**106**		**100.0 %**	**0.33 [0.01, 7.99]**
Total events: 0 (LMWH), 1 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					



(1) Not clear whether symptomatic

(2) Not clear whether events symptomatic

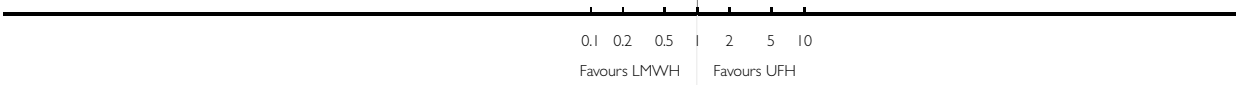
Analysis 4.4. Comparison 4 Caesarean section: LMWH versus UFH, Outcome 4 Bleeding episodes ("haemorrhagic events").

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

Comparison: 4 Caesarean section: LMWH versus UFH

Outcome: 4 Bleeding episodes ("haemorrhagic events")

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gibson 1998	0/11	0/6			Not estimable
Total (95% CI)	**11**	**6**			**Not estimable**
Total events: 0 (LMWH), 0 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

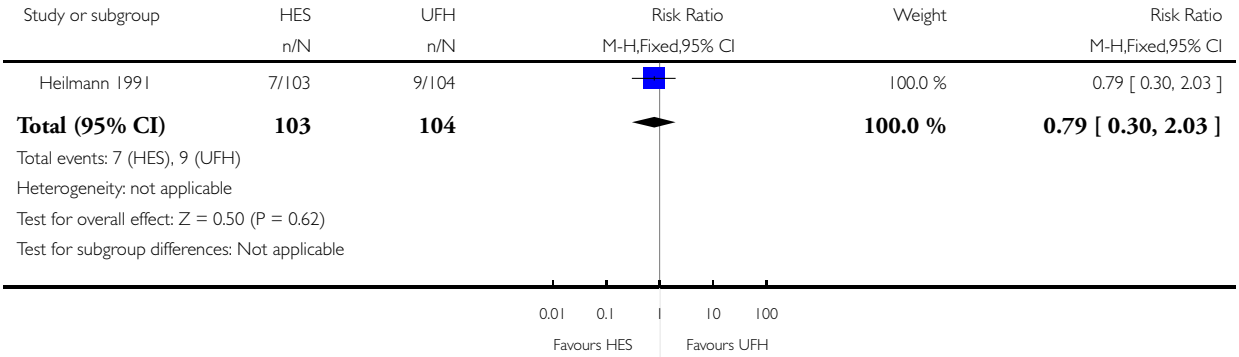


Analysis 5.1. Comparison 5 Caesarean section: HES versus UFH, Outcome 1 Asymptomatic thromboembolic events.

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

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 1 Asymptomatic thromboembolic events

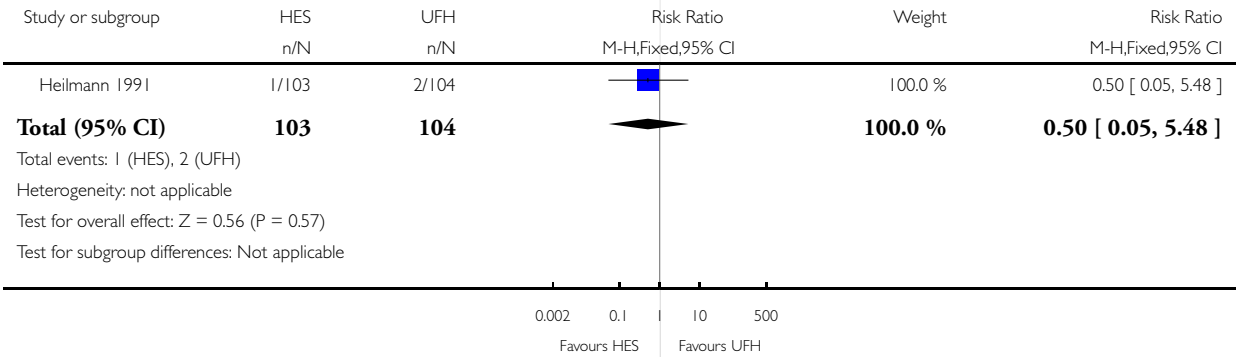


Analysis 5.2. Comparison 5 Caesarean section: HES versus UFH, Outcome 2 Blood transfusion.

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

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 2 Blood transfusion



Analysis 5.3. Comparison 5 Caesarean section: HES versus UFH, Outcome 3 Bleeding episodes.

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

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 3 Bleeding episodes

Study or subgroup	HES n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	2/103	5/104		100.0 %	0.40 [0.08, 2.03]
Total (95% CI)	**103**	**104**		**100.0 %**	**0.40 [0.08, 2.03]**
Total events: 2 (HES), 5 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Not applicable					

Analysis 5.4. Comparison 5 Caesarean section: HES versus UFH, Outcome 4 Serious wound complications.

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

Comparison: 5 Caesarean section: HES versus UFH

Outcome: 4 Serious wound complications

Study or subgroup	HES n/N	UFH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heilmann 1991	6/103	9/104		100.0 %	0.67 [0.25, 1.82]
Total (95% CI)	**103**	**104**		**100.0 %**	**0.67 [0.25, 1.82]**
Total events: 6 (HES), 9 (UFH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					
Test for subgroup differences: Not applicable					

Analysis 6.1. Comparison 6 Caesarean section: five-day LMWH versus 10-day LMWH, Outcome 1 Maternal death.

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

Comparison: 6 Caesarean section: five-day LMWH versus 10-day LMWH

Outcome: 1 Maternal death

Study or subgroup	5 day LMWH n/N	10 day LMWH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cruz 2011	0/311	0/335			Not estimable
Total (95% CI)	**311**	**335**			**Not estimable**

Total events: 0 (5 day LMWH), 0 (10 day LMWH)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Analysis 6.2. Comparison 6 Caesarean section: five-day LMWH versus 10-day LMWH, Outcome 2 Symptomatic thromboembolic events.

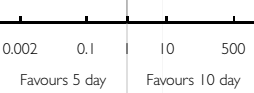
Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 6 Caesarean section: five-day LMWH versus 10-day LMWH

Outcome: 2 Symptomatic thromboembolic events

Study or subgroup	5 day LMWH n/N	10 day LMWH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cruz 2011	0/311	1/335		100.0 %	0.36 [0.01, 8.78]
Total (95% CI)	**311**	**335**		**100.0 %**	**0.36 [0.01, 8.78]**

Total events: 0 (5 day LMWH), 1 (10 day LMWH)
Heterogeneity: not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6 Caesarean section: five-day LMWH versus 10-day LMWH, Outcome 3 Symptomatic pulmonary embolism.

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

Comparison: 6 Caesarean section: five-day LMWH versus 10-day LMWH

Outcome: 3 Symptomatic pulmonary embolism

Study or subgroup	5 day LMWH n/N	10 day LMWH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cruz 2011	0/311	1/335		100.0 %	0.36 [0.01, 8.78]
Total (95% CI)	**311**	**335**		**100.0 %**	**0.36 [0.01, 8.78]**
Total events: 0 (5 day LMWH), 1 (10 day LMWH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: Not applicable					

Analysis 6.4. Comparison 6 Caesarean section: five-day LMWH versus 10-day LMWH, Outcome 4 Symptomatic deep vein thrombosis.

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

Comparison: 6 Caesarean section: five-day LMWH versus 10-day LMWH

Outcome: 4 Symptomatic deep vein thrombosis

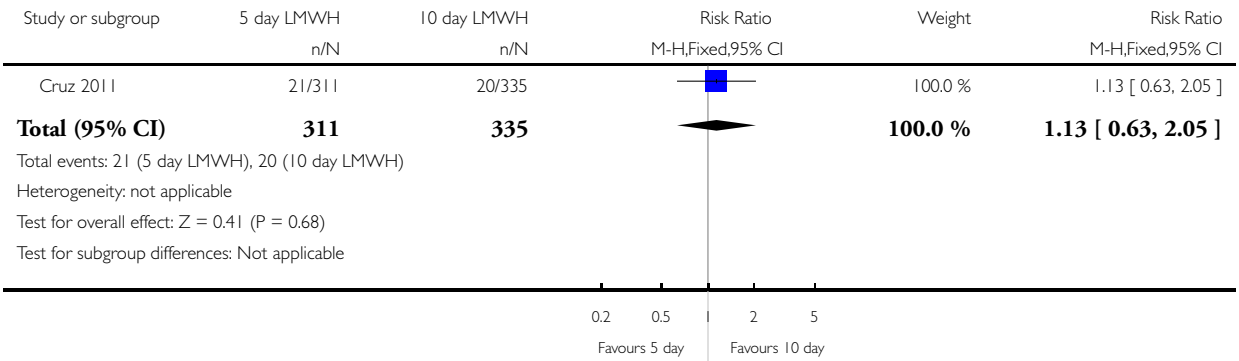
Study or subgroup	5 day LMWH n/N	10 day LMWH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cruz 2011	0/311	0/335			Not estimable
Total (95% CI)	**311**	**335**			**Not estimable**
Total events: 0 (5 day LMWH), 0 (10 day LMWH)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 6.5. Comparison 6 Caesarean section: five-day LMWH versus 10-day LMWH, Outcome 5 Post-caesarean infection.

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

Comparison: 6 Caesarean section: five-day LMWH versus 10-day LMWH

Outcome: 5 Post-caesarean infection

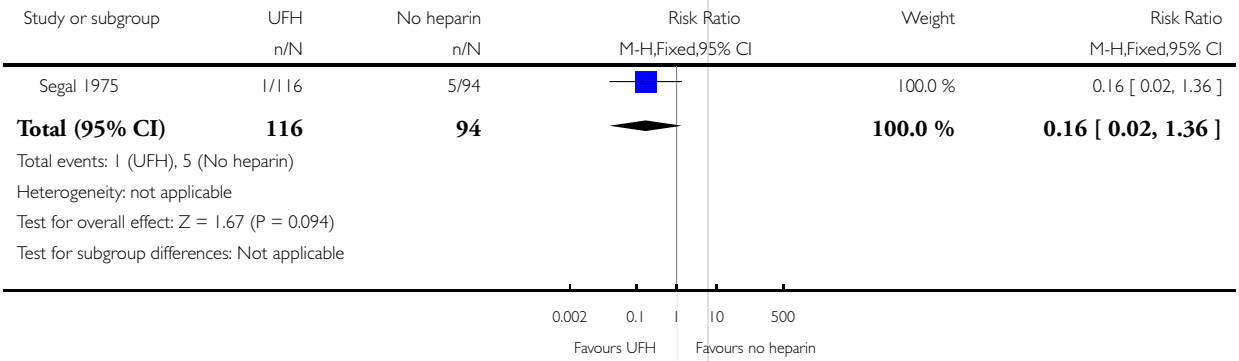


Analysis 7.1. Comparison 7 Postnatal (including after vaginal deliveries): UFH versus no treatment, Outcome 1 Symptomatic thromboembolic events.

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

Comparison: 7 Postnatal (including after vaginal deliveries): UFH versus no treatment

Outcome: 1 Symptomatic thromboembolic events



Analysis 7.2. Comparison 7 Postnatal (including after vaginal deliveries): UFH versus no treatment, Outcome 2 Symptomatic pulmonary embolism.

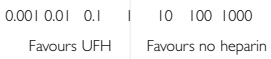
Review: Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period

Comparison: 7 Postnatal (including after vaginal deliveries): UFH versus no treatment

Outcome: 2 Symptomatic pulmonary embolism

Study or subgroup	UFH n/N	No heparin 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 (UFH), 2 (No heparin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7 Postnatal (including after vaginal deliveries): UFH versus no treatment, Outcome 3 Symptomatic deep vein thrombosis.

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

Comparison: 7 Postnatal (including after vaginal deliveries): UFH versus no treatment

Outcome: 3 Symptomatic deep vein thrombosis

Study or subgroup	UFH n/N	No heparin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Segal 1975	1/116	3/94		100.0 %	0.27 [0.03, 2.55]
Total (95% CI)	**116**	**94**		**100.0 %**	**0.27 [0.03, 2.55]**

Total events: 1 (UFH), 3 (No heparin)
Heterogeneity: not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Data on thromboembolic events from studies excluded based on indication for treatment

Trial	Inclusion criteria	Intervention and control	Thromboembolic events
Badawy 2008	Pregnant women, before 8 weeks' gestation, with a history of 3 of more consecutive first trimester miscarriages without identifiable aetiology after full investigations	**LMWH (n = 170)** LMWH 20 mg once daily from randomisation until 34 weeks' gestation and folic acid 0.5 mg daily until 13 weeks' gestation **Control (n = 170)** Folic acid 0.5 mg daily until 13 weeks' gestation.	**DVT** 2/170 in LMWH group versus 4/170 in control group. **Total thromboembolic events** 4 in intervention group (LMWH) (2 in pregnancy and 2 postpartum) ; not reported for the control group
Brenner 2005	Pregnant women at 5 to 10 weeks' gestation, with thrombophilia and a history of repeat pregnancy loss (with repeat pregnancy loss defined as 3 losses during the first trimester; 2 in the second trimester; or 1 intrauterine fetal death in the third trimester)	**Low-dose LMWH (n = 89)** LMWH 40 mg once daily from 5-10 weeks' gestation until 6 weeks postpartum **High-dose LMWH (n = 91)** LMWH 80 mg once daily from 5-10 weeks' gestation until 6 weeks postpartum	**Thrombotic episodes** No cases in either group.
de Vries 2005	Pregnant women at less than 12 weeks' gestation, who had had a previous birth at less than 34 weeks with a hypertensive disorder of pregnancy and/or a small-for-gestational-age infant; who had inheritable thrombophilia; and did not have antiphospholipid antibodies detected	**LMWH and aspirin (n = 70)** LMWH 5000 IU daily (weight-adjusted dose) from 6-12 weeks until labour and aspirin 80 mg daily from 12 weeks until 36 weeks **Aspirin (n = 69)** Aspirin 80 mg daily from 12 weeks until 36 weeks.	**Superficial thrombophlebitis (antepartum)** 0/70 in LMWH and aspirin group versus 1/69 in aspirin group. **DVT (postpartum)** 0/70 in LMWH and aspirin group versus 1/69 in aspirin group.
Farquharson 2002	Pregnant women, at less than 12 weeks' gestation, with antiphospholipid syndrome and recurrent miscarriage (defined as at least 3 consecutive pregnancy losses or 2 consecutive losses with proven fetal death after 10 weeks' gestation)	**LMWH and aspirin (n = 51)** LMWH 5000 U subcutaneously and low-dose aspirin 75 mg daily until birth **Aspirin (n = 47)** Low-dose aspirin 75 mg daily until birth.	**Thrombosis** No cases in either group.
Giancotti 2012	Pregnant women with a history of 2 or more pregnancy losses (including women who were both positive and negative to thrombophilic screening)	**Aspirin (n = 56)** Aspirin 100 mg daily until the third month of pregnancy. **LMWH (n = 53)** LMWH 40 mg daily until the third month of pregnancy. **LMWH and aspirin (n = 58)** LMWH 40 mg and aspirin 100 mg daily until the third month of pregnancy	**Thrombosis** No cases in the three groups; quote: "all patients did not show collateral effects, i.e. thrombosis"

Table 1. Data on thromboembolic events from studies excluded based on indication for treatment (*Continued*)

Gris 2010	Pregnant women with previous abruptio placentae but no fetal loss during their first pregnancy and negative for antiphospholipid antibodies	**LMWH (n = 80)** LMWH 4000 IU subcutaneously daily from pregnancy confirmation until 36 weeks or birth **No LMWH (n = 80)** No treatment.	**Symptomatic DVT** No cases in either group. **Symptomatic PE** No cases in either group. **Superfician vein thrombosis (postpartum)** 0/80 in LMWH group versus 2/80 in no LMWH group.
Gris 2011	Pregnant women with previous severe pre-eclampsia but no fetal loss during their first pregnancy and negative for antiphospholipid antibodies	**LMWH (n = 112)** LMWH 4000 IU subcutaneously daily from pregnancy confirmation **No LMWH (n = 112)** No treatment.	**Symptomatic DVT** No cases in either group. **Symptomatic PE** No cases in either group. **Superfician vein thrombosis** No cases in either group.
Rai 1997	Pregnant women with positive results for phospholipid antibodies on at least 2 occasions more than 8 weeks apart, with a history of 3 or more consecutive miscarriages	**UFH and aspirin (n = 45)** UFH 500 IU 12-hourly in addition to low-dose aspirin 75 mg daily until miscarriage or 34 weeks **Aspirin (n = 45)** Low-dose aspirin 75 mg daily until miscarriage of 34 weeks.	**Thromboembolic complications (during pregnancy or postpartum)** No cases in either group.
Visser 2011	Pregnant women, less than 7 weeks' gestation, with or without thrombophilia, with recurrent miscarriage (defined as 3 or more consecutive first trimester miscarriages; 2 or more second trimester miscarriages; or one-third trimester fetal loss with 1 first trimester miscarriage	**LMWH (n = 68)** LMWH 40 mg daily subcutaneously and placebo orally daily. **LMWH and aspirin (n = 63)** LMWH 40 mg subcutaneously and aspirin 100 mg orally daily. **Aspirin (n = 76)** Aspirin 100 mg orally daily. Aspirin and placebo were discontinued at 36 weeks; LMWH was continued until labour	**PE** 1/76 in aspirin group (at 8 weeks' gestation).

DVT: deep vein thrombosis
IU: international units
LMWH: low molecular weight heparin
PE: pulmonary embolism
UFH: unfractionated heparin

FEEDBACK

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: 27 November 2013.

Date	Event	Description
27 November 2013	New search has been performed	Review updated. Three new authors contributed to this update
27 November 2013	New citation required but conclusions have not changed	Search updated. Four new trials have been included (Cruz 2011; De Veciana 2001; Hamersley 1998; O'Riordan 2008); two of which were awaiting classification in the previous version of the review. Seven studies have been excluded (Gris 2010; Gris 2011; Harenberg 1993; Kamin 2008; Pyregov 2012; Ratiu 2009; Visser 2011) (two trials were awaiting classification in the previous version of the review, and one was previously included (Harenberg 1993)). Six new trials have been classified as ongoing. Two studies remain awaiting classification. The main conclusions are unaltered

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 2, 2002

Date	Event	Description
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.
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, E Bain and A Wilson assessed study eligibility and carried out data extraction, in conjunction with P Middleton. All review authors contributed to the interpretation of results, text of the review and commented on drafts.

DECLARATIONS OF INTEREST

S Gates and L-J Davis were involved in the conduct of two studies included in this review (Gates 2004a; Gates 2004b); the other review authors assessed these studies for inclusion, extracted data and assessed the risk of bias.

SOURCES OF SUPPORT

Internal sources

- The University of Liverpool, UK.
- ARCH, The Robinson Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

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

This grant provided support for the 2010 published version of this review (Tooher 2010).

- National Health and Medical Research Council, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this updated version, the background and the methods section, including 'Risk of bias' assessment, have been updated. We have clarified that we will include studies reported only as abstracts in analyses where it is possible to extract relevant data from the text. When this is not possible, we will include the studies in awaiting assessment, pending full publication of their results, or further contact from the study authors.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy