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Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period (Review)

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[Intervention Review]

Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period

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ABSTRACT

Background

Venous thromboembolism (VTE), although rare, is a major cause of maternal mortality and morbidity. Some women are at increased risk of VTE during pregnancy and the early postnatal period (e.g. caesarean section, family history of VTE, or thrombophilia), and so prophylaxis may be considered. As some methods of prophylaxis carry risks of adverse effects, and risk of VTE is often low, benefits of thromboprophylaxis may be outweighed by harms.

Objectives

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

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (18 October 2019). In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (18 October 2019).

Selection criteria

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

Data collection and analysis

At least two review authors assessed trial eligibility, extracted data, assessed risk of bias, and judged certainty of evidence for selected critical outcomes (using GRADE). We conducted fixed-effect meta-analysis and reported data (all dichotomous) as summary risk ratios (RRs) with 95% confidence intervals (CIs).

Main results

Twenty-nine trials (involving 3839 women), overall at moderate to high risk of bias were included. Trials were conducted across the antenatal, peripartum and postnatal periods, with most in high-income countries. Interventions included types and regimens of heparin (low molecular weight heparin (LMWH) and unfractionated heparin (UFH)), hydroxyethyl starch (HES), and compression stockings or devices. Data were limited due to a small number of trials in comparisons and/or few or no events reported. All critical outcomes (assessed

for comparisons of heparin versus no treatment/placebo, and LMWH versus UFH) were considered to have very low-certainty evidence, downgraded mainly for study limitations and imprecise effect estimates. Maternal death was not reported in most studies.

Antenatal (± postnatal) prophylaxis

For the primary outcomes symptomatic thromboembolic events pulmonary embolism (PE) and/or deep vein thrombosis (DVT), and the critical outcome of adverse effects sufficient to stop treatment, the evidence was very uncertain.

Symptomatic thromboembolic events:

- heparin versus no treatment/placebo (RR 0.39; 95% CI 0.08 to 1.98; 4 trials, 476 women; very low-certainty evidence);

- LMWH versus UFH (RR 0.47; 95% CI 0.09 to 2.49; 4 trials, 404 women; very low-certainty evidence);

Symptomatic PE:

- heparin versus no treatment/placebo (RR 0.33; 95% CI 0.02 to 7.14; 3 trials, 187 women; very low-certainty evidence);

- LMWH versus UFH (no events; 3 trials, 287 women);

Symptomatic DVT:

- heparin versus no treatment/placebo (RR 0.33; 95% CI 0.04 to 3.10; 4 trials, 227 women; very low-certainty evidence);

- LMWH versus UFH (no events; 3 trials, 287 women);

Adverse effects sufficient to stop treatment:

- heparin versus no treatment/placebo (RR 0.49; 95% CI 0.05 to 5.31; 1 trial, 139 women; very low-certainty evidence);

- LMWH versus UFH (RR 0.07; 95% CI 0.01 to 0.54; 2 trials, 226 women; very low-certainty evidence).

Peripartum/postnatal prophylaxis

Vaginal or caesarean birth

When UFH and no treatment were compared, the effects on symptomatic thromboembolic events (RR 0.16; 95% CI 0.02 to 1.36; 1 trial, 210 women; very low-certainty evidence), symptomatic PE (RR 0.16; 95% CI 0.01 to 3.34; 1 trial, 210 women; very low-certainty evidence), and symptomatic DVT (RR 0.27; 95% CI 0.03 to 2.55; 1 trial, 210 women; very low-certainty evidence) were very uncertain. Maternal death and adverse effects sufficient to stop treatment were not reported.

Caesarean birth

Symptomatic thromboembolic events:

- heparin versus no treatment/placebo (RR 1.30; 95% CI 0.39 to 4.27; 4 trials, 840 women; very low-certainty evidence);

- LMWH versus UFH (RR 0.33; 95% CI 0.01 to 7.99; 3 trials, 217 women; very low-certainty evidence);

Symptomatic PE:

- heparin versus no treatment/placebo (RR 1.10; 95% CI 0.25 to 4.87; 4 trials, 840 women; very low-certainty evidence);

- LMWH versus UFH (no events; 3 trials, 217 women);

Symptomatic DVT:

- heparin versus no treatment/placebo (RR 1.30; 95% CI 0.24 to 6.94; 5 trials, 1140 women; very low-certainty evidence); LMWH versus UFH (RR 0.33; 95% CI 0.01 to 7.99; 3 trials, 217 women; very low-certainty evidence);

Maternal death:

- heparin versus placebo (no events, 1 trial, 300 women);

Adverse effects sufficient to stop treatment:

- heparin versus placebo (no events; 1 trial, 140 women).

Postnatal prophylaxis

No events were reported for LMWH versus no treatment/placebo for: symptomatic thromboembolic events, symptomatic PE and symptomatic DVT (all 2 trials, 58 women), or maternal death (1 trial, 24 women). Adverse effects sufficient to stop treatment were not reported.

We were unable to conduct subgroup analyses due to lack of data.

Sensitivity analysis including the nine studies at low risk of bias did not impact overall findings.

Authors' conclusions

The evidence is very uncertain about benefits and harms of VTE thromboprophylaxis in women during pregnancy and the early postnatal period at increased risk of VTE. Further high-quality very large-scale randomised trials are needed to determine effects of currently used treatments in women with different VTE risk factors. As sufficiently large definitive trials are unlikely to be funded, secondary data analyses based on high-quality registry data are important.

PLAIN LANGUAGE SUMMARY

Preventing venous thromboembolism in women during pregnancy, childbirth and after birth

We set out to determine from randomised controlled trials the benefits and harms of treatments during pregnancy, childbirth, and after birth to prevent deep vein clots in women who are at increased risk.

What is the issue?

A blood clot can form in a deep vein, usually in the legs. This is known as deep vein thrombosis (DVT). If part of the clot breaks off it can be carried in the blood to the lungs and block blood vessels there. This is called a pulmonary embolism (PE), and can cause death, although this is rare. Together these are known as venous thromboembolism (VTE) disease. A women's clotting system is more active during pregnancy to protect her from excessive bleeding during birth. Some women are at a higher risk of VTE during pregnancy and around the time of childbirth including women with previous VTE, thrombophilia (a condition which makes people more likely to develop clots) and following a caesarean birth.

Why is this important?

Women at increased risk of VTE during pregnancy and in the six weeks following childbirth are commonly given treatments to prevent blood clots. Treatments vary due to lack of clear guidelines. The treatments to prevent VTE include heparin type drugs, aspirin and the wearing of compression stockings to improve blood flow in the legs. Some of the treatments can potentially harm women, for example, by increasing blood loss after childbirth or interfering with wound healing.

What evidence did we find?

This is an update of a Cochrane Review published in 2014. We searched for new evidence in October 2019. Twenty-nine randomised controlled studies, involving 3839 women, are now included. The studies were published from 1975 to 2016 and were mainly carried out in high-income countries. They included women at increased risk of VTE who were pregnant, in childbirth, and after the birth. Treatments assessed included different types and doses of heparin (of low molecular weight heparin and unfractionated heparin), and compression stockings or devices. No deaths occurred. The reported findings were supported by very low-certainty evidence.

Starting treatment during pregnancy (with or without treatment after childbirth): we looked at the occurrence of symptomatic VTE and adverse effects that caused women to stop treatment. Any benefits of heparin were unclear when compared with no treatment or a placebo (assessed in up to four studies with 476 women). Similarly, for different types of heparin (assessed in up to four studies with 404 women), different doses of low molecular weight heparin (in one study with 144 women), and for compression stockings compared with no stockings (in one study with 44 women).

For treatment during and following vaginal or caesarean birth: we are very uncertain about the effects of heparin when compared with no treatment on the occurrence of symptomatic VTE (assessed in one study with 210 women). This study did not report on adverse effects that led women to stop treatment.

For treatment during and following caesarean birth: we are very uncertain about the effects of heparin compared with no treatment or a placebo (assessed in up to five studies with 1140 women). The studies looked at different types or doses of heparin, and compression devices compared with bed rest (in one study of 49 women). No adverse effects stopping treatment were reported.

Looking at treatment following vaginal or caesarean birth: no symptomatic VTEs were reported in women receiving either heparin or no treatment or placebo in two studies (58 women). No study reported on adverse effects leading to women stopping treatment.

What does this mean?

We are very uncertain if the benefits of treatments used to prevent deep vein clots in high-risk women during pregnancy and around the time of childbirth outweigh any harms. Small numbers of studies were included in the comparisons with a range of outcomes measured and low numbers of events. Some studies had design limitations and definitions of blood clotting risk factors and outcomes were not always clear. More, large, high-quality studies are needed.

SUMMARY OF FINDINGS

Summary of findings 1. Antenatal (± postnatal) prophylaxis: heparin (LMWH or UFH) versus no treatment/placebo

Antenatal (± postnatal) prophylaxis: heparin (LMWH or UFH) versus no treatment/placebo for venous thromboembolic disease

Population: pregnant women at increased risk of VTE during pregnancy and the early postnatal period

Settings: UK (2 trials), Australia and Sweden (1 trial), Canada and USA (1 trial), Australia, the Netherlands and Sweden (1 trial)

Intervention: heparin (LMWH (4 trials) or UFH (1 trial))

Comparison: no treatment (3 trials) or placebo (2 trials)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment/placebo	Risk with heparin				
Maternal death	Not reported					
Symptomatic thromboembolic events (follow-up: 6 weeks postpartum)	Study population		RR 0.39 (0.08 to 1.98)	476 (4 trials)	⊕⊖⊖⊖ very low [1, 2, 3]	1 trial reported no events.
	17 per 1000	7 per 1000 (1 to 34)				
Symptomatic PE (follow-up: 6 weeks postpartum)	Study population		RR 0.33 (0.02 to 7.14)	187 (3 trials)	⊕⊖⊖⊖ very low [1, 2, 3, 4]	2 trials reported no events.
	11 per 1000	4 per 1000 (0 to 77)				
Symptomatic DVT (follow-up: 6 weeks postpartum)	Study population		RR 0.33 (0.04 to 3.10)	227 (4 trials)	⊕⊖⊖⊖ very low [1, 3, 4]	2 trials reported no events.
	18 per 1000	6 per 1000 (1 to 55)				
Adverse effects sufficient to stop treatment	Study population		RR 0.49 (0.05 to 5.31)	139 (1 trial)	⊕⊖⊖⊖ very low [1, 3, 4]	3 events: heparin (LMWH) 1 event (bleeding from placental praevia); no treatment 2 events (both stomach complaints)
	29 per 1000	14 per 1000 (1 to 154)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **DVT:** deep vein thrombosis; **LMWH**: low molecular weight heparin; **PE:** pulmonary embolism; **RR:** Risk Ratio;**UFH**: unfractionated heparin; **VTE**: venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Design limitations (-1): unclear risk of selective reporting bias; not downgraded for lack of blinding as unlikely to have influenced objective outcome
[2] Imprecision (-2): few events and wide confidence intervals crossing the line of no effect
[3] Indirectness (-1): women had specific risk factors for VTE during pregnancy and the postpartum period which varied across the trials, and risk factors also varied across women within the trials, limiting applicability of results to all pregnant women and women in the early postnatal period at increased risk of VTE
[4] Imprecision (-2): few events and small sample size

Summary of findings 2. Antenatal (± postnatal) prophylaxis: LMWH versus UFH

Antenatal (± postnatal) prophylaxis: LMWH versus UFH for venous thromboembolic disease

Population: pregnant women at increased risk of VTE during pregnancy and the early postnatal period

Settings: Finland (1 trial), USA (3 trials)

Intervention: LMWH

Comparison: UFH

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with UFH	Risk with LMWH				
Maternal death	Not reported					
Symptomatic thromboembolic events (Follow-up: during or immediately following delivery or 6-8 weeks postpartum)	Study population		RR 0.47 (0.09 to 2.49)	404 (4 trials)	⊕⊝⊝⊝ very low [1, 2, 3]	3 trials reported no events.
	20 per 1000	9 per 1000 (2 to 50)				
Symptomatic PE	Study population		NA	287 (3 trials)	⊕⊝⊝⊝	No events

(Follow-up: during or immediately following delivery or 6-8 weeks postpartum)	NA	NA			very low [1, 4, 5]	
Symptomatic DVT (Follow-up: during or immediately following delivery or 6-8 weeks postpartum)	Study population NA	 NA	NA	287 (3 trials)	⊕⊖⊖⊖ very low [1, 4, 5]	No events
Adverse effects sufficient to stop treatment	Study population 113 per 1000	 8 per 1000 (1 to 61)	RR 0.07 (0.01 to 0.54)	226 (2 trials)	⊕⊖⊖⊖ very low [1, 6, 7]	13 events in UFH group: 1 stopped due to an allergic reaction, 1 due to mild anaemia with no confirmed bleeding and 11 due to excess bruising/allergic rashes (these 11 stopped switched to LMWH (dalteparin) and the adverse effects resolved)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **DVT**: deep vein thrombosis; **LMWH**: low molecular weight heparin; **NA**: not applicable;**PE:** pulmonary embolism; **RR:** Risk Ratio;**UFH**: unfractionated heparin; **VTE**: venous thromboembolism

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Design limitations (-1): unclear risk of selection, attrition and selective reporting bias; not downgraded for lack of blinding as inadequate blinding unlikely to have influenced objective outcome
[2] Imprecision (-2): few events and wide confidence interval crossing line of no effect
[3] Indirectness (-1): not clear if the events were symptomatic, described as "recurrent thrombosis"; further women had specific risk factors, limiting applicability of results to all pregnant women and women in the early postnatal period at increased risk of VTE
[4] Imprecision (-2): no events and small sample size
[5] Indirectness (-1): women had specific risk factors, limiting applicability of results to all pregnant women and women in the early postnatal period at increased risk of VTE
[6] Few events and small sample size
[7] Indirectness (-1): risk factors for VTE poorly described in 1 of the trials (with most weight in the meta-analysis)

Summary of findings 3. Peripartum/postnatal prophylaxis: UFH versus no treatment

Peripartum/postnatal prophylaxis: UFH versus no treatment for venous thromboembolic disease

Population: women with varicose veins before birth, having a caesarean (elective or emergency) or vaginal birth

Settings: Israel (1 RCT)

Intervention: UFH

Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no UFH	Risk with UFH				
Maternal death	Not reported					
Symptomatic thromboembolic events (follow-up: 6 weeks postpartum)	Study population		RR 0.16 (0.02 to 1.36)	210 (1 trial)	⊕⊖⊖⊖ very low [1, 2, 3]	
	53 per 1000	0 per 1000 (1 to 72)				
Symptomatic PE (follow-up: 6 weeks postpartum)	Study population		RR 0.16 (0.01 to 3.34)	210 (1 trial)	⊕⊖⊖⊖ very low [1, 2, 3]	
	21 per 1000	0 per 1000 (0 to 71)				
Symptomatic DVT (follow-up: 6 weeks postpartum)	Study population		RR 0.27 (0.03 to 2.55)	210 (1 trial)	⊕⊖⊖⊖ very low [1, 2, 3]	
	32 per 1000	0 per 1000 (1 to 81)				
Adverse effects sufficient to stop treatment	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **DVT:** deep vein thrombosis; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **RR:** Risk Ratio; **UFH**: unfractionated heparin; **VTE**: venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Design limitations (-1): unclear risk of all sources of bias other than attrition (low risk); not downgraded for lack of blinding as objective outcome
[2] Imprecision (-2): wide confidence intervals crossing line of no effect, few events, and small sample size
[3] Indirectness (-1): specific risk factors for VTE of included women limits applicability of findings to all women at increased risk of VTE intrapartum and in the early postnatal period

Summary of findings 4. Peripartum/postnatal prophylaxis (caesarean): heparin (LMWH or UFH) versus no treatment/placebo

Peripartum/postnatal prophylaxis (caesarean): heparin (LMWH or UFH) versus no treatment/placebo for venous thromboembolic disease

Population: women giving birth by elective or emergency caesarean (elective only (1 trial), emergency or elective (4 trials))

Settings: Australia (1 trial), Saudi Arabia (1 trial), Switzerland (1 trial), UK (2 trials)

Intervention: heparin**(**LMWH (3 RCTs), UFH (2 RCTs))

Comparison: no treatment (1 trial) or placebo (4 trials)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no heparin	Risk with heparin				
Maternal death (timing of assessment unclear)	Study population NA	NA	NA	300 (1 trial)	⊕⊖⊖⊖ very low [1, 2]	No events
Symptomatic thromboembolic events (timing of assessment unclear, within 6 weeks postpartum)	Study population 9 per 1000	0 per 1000 (4 to 29)	RR 1.30 (0.39 to 4.27)	840 (4 trials)	⊕⊖⊖⊖ very low [3, 4]	
Symptomatic PE (timing of assessment unclear, within 6 weeks postpartum)	Study population 7 per 1000	0 per 1000 (2 to 33)	RR 1.10 (0.25, 4.87)	840 (4 trials)	⊕⊖⊖⊖ very low [3, 4]	

Symptomatic DVT (timing of assessment unclear, within 6 weeks postpartum)	Study population		1.30 (0.24, 6.94)	1140 (5 trials)	⊕⊖⊖⊖ very low [3, 4]	
	3 per 1000	0 per 1000 (1 to 22)				
Adverse effects sufficient to stop treatment	Study population		NA	140 (1 trial)	⊕⊖⊖⊖ very low [2, 5]	No events
	NA	NA				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **DVT:** deep vein thrombosis; **NA**: not applicable; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **RR:** Risk Ratio; **VTE**: venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Design limitations (-2) one trial at unclear risk of all sources of bias
[2] Imprecision (-2): no events and small sample size
[3] Design limitations (-2): most trials at unclear risk of selection bias, all trials at unclear risk of selective reporting; not downgraded for lack of blinding as objective outcome
[4] Imprecision (-1): wide confidence intervals crossing line of no effect
[5] Design limitations (-1): unclear risk of selective reporting bias

Summary of findings 5. Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH

Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH for venous thromboembolic disease

Population: women giving birth by elective or emergency caesarean (elective or emergency (1 trial), elective cesarean only (1 trial), elective/emergency unclear (1 trial))

Settings: German (2 trials); UK (1 trial)

Intervention: LMWH

Comparison: UFH

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with UFH	Risk with LMWH				

Maternal death	Not reported					
Symptomatic thromboembolic events (timing of assessment unclear, within 6 weeks postpartum)	Study population		RR 0.33 (0.01 to 7.99)	217 (3 trials)	⊕⊖⊖⊖ very low[1, 2]	All the events were symptomatic DVT
	9 per 1000	0 per 1000 2 to 75)				
Symptomatic PE (timing of assessment unclear, within 6 weeks postpartum)	Study population		NA	217 (3 trials)	⊕⊖⊖⊖ very low [1, 3]	No events
	NA	NA				
Symptomatic DVT (timing of assessment unclear, within 6 weeks postpartum)	Study population		RR 0.33 (0.01 to 7.99)	217 (3 trials)	⊕⊖⊖⊖ very low [1, 2]	
	9 per 1000	0 per 1000 2 to 75)				
Adverse effects sufficient to stop treatment	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **DVT:** deep vein thrombosis; **LMWH**: low molecular weight heparin; **NA**: not applicable; PE: pulmonary embolism; **RR:** Risk Ratio; **UFH**: unfractionated heparin.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Design limitations (-2): all trials at unclear risk of selection bias, selective reporting and other bias; not downgraded for lack of blinding as objective outcome
[2] Imprecision (-2): wide confidence intervals crossing line of no effect, few events and small sample size
[3] Imprecision (-2): no events and small sample size

Summary of findings 6. Postnatal prophylaxis: LMWH versus no treatment/placebo

Postnatal prophylaxis: LMWH versus no treatment/placebo for venous thromboembolic disease

Population: women at increased risk of VTE in the early postpartum period

Settings: multi-country, Canada and USA (2 trials)

Intervention: LMWH

Comparison: no treatment (1 trial) or placebo (1 trial)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with no heparin treatment or placebo	Assumed risk with LMWH				
Maternal death	Study population		NA	24 (1 trial)	⊕⊖⊖⊖ very low [1, 2]	No events Maternal death only reported as: "no… other unexpected serious adverse events related to the intervention during follow-up"
	NA	NA				
Symptomatic thromboembolic events (follow-up: 10-90 days postpartum)	Study population		NA	58 (2 trials)	⊕⊖⊖⊖ very low [2, 3]	No events
	NA	NA				
Symptomatic PE (follow-up: 10-90 days postpartum)	Study population		NA	58 (2 trials)	⊕⊖⊖⊖ very low [2, 3]	No events
	NA	NA				
Symptomatic DVT (follow-up: 10-90 days postpartum)	Study population		NA	58 (2 trials)	⊕⊖⊖⊖ very low [2, 3]	No events
	NA	NA				
Adverse effects sufficient to stop treatment	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **DVT:** deep vein thrombosis; **NA**: not applicable; **PE:** pulmonary embolism; **RR:** Risk Ratio; **VTE**: venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

1 Design limitations (-1): unclear risk of selective reporting and other bias
2 Imprecision (-2): no events and small sample size
3 Design limitations (-1): unclear risk of selective reporting and other bias; not downgraded for lack of blinding as objective outcome

BACKGROUND

Description of the condition

Venous thromboembolic disease in pregnancy and the early postnatal period

Venous thromboembolism (VTE) is a condition where the blood clots inappropriately, and which may lead to considerable morbidity and even death. 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) (Di Nisio 2017; 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 result in collapse and sudden death (ACOG 2018 Di Nisio 2017; Abbasi 2014 ; Greer 2012; Knight 2008 ; Jacobsen 2008; James 2006). Approximately 75% to 80% of cases of pregnancy-associated VTE are caused by DVT, and 20% to 25% of cases are caused by PE (Blanco-Molina 2010; James 2006; Simpson 2001).

Pregnancy is associated with a number of physiological and anatomic changes that can increase the risk of VTE (ACOG 2018; Antony 2017).

Description of the intervention

Thromboprophylaxis

The intervention assessed in this review covers VTE thromboprophylaxis (measures taken in order to prevent thrombosis), including pharmacological agents and non pharmacological methods. Despite evidence correlating risk factors and the occurrence of pregnancy-related VTE being imprecise (ACOG 2018; Okoroh 2012), there is broad agreement that women should be assessed for VTE risk preconception, and again during pregnancy, in order to guide VTE thromboprophylaxis (Friedman 2016; NHMRC 2009).

Globally, guidelines (for example of the American College of Obstetricians and Gynecologists (ACOG) (ACOG 2018), the American College of Chest Physicians (ACCP) (Bates 2012), National Institute for Health and Care Excellence (NICE 2018) and the Royal College of Obstetricians and Gynaecologists (RCOG) (RCOG 2015)), are unanimous in their recommendations that all women undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy, and women judged to be at high risk of VTE be offered thromboprophylaxis, where benefit is likely to outweigh potential harms. However, the available guidelines do not reach consensus regarding groups of women at higher risk of VTE, and which type of thromboprophylaxis should be offered. They also differ in the treatment options advised for particular groups of women at increased risk of VTE, including timing of interventions (starting points and lengths of treatments). Pregnancy-specific guidelines for thromboprophylaxis in COVID-19 have been published, though are lacking high-certainty evidence to inform clinical practice (D'Souza 2020).

ACCP and ACOG guidelines advise antenatal and postpartum pharmacologic prophylaxis for a small group of particularly high-risk women - those women with prior events, and/or thrombophilias. For women undergoing caesarean birth, ACOG supports universal perioperative mechanical prophylaxis and ACCP recommends pharmacologic prophylaxis based on risk factors. In comparison, RCOG recommends pharmacologic prophylaxis to a much larger proportion of women based on common risk factors (ACOG 2018 ; Friedman 2016).

Pharmacological agents that have been used to prevent thrombosis around pregnancy include:

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

Non-pharmacological methods used include:

- graduated compression stockings;
- intermittent pneumatic compression;
- early mobilisation;
- surveillance.

How the intervention might work

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

Thrombin has a key role in haemostasis and thrombosis, and thus anticoagulant strategies 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 or intermittent pneumatic compression may work through their ability to reduce venous stasis and blood stagnation by promoting venous blood flow through external compression (NHMRC 2009).

Despite previously established benefits of thromboprophylaxis for VTE in non-pregnant patient groups, evidence on the effects, and cost-effectiveness of thromboprophylaxis is scant and unclear (Ellis-Kahana 2020; Friedman 2016; Palmerola 2015). There is ongoing debate about whether potential benefits outweigh potential harms in some groups of high-risk women (ACOG 2018), and whether they should be routinely screened for treatment.

Routine screening of all pregnant women to identify women with thrombophilia, for example, has not been recommended (Okoroh 2012), and antenatal prophylaxis for all women with known thrombophilia remains controversial (Brenner 2003; de Jong 2014; Friedman 2016; Middeldorp 2003; Okoroh 2012; Wu 2005).

Pharmacological prophylaxis may cause adverse effects that could be sufficiently severe 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 result in adverse effects for the mother (Nelson-Piercy 1997); there is a risk of thrombocytopenia (low numbers of 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 for most women. In addition, LMWHs are understood to have a lower risk of adverse effects such as osteoporosis, and thrombocytopenia (Bauersachs 2009). Warfarin is known to cause congenital anomalies (Hall 1980) and 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 are regarded to be safe for mothers who are breastfeeding (Bauersachs 2009; Letsky 1997; Orme 1977).

Low-dose (e.g. 60 mg to 150 mg) aspirin has been widely used in pregnancy in an attempt to prevent the development of pre-eclampsia (Roberge 2017; Rolnik 2017;). 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). HES has been used for thromboprophylaxis in the past however, it is not commonly prescribed due to concerns about its association with increased 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 (Bain 2014), which was an update of an earlier version (Tooher 2010). Both previous versions of this review 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 controlled 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 possible that any benefits of thromboprophylaxis may be outweighed by harm. Current guidelines for clinical practice are based largely on expert opinion, rather than high-certainty evidence from randomised trials, and guidelines differ in the thromboprophylaxis measures they recommend for women who are pregnant, in birth, or have recently given birth.

The current version of the Cochrane Review on prophylaxis for VTE in pregnancy and the early postnatal period (Bain 2014) searched up to 27 November 2013 and included 19 randomised controlled trials; with 16 trials involving 2529 women contributing data to the review. Additional trials on prophylaxis for VTE have since been performed, which provide new data on the effects of relevant interventions.

OBJECTIVES

To assess the effects of thromboprophylaxis during pregnancy and the early postnatal period in women at increased risk of venous thromboembolism (VTE) on the risk 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 venous thromboembolism (VTE) versus placebo or no treatment, or two or more interventions for the prevention of VTE. We excluded quasi-randomised trials and cross-over trials, however planned to include cluster-randomised trials. We included studies reported only as abstracts where it was possible to extract relevant data from the text. When this was not possible, we included these as awaiting assessment studies, pending further publication of their results.

Types of participants

Women who were pregnant or had given birth in the previous six weeks, at increased risk of VTE, were included. Women at increased risk were those having/following a caesarean section, with an acquired or inherited thrombophilia, and/or other risk factors for VTE. Women with artificial heart valves were excluded.

This is one of a series of Cochrane Reviews assessing the effects of interventions to prevent VTE in women at increased risk of VTE. Thromboprophylaxis has been widely used to prevent miscarriage in women with recurrent pregnancy loss. One Cochrane Review examines effects of aspirin and/or heparin for women with unexplained recurrent miscarriage, with or without thrombophilia (de Jong 2014). Another evaluates the effects of aspirin or heparin, or both, for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent miscarriage (Hamulyák 2020). A further Cochrane Review assesses the effects of antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction (Dodd 2013). To avoid duplication, we therefore have not included studies focused on assessing the effects of aspirin and/or heparin or both on the prevention of miscarriage, or the effects of antithrombotic therapy in women considered at risk of placental dysfunction (not otherwise considered to be at increased risk of VTE).

Types of interventions

Any thromboprophylaxis measure (i.e. intervention that may reduce risk of VTE) was eligible, including the following.

1. Pharmacological interventions:

- unfractionated heparin (UFH);
- low molecular weight heparin (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

Outcomes were all dichotomous and were measured at the end of the intervention or follow-up period, as reported by the individual studies.

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 (undesired harmful effect resulting from the intervention considered serious enough to stop treatment, all author reports).
10. Adverse effects not sufficient to stop treatment (undesired harmful effect resulting from the intervention that was not considered serious enough to stop treatment, all author reports).
11. Symptomatic osteoporosis*.
12. Fetal loss < 20 weeks**.
13. Fetal loss ≥ 20 weeks**.
14. Thrombocytopenia*.
15. Fetal anomalies**.

* Mostly applicable for studies involving use of antenatal heparin.

** Mostly applicable for studies involving use of antenatal heparin or aspirin.

Search methods for identification of studies

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

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (18 October 2019). We updated this search on 17 February 2021 and added the results to Studies awaiting classification.

The Register is a database containing over 26,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (this includes a Cochrane centralised search feed from WHO International Clinical Trials Registry Platform (ICTRP) ;
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies, Excluded studies, Studies awaiting classification, Ongoing studies).

Searching other resources

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (18 October 2019). We updated the search of ClinicalTrials.gov on 17 February 2021 and added the results to Studies awaiting classification (see Appendix 1 for search methods used).

Data collection and analysis

For methods used in the previous version of this review, see Bain 2014.

For this update, the following methods were used for assessing the reports that were identified as a result of the updated search plus the ongoing, awaiting assessment and relevant excluded studies in the previous version of this review.

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

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 2014) 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 for which data were combined from trials in meta-analysis, were measured in the same way by the included 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 intra cluster 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.

Multiple-armed trials

We combined relevant groups in the multi-arm trials or included relevant arms as separate comparisons, to create appropriate single pair-wise comparisons for inclusion in the review analyses, thereby avoiding unit of analysis errors.

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 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 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 2014). We used fixed-effect meta-analysis for combining data, as it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. 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 summarised results for 13 intervention comparisons under the following four main headings, based on the intervention time points antenatal ± postnatal, intrapartum + postnatal, postnatal, and the distinction between type of delivery in the intrapartum and postnatal interventions assessed:

- antenatal (± postnatal) prophylaxis;
- peripartum prophylaxis (vaginal birth or caesarean);
- peripartum/postpartum prophylaxis (caesarean);
- postnatal prophylaxis.

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 the primary review outcomes. We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2014) and report the results of subgroup analyses quoting the Chi² 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. There was no heterogeneity observed.

Sensitivity analysis

We carried out sensitivity analyses to explore the effects of trial quality by omitting trials rated 'high' or 'unclear' risk of selection bias (allocation concealment and sequence generation) or attrition bias, restricting these analyses to the primary outcomes. We were able to conduct these analyses for three of the13 review comparisons, and three of the five primary review outcomes (symptomatic thromboembolic events, symptomatic PE, and symptomatic DVT), using data from nine trials.

Summary of findings and assessment of the certainty of the evidence

For this update we assessed the certainty of the evidence where possible (data allowed) using the GRADE approach as outlined in the GRADE handbook, including the main comparisons (all comparisons of heparin (LMWH or UFH) versus no treatment/ placebo, and LMHW versus UFH) and the following five outcomes, selected due to their importance (potential to change practise):

1. maternal death;
2. symptomatic thromboembolic events;
3. symptomatic PE;
4. symptomatic DVT;
5. adverse effects sufficient to stop treatment.

The GRADEpro Guideline Development Tool was used to import data from Review Manager 5.4 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of certainty for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

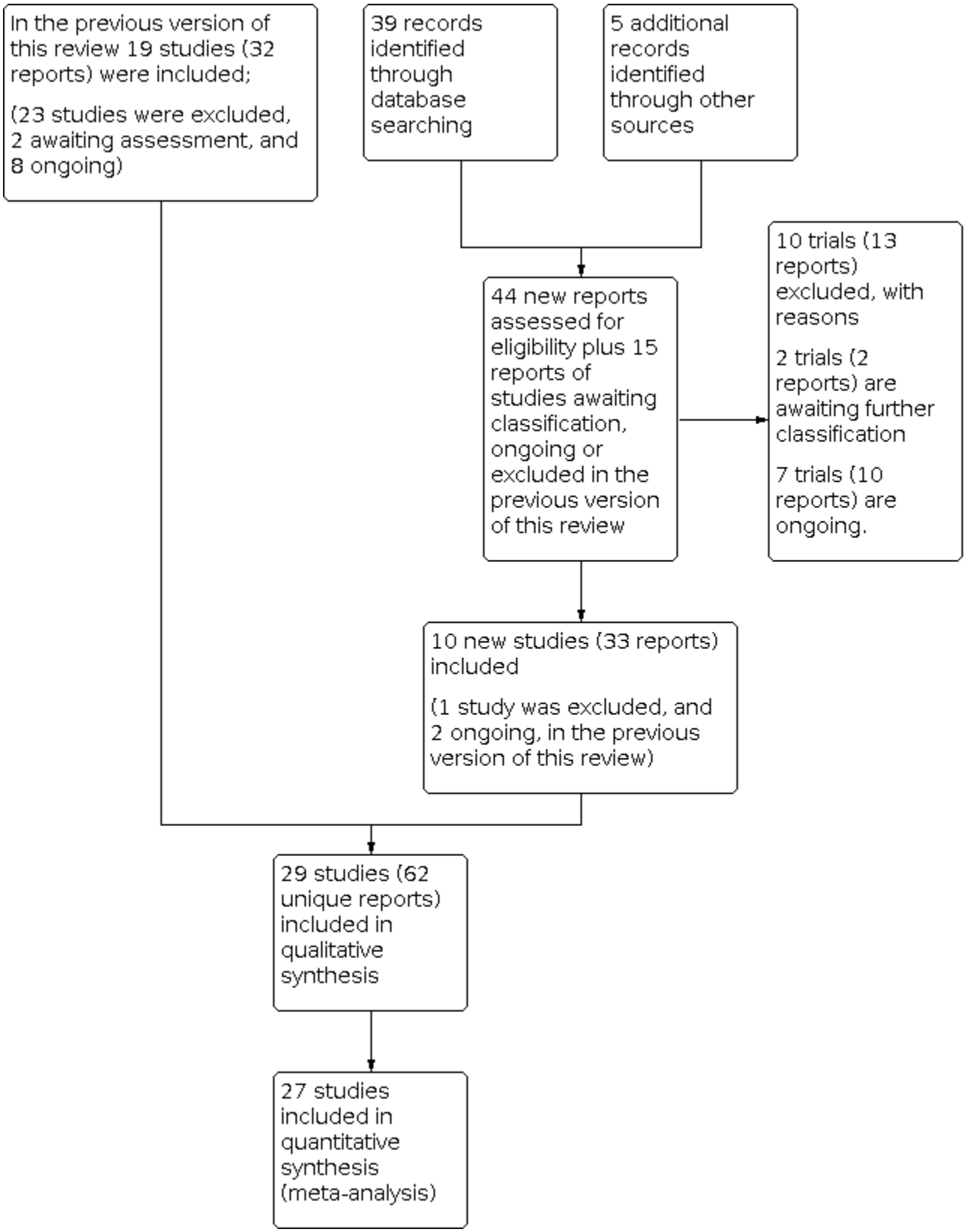
Description of studies

Results of the search

In the previous version of the review (Bain 2014), 19 trials (32 reports) were included, 23 studies were excluded, eight studies (13 reports) were assessed as ongoing, and two reports were classified awaiting further classification. Updated searches of the Cochrane Pregnancy and Childbirth's Trials Register on 18 October 2019 identified 39 new records; additional searching found five new records. For this update we assessed these new records, plus the two awaiting classification study records and 13 ongoing study records from Bain 2014.

We included 10 new trials (Algahtani 2015; de Vries 2012; Heller 2016; Reddick 2014; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; Stephenson 2016; van Hoorn 2016), and excluded 10 studies (Aina 2006; Alalaf 2015; de Jong 2015; Guven 2014; Langer 2013; Laskin 2007; Milic 2018; Rodger 2017; Samantha 2013; Schleussner 2015). Seven studies are listed as ongoing (Dargaud 2018; Heller 2016b; NCT00225108; NCT00878826; NCT01019655; NCT01828697; NCT04153760); and two studies (Dittmer 1991; Nagornaya 2012) remain awaiting classification. See Figure 1.

Figure 1. Study flow diagram



We updated the search in February 2021 and identified 10 trial reports. Two of these are additional reports of an ongoing study (NCT01828697), one is an additional report of Gris 2011, and six trials (seven reports) are awaiting further classification (Abdolvand

2019; Ganer 2020; Movahedi 2020; NCT02856295; NCT04305756; NCT04635839.

In summary, the current review update includes: a total of 29 studies (66 reports or 62 unique reports (Gates 2004a and Gates 2004b have three references in common and Rodger 2015; Rodger 2016 have one reference in common)); 32 excluded studies (38 reports); seven ongoing studies (13 reports); and eight studies (nine reports) in awaiting classification.

Included studies

A total of 29 trials (involving 3839 women) (Algahtani 2015; Burrows 2001; Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; de Vries 2012; Ellison 2001; Gates 2004a; Gates 2004b; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; Segal 1975; Stephenson 2016; van Hoorn 2016; Welti 1981) are included in this review update. Two of the trials (Cornette 2002; O'Riordan 2008) reported no relevant outcome data, and thus 27 studies contribute to quantitative analyses. All of the included studies were individually-randomised trials. Three of the trials each had three arms (Ellison 2001; Gibson 1998; Heilmann 2007).

de Vries 2012 and van Hoorn 2016 are both part of the 'FRUIT RCT' - with van Hoorn 2016 recruiting women with antiphospholipid antibodies.

Of the 27 trials contributing data for the review analysis, 11 assessed **antenatal (± postnatal) prophylaxis**, with five assessing heparin (low molecular weight heparin (LMWH) or unfractionated heparin (UFH)) versus no treatment or placebo (de Vries 2012; Gates 2004a; Howell 1983; Rodger 2014; van Hoorn 2016); four assessing LMWH versus UFH (Casele 2006; De Veciana 2001; Hamersley 1998; Pettila 1999), one assessing adjusted-dose versus fixed-dose LMWH (Salim 2016), and one assessing compression stockings versus none (Heller 2016). Fourteen trials assessed **peripartum/postnatal prophylaxis**, with one trial assessing UFH versus no treatment, in women having a vaginal or caesarean birth (Segal 1975); and the remaining 13 trials assessing interventions in women having a caesarean birth; including five assessing heparin (LMWH or UFH) versus no treatment or placebo (Algahtani 2015; Burrows 2001; Gates 2004b; Hill 1988; Welti 1981), one assessing hydroxyethyl starch (HES) versus UFH (Heilmann 1991), three assessing LMWH versus UFH (Gibson 1998; Heilmann 2007; Krauss 1994), one assessing five- versus 10-day LMWH (Cruz 2011), one assessing weight-based versus fixed-dose LMWH (Stephenson 2016), one assessing LMWH versus LMWH (different types) (Ellison 2001), and one assessing compression devices versus bed rest (Reddick 2014). The remaining two trials (Rodger 2015 and Rodger 2016), assessed **postnatal prophylaxis**, comparing LMWH with no treatment or placebo. Therefore, 13 comparisons of thromboprophylaxis in pregnancy and the early postnatal period (first six weeks after birth), were included in this review.

The included trials have been published over four decades - from 1975 to 2016.

For further details, see Characteristics of included studies and Table 1.

Settings

Almost all of the 29 trials were conducted in high-income countries. Six were conducted in the UK (Ellison 2001; Gates 2004a; Gates 2004b; Gibson 1998; Hill 1988; Howell 1983), and six in the USA (Casele 2006; De Veciana 2001; Hamersley 1998; Heller 2016; Reddick 2014; Stephenson 2004). Of the remaining 17 trials, three were conducted in Germany (Heilmann 1991; Heilmann 2007; Krauss 1994), two in Israel (Salim 2016; Segal 1975), and one each in Australia (Burrows 2001), Saudi Arabia (Algahtani 2015), Spain (Cruz 2011), Ireland (O'Riordan 2008), Finland (Pettila 1999), and Switzerland (Welti 1981). Five trials were performed in more than one country: de Vries 2012 (Australia, Sweden, the Netherlands); Rodger 2014 (Australia, Canada, France, UK, USA); van Hoorn 2016 (Australia, Sweden); and Rodger 2015 and Rodger 2016 (both Canada and USA). The study setting for Cornette 2002 was unclear (though the authors reported that they were from Belgium).

Participants

All participants in the trials were women who were pregnant, giving birth or who had given birth in the previous six weeks and were judged to be at increased risk of venous thromboembolism (VTE). The number of women randomised varied widely across the trials, however most trials were relatively small. Gates 2004a and Gibson 1998 were the two smallest trials, randomising 16 and 17 women, respectively. The two trials evaluating postnatal prophylaxis randomised only 25 women (Rodger 2015) and 37 women (Rodger 2016). Cruz 2011, which randomised 646 women, and Welti 1981, which randomised 580 women, were the largest trials.

Characteristics of the included women are summarised below, including age, personal history of VTE, thrombophilia, pre-eclampsia, obesity, and caesarean type (elective versus emergency, relevant for the trials assessing prophylaxis in women scheduled for, undergoing, or after caesarean birth). For further details see Table 2.

Age

Nineteen of the 29 trials (Burrows 2001; Casele 2006; Cruz 2011; de Vries 2012; Ellison 2001; Gates 2004a; Gates 2004b; Heilmann 1991; Heilmann 2007; Heller 2016; Howell 1983; Krauss 1994; Pettila 1999; Reddick 2014; Rodger 2014; Salim 2016; Stephenson 2016; van Hoorn 2016; Welti 1981), included a mix of women of advanced age (≥ 35 years) and younger women. In one trial (Algahtani 2015), no women older than 35 years were included. In the remaining nine trials, due to limited information provided, age ranges of women were unclear (Cornette 2002; De Veciana 2001; Hamersley 1998; Hamersley 1998; Hill 1988; O'Riordan 2008; Rodger 2015; Rodger 2016; Segal 1975).

Personal history of venous thromboembolism (VTE

In six of the included trials, a mix of women with and without a personal history of VTE were included (De Veciana 2001; Heilmann 1991; Pettila 1999; Rodger 2014; Salim 2016; Segal 1975). In eight trials none of the women had a personal history of VTE (Algahtani 2015; Burrows 2001; de Vries 2012; Gates 2004b; Hill 1988; Reddick 2014; Stephenson 2016; van Hoorn 2016), and in two trials all women had a personal history of VTE (Gates 2004a; Howell 1983). In the remaining 13 trials, personal history of VTE was not reported (Casele 2006; Cornette 2002; Cruz 2011; Ellison 2001; Gibson

1998; Hamersley 1998; Heilmann 2007; Heller 2016; Krauss 1994; O'Riordan 2008; Rodger 2015; Rodger 2016; Welti 1981).

Thrombophilia (acquired or inherited)

In six trials all the women included had acquired or inherited thrombophilia (de Vries 2012; Hamersley 1998; Heilmann 2007; Rodger 2014; Salim 2016; van Hoorn 2016). In four trials none of the included women had thrombophilia (Algahtani 2015; Cornette 2002; Hill 1988; Reddick 2014). Six trials included women with and without thrombophilia (De Veciana 2001; Gates 2004a; Gates 2004b; Pettila 1999; Rodger 2014; Rodger 2015). However, participant thrombophilia status was poorly reported. Authors of 10 trials provided insufficient information to determine thrombophilia status (Ellison 2001; Gibson 1998; Heilmann 1991; Heller 2016; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Stephenson 2016; Welti 1981). In the remaining three trials, whilst this was not clearly reported, information provided suggests that two (Burrows 2001; Cruz 2011) included no women with thrombophilia, and one (Casele 2006) included some women with thrombophilia.

Pre-eclampsia

Pre-eclampsia status of women in the included trials was also poorly reported. In five of the 29 trials, authors reported that no women had pre-eclampsia (Algahtani 2015; Cornette 2002; de Vries 2012; Reddick 2014; Salim 2016). In two trials (Pettila 1999; Rodger 2014) pre-eclampsia was reported as a study outcome (thus it may be assumed that no women had pre-eclampsia at baseline). In the Hill 1988 trial, it is likely that none of the women had pre-eclampsia (although this is not stated), as women with pregnancy-induced hypertension were not eligible. In eight trials it is clear that women with and without pre-eclampsia were included (Burrows 2001; Cruz 2011; Ellison 2001; Gates 2004b; Rodger 2015; Rodger 2016; Stephenson 2016; van Hoorn 2016). In the remaining 13 trials the pre-eclampsia status of women was unclear due to insufficient information (Casele 2006; De Veciana 2001; Gates 2004a; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981).

Obesity

One trial (Algahtani 2015) included no obese women and one trial (Stephenson 2016) included only obese women. In 14 trials a mix of obese women, and women of other weight categories were included (Burrows 2001; Cruz 2011; De Veciana 2001; de Vries 2012; Ellison 2001; Heilmann 1991; Heller 2016; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; van Hoorn 2016). In the remaining 13 trials (Casele 2006; Cornette 2002; Gates 2004a; Gates 2004b; Gibson 1998; Hamersley 1998; Heilmann 2007; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975;Welti 1981), the weight status of women was unclear.

Emergency versus elective caesarean

Seventeen of the 29 trials, assessed thromboprophylaxis in women having a caesarean (Algahtani 2015; Burrows 2001; Cornette 2002; Cruz 2011; Ellison 2001; Gates 2004b; Heilmann 1991; Heilmann 2007; Hill 1988; Krauss 1994; O'Riordan 2008; Reddick 2014; Rodger 2015; Rodger 2016; Segal 1975; Stephenson 2016; Welti 1981). Four trials included women undergoing elective caesarean birth only (Cornette 2002; Heilmann 2007; Hill 1988; Reddick 2014). In one trial (Heilmann 1991), the status of included caesarean section births (emergency/elective) was unclear. In the remaining 12 trials, women scheduled for, undergoing, or who had an emergency or elective caesarean surgery were included.

Interventions

Eleven of the 29 trials assessed antenatal (± postnatal) thromboprophylaxis, with 10 assessing pharmacological interventions (Casele 2006; De Veciana 2001; de Vries 2012; Gates 2004a; Hamersley 1998; Howell 1983; Pettila 1999; Rodger 2014; Salim 2016; van Hoorn 2016), and one assessing a mechanical intervention (compression stockings) (Heller 2016). Sixteen trials assessed peripartum/postnatal thromboprophylaxis (Algahtani 2015; Burrows 2001; Cornette 2002; Cruz 2011; Ellison 2001; Gates 2004b; Gibson 1998; Heilmann 1991; Heilmann 2007; Hill 1988; Krauss 1994; O'Riordan 2008; Reddick 2014; Salim 2016; Stephenson 2016; Welti 1981). All except one (Salim 2016), were in women having a caesarean birth, and all but one (Reddick 2014), assessed pharmacological interventions. The remaining two trials assessed postnatal thromboprophylaxis (Rodger 2015; Rodger 2016), and pharmacological interventions (following vaginal or caesarean birth).

The interventions assessed by each trial are briefly described below.

Antenatal (± postnatal) prophylaxis

Heparin (LMWH or UFH) versus no treatment or placebo (Comparison 1).

- de Vries 2012 assessed once-daily weight-adjusted LMWH (dalteparin (fragmin) 5000 international units (IU) subcutaneously starting between six and 12 weeks' gestation up to the onset of labour; combined with 80 mg oral aspirin daily), starting before 12 weeks' gestation, and continued until 36 weeks' gestation (Australian participants received 100 mg aspirin; Swedish participants received 75 mg aspirin), compared with antenatal aspirin daily (80 mg orally, from 12 to 26 weeks' gestation). All women received weight-adjusted LMWH (dalteparin) in the early postpartum period.
- Gates 2004a assessed once-daily subcutaneous 40 mg enoxaparin (LMWH) from antenatal recruitment until a maximum of six weeks after birth, versus once-daily subcutaneous placebo (same timing).
- Howell 1983 assessed subcutaneous antenatal UFH throughout pregnancy (calcium, 10,000 IU twice daily, commencing shortly after the first antenatal visit) and UFH for six weeks postpartum (8000 IU twice daily) compared with no antenatal heparin and the same postpartum UFH treatment.
- Rodger 2014 assessed antepartum LMWH (dalteparin 5000 IU once daily by subcutaneous self-injection from the day of randomisation until 20 weeks' gestation followed by 5000 IU twice daily from 20 weeks until at least 37 weeks' gestation), compared with placebo. All participants received postpartum dalteparin (5000 IU daily) by subcutaneous self-injection starting six to 28 hours after birth until day 42.
- van Hoorn 2016 assessed the same intervention as the de Vries 2012 trial in a different population.

LMWH versus UFH (Comparison 2)

- Casele 2006 assessed self-administered enoxaparin sodium (30 mg twice daily, starting from before 24 weeks up to 28 weeks'

gestation, then 40 mg twice daily until birth), versus heparin sodium (7500 units twice daily, starting before 24 weeks until 28 weeks, then 10,000 units twice daily until birth). All women received adjusted-dose coumadin for six to eight weeks after birth.

- De Veciana 2001 assessed dalteparin (initial dosing 2500 IU (5000 IU if > 70 kg) subcutaneously once daily then increased to a maximum of 10,000 IU/day to maintain alpha-Factor Xa levels at 0.1 to 0.3 IU/mL), compared with UFH (women were dosed with the standard 5000 IU (8000 IU if > 68 kg) subcutaneously twice daily) (intervention start time not reported).
- Hamersley 1998 dose-adjusted heparin (adjusted to maintain an anti-Xa (heparin assay) level between 0.03 to 0.05 U/mL) versus UFH, with women in both groups also prescribed daily aspirin (81 mg) (intervention not further specified in the conference abstract) (intervention start time and duration not reported).
- Pettila 1999 assessed subcutaneous antenatal plus postnatal dalteparin (Fragmin, once daily starting at 20 weeks' gestation, with a starting dose of 5000 IU (women weighing < 85 kg) or 7500 IU (women weighing ≥ 85 kg), dose adjusted based on anti-Xa measurements; during birth, 2500 IU dalteparin was administered 18 hours after the previous dose if the woman had not yet given birth; if she gave birth within 18 hours, 5000 IU was given 24 hours after the previous injection; the daily dose postpartum, for six weeks, was 2500 IU lower than during the third trimester; and two weeks after birth, if anti-Xa was < 0.20, the dose was increased by 2500 IU), versus subcutaneous UFH (7500 IU, adjusted according to the activated partial thromboplastin time (APTT) target values, twice daily starting at 20 weeks' gestation and for six weeks postpartum; at the time of birth, and on the first day postpartum 7500 IU UFH was given at 12-hour intervals, and then according to APTT target values).

Adjusted-dose versus fixed-dose LMWH (Comparison 3)

- Salim 2016 assessed antepartum enoxaparin according to the results of anti-FXa levels (initial dose of 40 mg, increased by fractions of 20 mg according to anti-FXa level with targeted prophylactic level 0.2 IU/mL or more 3.5 to 4 hours post-injection) versus a fixed antenatal daily dose of enoxaparin (40 mg daily, by subcutaneous self-injection) regardless of the results of anti-factor Xa, until birth. All women were prescribed enoxaparin (40 mg once daily by subcutaneous injection) from day one until day 42 after birth.

Compression stockings versus none (Comparison 4)

- Heller 2016 assessed advice to wear 20 to 30 mm Hg maternity pantyhose versus no such advice (intervention timing unclear, although authors report that women were visited three times, between eight to 20 weeks, and 32 ± 4 weeks before the birth, plus at eight weeks postpartum±2 weeks).

Peripartum/postnatal prophylaxis

Vaginal birth or caesarean

UFH versus no treatment (Comparison 5)

- Segal 1975 assessed subcutaneous UFH (50 mg (5000 IU) every 12 hours for four to five days after birth, about two-thirds of women having a vaginal birth had the first dose in active labour and a third after birth; for women having a caesarean section UFH was given two hours before surgery, at the end of surgery, and at 12-hour intervals; for women having an emergency caesarean, the initial dose was immediately following the decision), versus standard care/no treatment.

Caesarean

Heparin (LMWH or UFH) versus no treatment or placebo (Comparison 6)

- Algahtani 2015 assessed tinzaparin (4500 IU subcutaneously once daily), starting from 12 to 24 hours after caesarean section continuing for two weeks, compared with placebo. All women in this trial also received non-pharmacological prophylaxis using graduated compression stockings.
- Burrows 2001 assessed dalteparin (2500 IU once daily) versus placebo (saline) once daily for four to five days, with the interventions starting four to 24 hours after caesarean section.
- Gates 2004b assessed once-daily self-injected subcutaneous 40 mg enoxaparin in 1 mL versus once-daily self-injected subcutaneous placebo (normal saline 1 mL). Treatment with the study drug began within 12 hours of the caesarean section, and its duration was determined by the attending clinician.
- Hill 1988 assessed UFH 1000 units, one hour before caesarean, then twice daily for five days versus placebo (saline) one hour before caesarean, then twice daily for five days.
- Welti 1981 assessed twice-daily subcutaneous 5000 IU heparin (UFH) with physiotherapy versus physiotherapy without heparin (intervention timing unclear).

HES versus UFH (Comparison 7)

- Heilmann 1991 assessed HES 6%, 3 x 500 mL (first 500 mL administered during the caesarean, second in the evening of the day of the operation, third in the evening of the first postoperative day), versus UFH 5000 IU (first dose two hours after the operation followed by every eight hours for seven days).

LMWH versus UFH (Comparison 8)

- Gibson 1998** assessed enoxaparin 20 mg once daily versus enoxaparin 40 mg once daily versus UFH 7500 IU every 12 hours, with each of the interventions starting after the caesarean section (duration of intervention unclear).
- Heilmann 2007** assessed dalteparin 5000 IU/daily for seven days post operatively, with the first dose six hours following caesarean section and then at 24-hourly intervals versus calciparin 2 x 5000 IU daily, with the first dose six hours following caesarean section, (and then at eight-hour intervals) versus no pharmacological prophylaxis but compression stockings according to the guidelines during hospital days (third group not randomly assigned and excluded in this review).
- Krauss 1994 assessed fragmin (2500 to 5000 anti-Xa units) once daily versus 5000 units UFH (Liquemin) + 500 mL dextran 60 administered two to three times daily with treatment continuing 10 days after surgery (when the intervention commenced is unclear).

Five-day versus 10-day LMWH (Comparison 9)

- Cruz 2011 assessed bemiparin (3500 IU once daily) starting at ≥ eight hours following caesarean for five days versus 10 days.

Weight-based versus fixed-dose LMWH (Comparison 10)

- Stephenson 2016 assessed 0.5 mg/kg enoxaparin every 12 hours (dose not capped and rounded to the nearest 5 mg unit) versus 40 mg enoxaparin daily, with the enoxaparin starting between eight and 12 hours after caesarean birth and given as a subcutaneous injection in the abdomen.

LMWH versus LMWH (different types) (Comparison 11)

- Ellison 2001** evaluated dalteparin (5000 IU) versus enoxaparin (4000 IU) versus tinzaparin (50 IU/kg based on booking weight), all administered once daily, starting from six hours following caesarean section, and continuing for five days.
- (O'Riordan 2008)* daily enoxaparin (40 mg) versus daily tinzaparin (4500 units) following caesarean section.

Compression devices versus bed rest (Comparison 12)

- Reddick 2014: assessed intermittent pneumatic compression during caesarean birth (Aircast Venaflow Calf Cuff—DJO, LLC, Vista, CA, placed on their lower extremities, starting one hour before surgery and continuing ≥ 30 minutes following), versus bed rest beginning one hour before the start of surgery.

Timing of LMWH

Cornette 2002* evaluated LMWH (0.3 mL nadroparin calcium) 12 hours before versus 12 hours after elective caesarean birth.

Postnatal prophylaxis

LMWH versus no treatment or placebo (Comparison 13)

- Rodger 2015 assessed daily prophylactic dalteparin (5000 IU subcutaneous injections starting approximately 36 hours following delivery of the placenta, continued for three weeks), versus placebo.
- Rodger 2016 assessed the same intervention as Rodger 2015, however the dalteparin was administered for longer, following delivery of the placenta (for 10 days), and LMWH was compared with no treatment.

*Trial contributed no data for analysis.

**Trial included more than two arms.

For further details see Characteristics of included studies.

Multi-arm trials

We combined relevant groups in the multi-arm trials or included relevant arms as separate comparisons, to create appropriate single pair-wise comparisons for inclusion in the review analyses, thereby avoiding unit of analysis errors; specifically:

- Ellison 2001: three arms assessing different types of intrapartum (+ postnatal) LMWH treatment (dalteparin, enoxaparin, tinzaparin) in women undergoing caesarean: we included all three arms in three pair-wise comparisons as dalteparin versus enoxaparin, dalteparin versus tinzaparin, and enoxaparin versus tinzaparin (Analysis 11).
- Gibson 1998: three arms of intrapartum (+ postnatal) caesarean prophylaxis (LMWH enoxaparin (20 mg daily) versus LMWH enoxaparin (40 mg daily) versus UFH (7500 IU every 12 hours)): we combined the two enoxaparin groups and included this trial in Comparison 8 as LMWH versus UFH.
- Heilmann 2007: three arms; two randomised (LMWH dalteparin (5000 IU/daily for seven days post operatively) and UFH (calciparin 2 x 5000 IU daily)), and one not randomised, a control group (a control group received no pharmacological prophylaxis but compression stockings according to guidelines). We included the two randomised groups only, as a pair-wise comparison of intrapartum (+ postnatal) prophylaxis LMWH versus UFH in Analysis 8.

Outcomes

Primary outcomes: maternal death was reported by three trials (Algahtani 2015; Cruz 2011; Rodger 2015) in three separate comparisons. Symptomatic thromboembolic events were reported by 23 trials in 11 of the 13 review comparisons, with between one and four trials in each. Symptomatic PE was reported by 20 trials in 11 comparisons with between one and four trials in each. Symptomatic DVT was reported by 23 trials in 12 comparisons, with between one and five trials in each.

Each of our secondary outcomes was reported by at least one/some of the trials, although most in very few comparisons with only one or two trials in each.

Sources of trial funding

Thirteen of the 29 included trials reported funding sources: Pharmacia and Upjohn (provided the dalteparin and saline placebo medication, no other intellectual or financial support) (Burrows 2001); Laboratorios Fcos. ROVI, SA (Cruz 2011); two-year investigator grant by Pfizer (de Vries 2012); National Health Service Executive South East Region Research and Development and a donation to the National Perinatal Epidemiology Unit by Rhone-Poulenc Rorer (Gates 2004a); donation by Rhone-Poulenc Rorer (Gates 2004b); Leo Laboratories and the South East Thames Regional Health Authority (grant LORS No 77/19) (Hill 1988); Helsinki University Central Hospital, and Pharmacia and Upjohn (Pettila 1999); Hammond Research Fund, Duke University School of Medicine (Reddick 2014); Canadian Institutes of Health Research and Heart and Stroke Foundation of Canada, drugs supplied by Pharmacia and Upjohn (Rodger 2014); National Institutes of Health Research grant (# NIH 1R34HL107725–01) and Canadian Institutes of Health Research grant (#MOP 106641), Dr. Rodger supported by a Heart and Stroke Foundation Career Investigator Award and a University of Ottawa, Faculty of Medicine Chair in Venous Thrombosis and Thrombophilia, Dr. Kahn supported by a National Research Scholar award from the Fonds de recherche santé Québec (Rodger 2015 and Rodger 2016); Long Beach Memorial Medical Center Foundation (Stephenson 2016); single two-year investigator grant period 2000–2001 by Pfizer, formerly Pharmacia, grant number 524E-CVD-9101-0001 (Pharmacia was not the sponsor of the study), and a follow-up study of the trial received a one-year investigator grant period in 2014 by Pfizer (van Hoorn 2016). In four of these trials (Gates 2004a; Gates 2004b; Pettila 1999; van Hoorn 2016) industry was a source of trial support.

The remaining 16 trials did not report sources of trial funding.

Trial authors' declarations of interest

In 21 of the included trials authors did not report declarations of interest (Algahtani 2015; Burrows 2001; Casele 2006; Cornette 2002;

Cruz 2011; De Veciana 2001; Ellison 2001; Gates 2004a; Gates 2004b; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Pettila 1999; Rodger 2016; Segal 1975; Welti 1981). Two trials reported potential conflicts of interest: Heller 2016 declared relevant interests on the part of one author, J. Heller: Consultant/advisory board for BMS/Pfizer; Rodger 2014 declared relevant interests for one author, A.M. Clement: honoraria for educational activities from Leo Pharma, Sanofi, and Bayer. The authors of these studies reported no other relevant potential conflict of interest. Trial authors of the remaining six included trials declared no conflicts of interest (de Vries 2012; Reddick 2014; Rodger 2015; Salim 2016; Stephenson 2016; van Hoorn 2016).

Excluded studies

We excluded 32 studies. Eight were excluded as they were not randomised controlled trials (Alalaf 2015; Blomback 1998; Kutteh 1996a; Kutteh 1996b; Noble 2005; Pyregov 2012; Ratiu 2009; Samantha 2013) (some of these studies were also not eligible based on their study population). Aina 2006 was excluded as it was a protocol reporting a terminated trial.

Eighteen studies were excluded as their primary focus was prevention of recurrent miscarriage (Badawy 2008; Brenner 2005; Dendrinos 2007; de Jong 2015; Farquharson 2002; Giancotti 2012; Guven 2014; Kamin 2008; Kaandorp 2010; Langer 2013; Laskin 2007; Rai 1997; Rodger 2017;Schleussner 2015; Stephenson 2004; Thaler 2004; Tulppala 1997; Visser 2011). Two 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 increased risk of VTE (Gris 2010; Gris 2011). Three trials were excluded as they did not include pregnant women at increased risk of VTE (Harenberg 1993; Milic 2018; Rey 2009).

For further details, see Characteristics of excluded studies.

Risk of bias in included studies

For most of the trials a number of the 'Risk of bias' items were judged 'unclear' due to insufficient methodological detail. Overall, the trials were judged at moderate to high risk of bias. See Figure 2 and Figure 3.

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

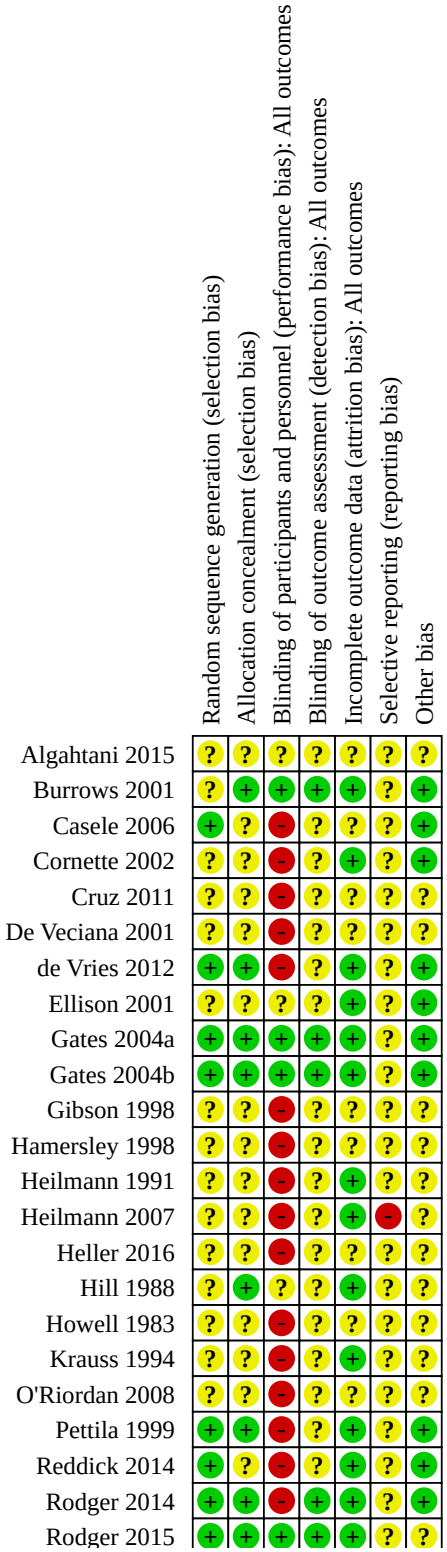


Figure 2. (Continued)

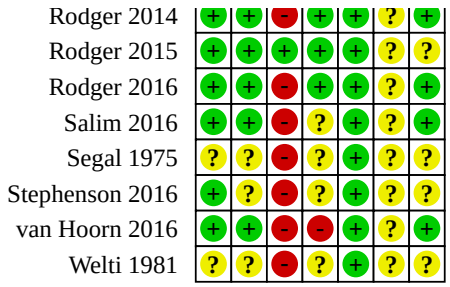
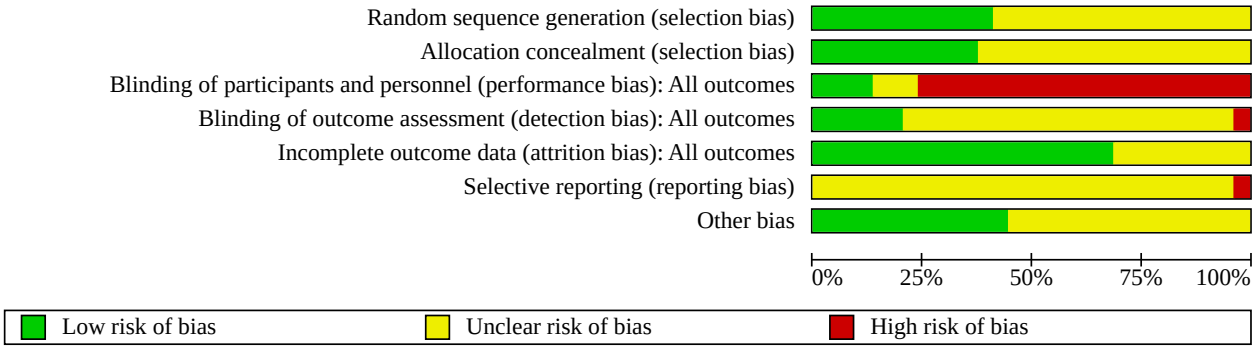


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Generation of the randomisation sequence was considered adequate in 12 trials (Casele 2006; de Vries 2012; Gates 2004b; Gates 2004a; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; Stephenson 2016; van Hoorn 2016) and unclear in 17 trials (Algahtani 2015; Burrows 2001; Cornette 2002; Cruz 2011; De Veciana 2001; Ellison 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Segal 1975; Welti 1981). Adequate methods of sequence generation included use of a random number table (Casele 2006; Rodger 2015; Rodger 2016); use of a central telephone randomisation service (Gates 2004b; Gates 2004a); and use of a computer-generated list (Pettila 1999).

Methods of allocation concealment were judged as adequate in 10 trials, and included use of pre-prepared treatment packs dispensed by hospital pharmacy departments (Burrows 2001; Gates 2004b; Gates 2004a; Hill 1988; Rodger 2014), randomisation performed by an independent centre or study coordinator with randomisation codes concealed from the investigators (de Vries 2012; Rodger 2015; Rodger 2016; van Hoorn 2016), and sealed opaque envelopes (Pettila 1999). For the remaining 19 studies, the risk of selection bias due to inadequate concealment of allocation was judged to be unclear (Algahtani 2015; Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; Ellison 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Howell 1983; Krauss 1994; O'Riordan 2008; Reddick 2014; Salim 2016; Segal 1975; Stephenson 2016; Welti 1981).

Blinding

Twenty-two of the 29 trials were assessed to be at high risk of performance bias, as they did not report adequate attempts to blind participants and study personnel, and adequate blinding was considered unfeasible due to the type of interventions assessed (Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; de Vries 2012; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Howell 1983; Krauss 1994; O'Riordan 2008; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2016; Salim 2016; Segal 1975; Stephenson 2016; van Hoorn 2016; Welti 1981). Four trials reported adequate methods used to blind women and study personnel, and were judged at low risk of performance bias (Burrows 2001; Gates 2004a; Gates 2004b; Rodger 2015). Performance bias was judged unclear for the remaining three trials as while blinding of women and clinicians may have been feasible, there was insufficient information provided (Algahtani 2015; Ellison 2001; Hill 1988).

Few trials reported any information relating to blinding of outcome assessment, and 22 of the trials were assessed unclear risk of detection bias due to inadequate information provided (Algahtani 2015; Casele 2006; Cornette 2002; Cruz 2011; De Veciana 2001; de Vries 2012; Ellison 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Pettila 1999; Reddick 2014; Salim 2016; Segal 1975; Stephenson 2016; Welti 1981). One trial (van Hoorn 2016) was judged high risk of detection bias as the authors reported that outcome assessment was not blinded. Six trials were judged at low risk of detection bias as they reported that outcome assessment

was blinded (Burrows 2001; Gates 2004a; Gates 2004b; Rodger 2014; Rodger 2015; Rodger 2016).

Therefore, only four of the trials reported adequate blinding of women as well as study personnel and outcome assessors (all with the use of a placebo control), and were judged at low risk of performance and detection bias (Burrows 2001; Gates 2004a; Gates 2004b; Rodger 2015).

Incomplete outcome data

Twenty of the 29 trials were judged 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; de Vries 2012; Ellison 2001; Gates 2004b; Gates 2004a; Heilmann 1991; Heilmann 2007; Hill 1988; Krauss 1994; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; Segal 1975; Stephenson 2016; van Hoorn 2016; Welti 1981). While two of these studies appeared to have no losses to follow-up (Segal 1975; Welti 1981), they both reported very little methodological detail.

The remaining nine trials were assessed at unclear risk of attrition bias (Algahtani 2015; Casele 2006; Cruz 2011; De Veciana 2001; Gibson 1998; Hamersley 1998; Heller 2016; Howell 1983; O'Riordan 2008). Of these, six did not specify whether any losses or exclusions occurred (Algahtani 2015; Cruz 2011; De Veciana 2001; Gibson 1998; Hamersley 1998; O'Riordan 2008). In the Howell 1983 trial, 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 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. The Heller 2016 trial was assessed at unclear risk of attrition bias despite the authors reporting that "A total of 44 patients enrolled and completed the study", as this was in a conference abstract, the only report for this study.

Selective reporting

We judged all except one trial (Heilmann 2007) at unclear risk of selective reporting bias. In most cases, the reason for our assessment of unclear was the absence of a trial protocol. However, for Rodger 2014, the reason was multiple trial registrations (including on a website), and Rodger 2016 was assessed as unclear risk due to limited detail provided in the available study protocol. We assessed Rodger 2015 to be at unclear risk of selective reporting due to limited details in the trial registration available, no full protocol available, and results for clinical outcomes reported incompletely in text.

Heilmann 2007, 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 quote: "showed no differences in the blood loss...and thrombocytopenia or osteopenia".

Other potential sources of bias

Thirteen 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; de Vries 2012; Ellison 2001; Gates 2004b; Gates 2004a; Pettila 1999; Reddick 2014; Rodger 2014; Rodger 2016; Salim 2016; van Hoorn 2016).

The remaining 16 trials were judged at an unclear risk of other potential bias, largely due to a lack of methodological detail provided in the trial reports (Algahtani 2015; Cruz 2011; De Veciana 2001; Gibson 1998; Hamersley 1998; Heilmann 1991; Heilmann 2007; Heller 2016; Hill 1988; Howell 1983; Krauss 1994; O'Riordan 2008; Rodger 2015; Segal 1975; Stephenson 2016; Welti 1981).

Effects of interventions

See: **Summary of findings 1** Antenatal (± postnatal) prophylaxis: heparin (LMWH or UFH) versus no treatment/placebo; **Summary of findings 2** Antenatal (± postnatal) prophylaxis: LMWH versus UFH; **Summary of findings 3** Peripartum/postnatal prophylaxis: UFH versus no treatment; **Summary of findings 4** Peripartum/postnatal prophylaxis (caesarean): heparin (LMWH or UFH) versus no treatment/placebo; **Summary of findings 5** Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH; **Summary of findings 6** Postnatal prophylaxis: LMWH versus no treatment/placebo

Comparison 1: Antenatal (±*postnatal)* prophylaxis: heparin (LMWH or UFH) versus no treatment or placebo

Five trials (de Vries 2012; Gates 2004a; Howell 1983; Rodger 2014; van Hoorn 2016) involving 519 women were included. See Summary of findings 1.

Primary outcomes

No trial reported on maternal death.

The effects of heparin (LMWH or UFH) versus no treatment or placebo on symptomatic thromboembolic events (risk ratio (RR) 0.39; 95% confidence interval (CI) 0.08 to 1.98; 4 trials, 476 women; Analysis 1.1), symptomatic PE (RR 0.33; 95% CI 0.02 to 7.14; 3 trials, 187 women; Analysis 1.2) and symptomatic DVT (RR 0.33; 95% CI 0.04 to 3.10; 4 trials, 227 women; Analysis 1.3) were very uncertain - all very low-certainty evidence.

Secondary outcomes

Blood transfusion

No blood transfusions were reported (1 trial, 16 women; Analysis 1.4).

Bleeding episodes

Bleeding episodes were variably reported across four trials (Analysis 1.5). Effects of LMWH versus no treatment or placebo were very uncertain for placental abruption (RR 1.00; 95% CI 0.31 to 3.20; 3 trials, 463 women), peripartum haemorrhage (RR 0.65; 95% CI 0.24 to 1.79; 1 trial, 289 women); non-major/minor bleeding (a possible increase with LMWH was observed) (RR 2.12; 95% CI 1.15 to 3.93; 1 trial, 284 women); and major bleeding (RR 1.48; 95% CI 0.25 to 8.72; 1 trial, 284 women). Effects of UFH versus no treatment or placebo were very uncertain for antenatal vaginal bleeding (RR 1.00; 95% CI 0.16 to 6.42; 1 trial, 40 women) and postpartum haemorrhage (RR 3.00; 95% CI 0.13 to 69.52; 1 trial, 40 women).

Serious wound complications

There were no serious wound complications (1 trial, 16 women; Analysis 1.6).

Adverse effects sufficient to stop treatment

The effect of heparin versus no treatment or placebo on adverse effects sufficient to stop treatment was very uncertain (RR 0.49; 95% CI 0.05 to 5.31; 1 trial, 139 women; very low-certainty evidence; Analysis 1.7). There were 3 events: heparin (LMWH) 1 event (bleeding from placental praevia); no treatment 2 events (both stomach complaints).

Adverse effects not sufficient to stop treatment

Adverse effects not sufficient to stop treatment were variably reported across four trials. The effects of heparin versus no treatment or placebo were very uncertain for skin/allergic reactions (a possible increase with heparin was observed) (RR 5.11; 95% CI 2.00 to 13.08; 4 trials, 476 women), raised liver enzymes (a possible increase with heparin was observed) (RR 22.53; 95% CI 1.34 to 378.78; 1 trial, 289 women), haematoma (RR 3.98; 95% CI 0.46 to 34.23; 2 trials, 171 women), superficial thrombophlebitis (RR 0.33; 95% CI 0.01 to 7.93; 1 trial, 139 women) and 'other' adverse effects (including transient ischaemic attack, severe allergic reaction) (RR 0.98; 95% CI 0.06 to 15.51; 1 trial, 289 women) (Analysis 1.8).

Gates 2004a reported that "Few women reported side effects"; Howell 1983 reported “Minor side-effects from heparin prophylaxis included bruising at the injection site (reduced by good injection technique), epistaxis and the inconvenience of giving twice-daily injections"; and de Vries 2012 reported "70 women in the LMWH-aspirin group had to convert to LMWH prescription".

Symptomatic osteoporosis

The effect of heparin versus no treatment or placebo on thrombocytopenia was very uncertain (RR 3.00; 95% CI 0.13 to 69.52; 4 trials, 479 women; Analysis 1.9).

Fetal loss

The effect of heparin versus no treatment or placebo on fetal loss was very uncertain (Analysis 1.10): where gestation was unclear (RR 1.16; 95% CI 0.54 to 2.51; 2 trials, 329 women), at less than 20 weeks' gestation (RR 2.18; 95% CI 0.50 to 9.41; 2 trials, 171 women), and at least 20 weeks' gestation (RR 0.33; 95% CI 0.04 to 3.12; 2 trials, 166 women).

Thrombocytopenia

The effect of heparin versus no treatment or placebo on thrombocytopenia was very uncertain (RR 3.00; 95% CI 0.14 to 64.26; 5 trials, 511 women; Analysis 1.11).

Fetal anomalies

The effect of heparin versus no treatment or placebo on fetal anomalies was very uncertain (RR 2.94; 95% CI 0.61 to 14.32; 1 trial, 289 women; Analysis 1.12).

Secondary outcomes not reported

Asymptomatic thromboembolic events.

Comparison 2: Antenatal (±*postnatal)* prophylaxis: LMWH versus UFH

Four trials (Casele 2006; De Veciana 2001; Hamersley 1998; Pettila 1999) involving 404 women were included. See Summary of findings 2.

Primary outcomes

No trial reported on maternal death.

The effect of LMWH versus UFH on symptomatic thromboembolic events was very uncertain (RR 0.47; 95% CI 0.09 to 2.49; 4 trials, 404 women; very low-certainty evidence; Analysis 2.1). There were no cases of symptomatic PE (3 trials, 287 women; Analysis 2.2), or symptomatic DVT (3 trials, 287 women; Analysis 2.3) in the LWMH or UFH groups.

Secondary outcomes

Blood transfusion

The effect of LMWH versus UFH on blood transfusions was very uncertain (RR 0.22; 95% CI 0.01 to 4.47; 1 trial, 105 women; Analysis 2.4).

Bleeding episodes

Bleeding episodes were variably reported across three trials (Analysis 2.5). Effects of LMWH versus no treatment or placebo were very uncertain for bruises greater than 2.5 cm (a possible reduction with LMWH was observed) (RR 0.18; 95% CI 0.09 to 0.36; 1 trial, 121 women), bleeding at birth (RR 3.80; 95% CI 0.44 to 32.99; 1 trial, 117 women), and 'bleeding complications' (a possible reduction with LMWH was observed) (RR 0.28; 95% CI 0.15 to 0.53; 1 trial, 105 women).

Serious wound complications

No trial reported this outcome.

Adverse effects sufficient to stop treatment

LMWH compared with UFH may reduce adverse effects sufficient to stop treatment but this evidence was very uncertain (RR 0.07; 95% CI 0.01 to 0.54; 2 trials, 226 women; very low-certainty evidence; Analysis 2.6). There were 13 events in UFH group: 1 stopped due to an allergic reaction, 1 due to mild anaemia with no confirmed bleeding and 11 due to excess bruising/allergic rashes (these 11 stopped switched to LMWH (dalteparin) and the adverse effects resolved).

Adverse effects not sufficient to stop treatment

The effect of LMWH versus UFH on adverse effects (injection burning) not sufficient to stop treatment was very uncertain (RR 0.79; 95% CI 0.53 to 1.18; 1 trial, 121 women; Analysis 2.7).

Symptomatic osteoporosis

The effect of LMWH versus UFH on symptomatic osteoporosis was very uncertain (RR 0.43; 95% CI 0.06 to 2.98; 2 trials, 188 women; Analysis 2.8).

Fetal loss

The effect of LMWH versus UFH on fetal loss was very uncertain (Analysis 2.9): where gestation was unclear (RR 0.61; 95% CI 0.21 to 1.77; 2 trials, 222 women) and at less than 20 weeks' gestation (RR 0.38; 95% CI 0.14 to 1.00; 1 trial, 121 women).

Thrombocytopenia

The effect of LMWH versus UFH on thrombocytopenia was very uncertain (RR 0.18; CI 0.01 to 3.64; 95%; 3 trials, 287 women; Analysis 2.10).

Secondary outcomes not reported

Asymptomatic thromboembolic events; fetal anomalies.

Comparison 3: Antenatal (±*postnatal)* prophylaxis: adjusted-versus fixed-dose LMWH

One trial (Salim 2016) involving 144 women was included.

Primary outcomes

A single trial did not report on maternal death, and reported no events in either the adjusted-dose or fixed-dose groups for symptomatic thromboembolic events (Analysis 3.1), symptomatic PE (Analysis 3.2) or symptomatic DVT (Analysis 3.3); 140 women.

Secondary outcomes

Asymptomatic thromboembolic events

There were no asymptomatic thromboembolic events in the adjusted-dose or fixed-dose LMWH groups (1 trial, 140 women; Analysis 3.4).

Bleeding episodes

The trial reported variations of bleeding episodes (Analysis 3.5); the effects of adjusted-dose versus fixed-dose LMWH on placental abruption (RR 0.22; 95% CI 0.03 to 1.95; 1 trial, 140 women), postpartum haemorrhage (RR 0.08; 95% CI 0.00 to 1.44; 1 trial, 140 women) and 'bleeding side effects' (no events) were very uncertain.

Adverse effects sufficient to stop treatment

The effect of adjusted-dose versus fixed-dose LMWH on adverse effects sufficient to stop treatment (skin allergy) was very uncertain (RR 0.35, 95% CI 0.01 to 8.50; 1 trial, 144 women; Analysis 3.6).

Adverse effects not sufficient to stop treatment

The effect of adjusted-dose versus fixed-dose LMWH on adverse effects not sufficient to stop treatment (skin allergy) was very uncertain (RR 0.30, 95% CI 0.01 to 7.19; 1 trial, 140 women; Analysis 3.7).

Fetal loss

The effects of adjusted-dose versus fixed-dose LMWH on fetal loss at less than 20 weeks' gestation (RR 4.47; 95% CI 0.22 to 91.38; 1 trial, 140 women), and at least 20 weeks' gestation (RR 2.68; 95% CI 0.11 to 64.68; 1 trial, 140 women) were very uncertain (Analysis 3.8).

Thrombocytopenia

There were no cases of thrombocytopenia in the adjusted-dose or fixed-dose LMWH groups (1 trial, 140 women; Analysis 3.9).

Secondary outcomes not reported

Blood transfusion; serious wound complications; symptomatic osteoporosis; fetal anomalies.

Comparison 4: Antenatal (±*postnatal)* prophylaxis: compression stockings versus none

One trial (Heller 2016) involving 44 women was included.

Primary outcomes

The trial did not report on maternal death, symptomatic thromboembolic events or symptomatic VTE. There were no cases of symptomatic DVT in the compression stockings or no compression stockings groups (1 trial, 44 women Analysis 4.1).

Secondary outcomes

No cases of adverse effects sufficient to stop treatment were reported (1 trial, 44 women; Analysis 4.2).

Secondary outcomes not reported

Asymptomatic thromboembolic events; blood transfusion; bleeding episodes; serious wound complications; adverse effects sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 5: Peripartum prophylaxis: UFH versus no treatment

One trial (Segal 1975) involving 210 women was included. See Summary of findings 3.

Primary outcomes

The included trial (Segal 1975) did not report on maternal death. The effects of UFH versus no heparin on symptomatic thromboembolic events (RR 0.16; 95% CI 0.02 to 1.36; 1 trial, 210 women; Analysis 5.1), symptomatic PE (RR 0.16; 95% CI 0.01 to 3.34; 1 trial, 210 women; Analysis 5.2), and symptomatic DVT (RR 0.27; 95% CI 0.03 to 2.55; 1 trial; 210 women; Analysis 5.3) were very uncertain - all very low-certainty evidence.

Secondary outcomes

Secondary outcomes not reported

Asymptomatic thromboembolic events; blood transfusion; bleeding episodes; serious wound complications; adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 6: Peripartum/postnatal prophylaxis (caesarean): heparin (LMWH or UFH) versus no treatment or placebo

Five trials (Algahtani 2015; Burrows 2001; Gates 2004b; Hill 1988; Welti 1981) involving 1147 women were included. See Summary of findings 4.

Primary outcomes

There were no cases of maternal death (1 trial, 300 women; Analysis 6.1). The effects of heparin versus no treatment or placebo on symptomatic thromboembolic events (RR 1.30; 95% CI 0.39 to 4.27; 4 trials, 840 women; Analysis 6.2), symptomatic PE (RR 1.10; 95% CI 0.25 to 4.87; 4 trials, 840 women; Analysis 6.3), and symptomatic DVT (RR 1.30; 95% CI 0.24 to 6.94; 5 trials, 1140 women; Analysis 6.4) were very uncertain - all very low-certainty evidence.

Secondary outcomes

Blood transfusion

The effect of heparin versus no treatment or placebo on blood transfusion was very uncertain (RR 0.24; 95% CI 0.03 to 2.13; 3 trials, 266 women; Analysis 6.5).

Bleeding episodes

Bleeding episodes were variously reported across four trials. There were no cases of major bleeding (1 trial, 76 women) or major bruising (1 trial, 76 women). The effects of heparin versus no treatment or placebo were very uncertain for: bleeding complications (a possible increase with heparin was observed) (RR 5.03; 95% CI 2.49 to 10.18; 2 trials, 714 women), bleeding/bruising at discharge (RR 6.17; 95% CI 0.76 to 49.96; 1 trial, 140 women), blood loss less than 500 mL (RR 1.50; 95% CI 0.63 to 3.59; 1 trial, 50 women), blood loss 500 mL to 1000 mL (RR 0.81; 95% CI 0.50 to 1.31; 1 trial, 50 women), blood loss 1000 mL to 1500 mL (RR 0.50; 95% CI 0.05 to 5.17; 1 trial, 50 women), and blood loss 1500 mL to 2000 mL (RR 2.00; 95% CI 0.19 to 20.67; 1 trial, 50 women; Analysis 6.6).

Serious wound complications

Serious wound complications were variably reported in three trials; no major wound disruptions were reported in the heparin and no treatment or placebo groups (2 trials, 126 women); the effect of heparin versus no treatment or placebo on wound infection was very uncertain (RR 2.30; 95% CI 0.34 to 15.53; 2 trials, 216 women; Analysis 6.7).

Adverse effects sufficient to stop treatment

There were no cases of adverse effects sufficient to stop treatment (1 trial, 140 women; Analysis 6.8).

Adverse effects not sufficient to stop treatment

There were no cases of adverse effects insufficient to stop treatment (1 trial, 76 women; Analysis 6.9).

Secondary outcomes not reported

Asymptomatic thromboembolic events; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 7: Peripartum/postnatal prophylaxis (caesarean): HES versus UFH

One trial (Heilmann 1991) involving 207 women was included.

Primary outcomes

The trial did not report on maternal death, symptomatic thromboembolic events, symptomatic PE or symptomatic DVT.

Secondary outcomes

Asymptomatic thromboembolic events

The effect of HES versus UFH on asymptomatic thromboembolic events was very uncertain (RR 0.76; 95% CI 0.27 to 2.11; 1 trial, 207 women; Analysis 7.1).

Blood transfusion

The effect of HES versus UFH on blood transfusions was very uncertain (RR 0.50; 95% CI 0.05 to 5.48; 1 trial, 207 women Analysis 7.2).

Bleeding episodes

The effect of HES versus UFH on bleeding episodes was very uncertain (RR 0.40; 95% CI 0.08 to 2.03; 1 trial, 207 women; Analysis 7.3).

Wound complications

The effect of HES versus UFH on wound complications was very uncertain (RR 0.67; 95% CI 0.25 to 1.82; 1 trial, 207 women; Analysis 7.4).

Secondary outcomes not reported

Asymptomatic thromboembolic events; adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH

Three trials (Gibson 1998; Heilmann 2007; Krauss 1994) involving 217 women were included. See Summary of findings 5.

Primary outcomes

No trials reported on maternal death. The effects of LMWH versus UFH on symptomatic thromboembolic events (RR 0.33; 95% CI 0.01 to 7.99; 3 trials, 217 women; Analysis 8.1) and symptomatic DVT (RR 0.33; 95% CI 0.01 to 7.99; 3 trials, 217 women; Analysis 8.3), were very uncertain - both very low-certainty evidence. There were no cases of symptomatic PE (3 trials, 217 women; Analysis 8.2).

Secondary outcomes

Bleeding episodes

There were no cases of bleeding episodes (variously defined) in the LMWH and UFH groups: 'haemorrhagic event' (1 trial, 17 women), major bleeding (1 trial, 100 women), and post surgical haemorrhage (1 trial, 100 women) (Analysis 8.4).

Adverse effects not sufficient to stop treatment

There were no adverse effects not sufficient to stop treatment (1 trial, 100 women; Analysis 8.5).

Thrombocytopenia

There were no cases of thrombocytopenia (1 trial, 100 women; Analysis 8.6). Another trial (Heilmann 2007) reported that "The clinical outcome showed no differences in... the different prophylaxis groups and thrombocytopenia."

Secondary outcomes not reported

Asymptomatic thromboembolic events; blood transfusions; adverse effects sufficient to stop treatment; symptomatic osteoporosis; fetal loss; fetal anomalies.

Comparison 9: Peripartum/postnatal prophylaxis (caesarean): five-day versus 10-day LMWH

One trial (Cruz 2011) involving 646 women was included.

Primary outcomes

There were no maternal deaths (1 trial, 646 women; Analysis 9.1) or cases of symptomatic DVT (1 trial, 646 women; Analysis 9.4) in the five-day and 10-day LMWH groups. The effects of five-day versus 10-day LMWH on symptomatic thromboembolic events (RR 0.36; 95% CI 0.01 to 8.78; 1 trial, 646 women; Analysis 9.2) and symptomatic PE (RR 0.36; 95% CI 0.01 to 8.78; 1 trial, 646 women; Analysis 9.3) were very uncertain.

Secondary outcomes

Bleeding episodes

There were no bleeding episodes (1 trial, 646 women; Analysis 9.5).

Serious wound complications

The effects of five-day versus 10-day LMWH on post caesarean infection (RR 1.13; 95% CI 0.63 to 2.05; 1 trial, 646 women) and post caesarean seroma (RR 1.14; 95% CI 0.59 to 2.23; 1 trial. 646 women) were very uncertain (Analysis 9.6).

Thrombocytopenia

There were no cases of thrombocytopenia (1 trial, 646 women; Analysis 9.7).

Secondary outcomes not reported

Asymptomatic thromboembolic events; blood transfusions; adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment; symptomatic osteoporosis; fetal losses; fetal anomalies.

Comparison 10: Peripartum/postnatal prophylaxis (caesarean): weight-based versus fixed-dose LMWH

One trial (Stephenson 2016) involving 90 women was included.

Primary outcomes

Maternal death was not reported. There were no cases of symptomatic thromboembolic events (1 trial, 84 women; Analysis 10.1), symptomatic PE (1 trial, 84 women; Analysis 10.2) or symptomatic DVT (no events; 1 trial, 84 women; Analysis 10.3) in the weight-based and fixed-dose LMWH groups.

Secondary outcomes

Blood transfusion

No blood transfusions were reported (1 trial, 84 women; Analysis 10.4).

Adverse effects not sufficient to stop treatment

Stephenson 2016 reported narratively in text on one "possible case of heparin-induced skin necrosis" in the weight-based LMWH group.

Serious wound complications

The effects of weight-based versus fixed-dose LMWH on wound infection (RR 0.20; 95% CI 0.01 to 4.04; 1 trial, 84 women) and wound haematoma (RR 0.33; 95% CI 0.04 to 3.08; 1 trial, 84 women) were very uncertain (Analysis 10.5). There were no cases of wound dehiscence or reoperation (1 trial, 84 women) (Analysis 10.5).

Secondary outcomes not reported

Asymptomatic thromboembolic events; bleeding episodes; adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types)

One trial (Ellison 2001) involving 30 women was included.

Primary outcomes

Maternal death was not reported. There were no cases of symptomatic thromboembolic events, symptomatic PE or symptomatic DVT in comparisons of dalteparin versus enoxaparin, dalteparin versus tinzaparin, and enoxaparin versus tinzaparin (1 trial, 20 women in each comparison for each outcome; Analysis 11.1; Analysis 11.2; Analysis 11.3).

Secondary outcomes

Bleeding episodes

There were no bleeding episodes (excessive bruising) in comparisons of dalteparin versus enoxaparin, dalteparin versus tinzaparin, and enoxaparin versus tinzaparin (1 trial, 20 women in each comparison; Analysis 11.4).

Adverse effects not sufficient to stop treatment

There were no adverse effects (not sufficient to stop treatment (skin reactions)) in comparisons of dalteparin versus enoxaparin, dalteparin versus tinzaparin, and enoxaparin versus tinzaparin (1 trial, 20 women in each comparison; Analysis 11.5).

Secondary outcomes not reported

Asymptomatic thromboembolic events; blood transfusion; serious wound complications; adverse effects sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 12: Peripartum/postnatal prophylaxis (caesarean): compression devices versus bed rest

One trial (Reddick 2014) involving 50 women was included.

Primary outcomes

Maternal death was not reported. There were no cases of symptomatic thromboembolic events (1 trial, 49 women; Analysis 12.1), symptomatic PE (1 trial, 49 women; Analysis 12.2) or symptomatic DVT (1 trial, 49 women; Analysis 12.3) in the compression devices and bed rest groups.

Secondary outcomes

No blood transfusions were reported (1 trial, 49 women; Analysis 12.4).

Secondary outcomes not reported

Asymptomatic thromboembolic events; bleeding episodes; serious wound complications; adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment; symptomatic osteoporosis; fetal loss; thrombocytopenia; fetal anomalies.

Comparison 13: Postnatal prophylaxis: LMWH versus no treatment or placebo

Two trials (Rodger 2015; Rodger 2016) involving 62 women, were included. See Summary of findings 6.

Primary outcomes

There were no cases of maternal death (1 trial, 24 women; Analysis 13.1), symptomatic thromboembolic events (2 trials, 58 women; Analysis 13.2), symptomatic PE (2 trials, 58 women; Analysis 13.3),

or symptomatic DVT (2 trials, 58 women; Analysis 13.4) in the LMWH and no treatment or placebo groups.

Secondary outcomes

Assymptomatic thromboembolic events

There were no asymptomatic thromboembolic events (2 trials, 58 women; Analysis 13.5).

Bleeding episodes

Bleeding episodes were variably reported by the two trials. The effects of LMWH versus no treatment or placebo on major bleeding (RR 3.53; 95% CI 0.15 to 81.11; 2 trials, 59 women), clinically relevant bleeding events (RR 5.88; 95% CI 0.30-114.28; 1 trial, 35 women), and minor bleeding events (RR 3.53; 95% CI 0.15 to 81.11; 1 trial, 35 women) were very uncertain (Analysis 13.6).

Adverse effects not sufficient to stop treatment

The effect of LMWH versus placebo or no treatment on adverse effects not sufficient to stop treatment was very uncertain (RR 3.53; 95% CI 0.15 to 81.11; 2 trials, 59 women; Analysis 13.7).

Thrombocytopenia

There were no cases of thrombocytopenia (1 trial, 24 women; Analysis 13.8).

Secondary outcomes not reported

Blood transfusion; serious wound complications; adverse effects sufficient to stop treatment; symptomatic osteoporosis; fetal loss; fetal anomalies.

Sensitivity analysis

Nine high-quality trials (judged to be at low risk of both selection bias and attrition bias) (de Vries 2012; Gates 2004a; Gates 2004b; Pettila 1999; Rodger 2014; Rodger 2015; Rodger 2016; Salim 2016; van Hoorn 2016) were identified for sensitivity analyses. Sensitivity analyses for Comparisons 3 (Salim 2016) and 13 (Rodger 2015; Rodger 2016) were not replicated below; as trials for inclusion were the same as in the main analyses.

Comparison 1: Antental (± postnatal) prophylaxis: heparin (LMWH or UFH) versus no treatment or placebo

For the outcomes symptomatic thromboembolic events (Analysis 14.1) and symptomatic PE (Analysis 14.2), sensitivity analyses included the same trials (and thus results) as the main analyses. In the sensitivity analysis the effect of heparin versus no treatment or placebo on symptomatic DVT was very uncertain (RR 0.33; 95% CI 0.01 to 7.93; 3 trials, 187 women), as in the main analysis.

Comparison 2: Antental (± postnatal) prophylaxis: LMWH versus UFH

On sensitivity analysis, there were no symptomatic thromboembolic events, symptomatic PE or DVT reported (1 trial, 105 women) (Analysis 15.1; Analysis 15.2; Analysis 15.3). Unlike the main analysis for symptomatic thromboembolic events (where the effect was very uncertain), the sensitivity analysis included no cases (1 trial, 105 women) (Analysis 15.1).

Comparison 6: Peripartum/postnatal prophylaxis (caesarean): heparin (LMWH) versus no treatment or placebo

As in the main analyses, sensitivity analyses suggested the effects of heparin versus no treatment or placebo on symptomatic thromboembolic events and PE were very uncertain (both RR 3.09; 95% CI 0.13 to 74.51; 1 trial, 134 women; Analysis 16.1; Analysis 16.2). Unlike in the main analysis for symptomatic DVT (where the effect was very uncertain), the sensitivity analysis included no cases (1 trial, 134 women) (Analysis 16.3).

DISCUSSION

Summary of main results

In this updated review, we included 29 randomised controlled trials comparing effects of various methods of thromboprophylaxis in women who were pregnant or who had recently given birth and were at increased risk of venous thromboembolism (VTE). The included trials contributed data across 13 comparisons.

Antenatal (± postnatal) prophylaxis: effects were very uncertain (very low-certainty evidence, where assessed; or could not be determined due to no events) across all comparisons that reported symptomatic thromboembolic events, symptomatic pulmonary embolism (PE), symptomatic deep vein thrombosis (DVT) and/or adverse effects sufficient to stop treatment (heparin versus no treatment/placebo (maximum of four trials, 476 women); low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) (maximum of 4 trials, 404 women); adjusted-dose versus fixed-dose LMWH (maximum of one trial, 144 women); compression stockings versus none (maximum one trial, 44 women). Maternal death was not reported.

Peripartum/postnatal prophylaxis: ***for vaginal birth or caesarean birth:*** effects were very uncertain in the comparison of UFH versus no treatment for symptomatic thromboembolic events, symptomatic PE and symptomatic DVT (one trial, 210 women). Maternal death and adverse effects sufficient to stop treatment were not reported.

For caesarean birth: effects were very uncertain (very low-certainty evidence where assessed; or could not be determined due to no events) across all comparisons that reported maternal death, symptomatic thromboembolic events, symptomatic PE, symptomatic DVT, adverse effects sufficient to stop treatment (heparin versus no treatment/placebo (maximum of 5 trials, 1140 women); LMWH versus UFH (3 trials, 217 women); five-day versus 10-day LMWH (one trial, 646 women); weight-based versus fixed-dose LMWH (1 trial, 84 women); comparisons of different types of LMWH (1 trial; 30 women); compression devices versus bed rest (1 trial, 49 women).

Postnatal prophylaxis: there were no events in the comparison of LMWH versus no treatment/placebo for maternal death, symptomatic thromboembolic events, symptomatic PE and symptomatic DVT (maximum of 2 trials, 58 women). Adverse effects sufficient to stop treatment were not reported.

Subgroup analyses were unable to be conducted due to lack of data, and sensitivity analyses did not impact the main findings.

Overall completeness and applicability of evidence

The evidence to assess the effects of thromboprophylaxis during pregnancy and the early postnatal period in women at increased risk of VTE on the risk of venous thromboembolic disease and adverse effects is very incomplete. While maternal deaths were largely not reported (only three trials reported this outcome and observed no deaths), we cannot assume that none occurred. Due to differences in the interventions assessed by the trials, and/or difference in the types of included participants and their risk factors (when reported), we were able to combine only a few trials limiting ability to detect differences between interventions. Between one and five trials were included in the 13 review comparisons, with eight of these comparisons including single trials. In general the sample sizes of the trials were small. The three largest trials recruited 646 women (Cruz 2011), 580 women (Welti 1981), and 292 women (Rodger 2014). Sample sizes of this order are generally inadequate to detect differences in the incidences of rare outcomes such as thromboembolic events, or death from such events, particularly when two active treatments are compared.

The important secondary review outcome 'adverse effects sufficient to stop treatment' was only reported by five trials included within four comparisons. There was a paucity of data reported by the included trials for all other secondary outcomes (e.g. asymptomatic thromboembolic events were reported by only four trials across three comparisons). Unclear and different definitions used in the measurement of some of the secondary outcomes (e.g. bleeding episodes; adverse effects not sufficient to stop treatment) made comparing effects of trials difficult, and prevented synthesising individual effect measures in analyses. It is likely that trial authors had differing definitions of ‘serious”.

While the trials conducted to date (and included in this review), have assessed a large number of thromboprophylaxis comparisons, and this update included interventions not identified in the previous version of the review (Bain 2014), gaps remain. The full range of commonly-used interventions has not been assessed. For example, none of the included trials assessed intermittent pneumatic compression, early mobilisation or surveillance. Some of the older trials assessed thromboprophylaxis methods which are no longer used (such as hydroxyethyl starch (HES) (Paull 1987)), or are not used as frequently in current thromboprophylactic practice (such as the use of UFH rather than LMWH).

The focus of this review was on determining effects of different methods to prevent VTE in pregnancy and the early postpartum period, in women at increased risk of VTE due to a variety of risk factors; further evidence on the use of heparin and other thromboprophylactic drugs on the prevention of miscarriage and other pregnancy outcomes in specific groups of women at high risk of adverse pregnancy outcomes are examined in related Cochrane Reviews (see de Jong 2014; Dodd 2013; Hamulyák 2020).

Quality of the evidence

Overall, study-level risk of bias was moderate to high (Figure 2; Figure 3); while attrition bias was considered mostly low risk, there was high or unclear risk of reporting bias in over 80% of trials (due mostly to the absence of protocols and trials published as abstracts only), and over half of the trials were judged at unclear or high risk of selection bias. Most of the included studies had difficulties with adequate blinding of women and personnel due to the interventions they assessed, and in the majority of the trials it was unclear whether outcome assessors were blinded (though absence of blinding for these objective outcomes did not impact our ratings of the certainty of the evidence). The few potential differences in particular secondary outcomes reported in this review were largely derived from small trials which were not considered to be of high methodological quality; there is a strong possibility that they may be caused by bias or chance.

The certainty of evidence (assessed using the GRADE approach) assigned to all critical outcomes reported in 'Summary of findings' tables (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6) was very low certainty. Reasons for downgrading included design limitations and considerable imprecision (usually due to low event rates and small numbers of trials per outcome). Although, in a few instances, evidence was also downgraded for indirectness (concerns about applicability of results included vague definition of outcomes (e.g. lack of clarity about whether thromboembolic events were symptomatic), poorly defined VTE risk factors of women in the included trials, and specificity and variation in VTE risk factors of women in the included trials).

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 trials have been conducted but not published. Should such trials 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 trial selection, data extraction, quality and evidence-certainty assessments.

Agreements and disagreements with other studies or reviews

A narrative review (Andrew 2020) has described the latest evidence on postpartum VTE prevention in women with modest risk factors, such as those with mild thrombophilias, and transient situational risk factors around labour and birth, including caesareans. Congruent with our review, the authors highlight uncertainty surrounding the effects of postpartum thromboprophylaxis in this group of women, and call for the collection of robust prospective data on VTE risk factors and effects of postpartum thromboprophylaxis.

Three related Cochrane Reviews have assessed the effects of the use of thromboprophylaxis (including heparin) in pregnant women. The de Jong 2014 review (conducted prior to the inclusion of GRADE certainty assessments), assessed effects of anticoagulant agents (including aspirin and heparin) in women with a history of at least two unexplained miscarriages, with or without inherited thrombophilia (primary outcome live birth). Consistent with our review, no clear beneficial effects of anticoagulants in trials considered at low risk of bias were found - in the review's comparison of LMWH versus no treatment, no differences between groups were found in individual trials for pregnancy complications, bleeding or thromboembolic events.

The Hamulyák 2020 review, assessed the effects of aspirin and/or heparin for improving pregnancy outcomes in women

with persistent (on two separate occasions) antiphospholipid antibodies, either lupus anticoagulant, anticardiolipin or aβ2-glycoprotein-I antibodies or a combination, and recurrent pregnancy loss (two or more, which did not have to be consecutive).The review demonstrated low-certainty evidence that heparin plus aspirin versus aspirin alone may increase the number of live births and reduce the risk of pregnancy loss. Similar to our review, the authors were very uncertain if heparin (plus aspirin versus aspirin alone) has any effect on adverse effects (bleeding) in the mother; no cases of thrombocytopenia, allergic reactions, venous or arterial thromboembolism or congenital malformations were reported (Hamulyák 2020).

Trials assessing the effects of antithrombotic therapy for improving maternal or infant health outcomes specifically in women considered at risk of placental dysfunction were included in the Dodd 2013 review, which focused on outcomes largely different to those included in this review. While the review (also conducted prior to the inclusion of GRADE certainty assessments), demonstrated potential benefits of the use of heparin versus no treatment - with reductions in perinatal mortality, preterm birth and infant birthweight below the 10th centile for gestational age observed - similar to our review, a lack of reliable information regarding clinically relevant, serious adverse infant health outcomes was identified (Dodd 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence is very uncertain regarding the effects of thromboprophylaxis during pregnancy and the early postnatal period on the risk of venous thromboembolic disease and adverse effects in women at increased risk of venous thromboembolism (VTE).

Effects were very uncertain (or not estimable due to no events) across all antenatal, intrapartum and postnatal comparisons that reported critical outcomes: symptomatic thromboembolic events, symptomatic pulmonary embolism (PE), symptomatic deep vein thrombosis (DVT) and/or adverse effects sufficient to stop treatment. Evidence for these critical outcomes was assessed as very low-certainty due mainly to trial design limitations and considerable imprecision (usually due to low event rates and small numbers of trials and participants per outcome). No maternal deaths were reported.

Implications for research

There is a need for certain evidence from rigorously conducted large-scale randomised controlled trials assessing the effects of methods of thromboprophylaxis on rare outcomes such as thromboembolic events. However, the low number of eligible women, and the need to include very large numbers of women in each trial arm to show a difference in incidence of rare outcomes makes conducting trials of antenatal thromboprophylaxis extremely challenging. To achieve an adequate sample size, a trial needs to be conducted in a very large number of centres, in a range of countries, and involve much international collaboration. Acquiring funding for such trials is difficult, and highly unlikely. Rigorous observational studies based on registry data, for example the Riete Registry, the worlds largest database on patients with VTE, are more feasible, and are therefore warranted to address the gaps in evidence about the safety and effectiveness of VTE prophylaxis for high-risk women during pregnancy and the early postnatal period.

Future studies need to address currently used treatments. Standardised reporting of a comprehensive range of critical outcomes would facilitate combining effect estimates from individual trials in meta-analyses.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Algahtani 2015

Study characteristics	
Methods	RCT: NCT01321788
Participants	300 women were randomised Setting: Riyadh, Saudi Arabia. Dates of the study: not reported. **Inclusion criteria**: women aged 18 to 35 years, undergoing caesarean section. **Exclusion criteria**: not reported in abstracts, but detailed in trial registration as being at high risk for thromboembolism (any 1 of the following): aged > 35 years, obese, parity > 4, gross varicose veins, current infection, pre-eclampsia, immobility prior to surgery, major current disease (including heart of lung disease, cancer, inflammatory bowel disease and nephrotic syndrome), extended major pelvic or abdominal surgery, with a family history of VTE, or a history of superficial phlebitis); more than 36 hours since birth, with need for anticoagulation (women with confirmed thrombophilia, with paralysis of lower limbs, with a personal history of VTE, with antiphospholipid antibody syndrome, or mechanical heart valves), and no contraindications to heparin therapy.
Interventions	**Group 1** (n = 100): LMWH (tinzaparin), 4500 IU subcutaneously once daily, starting from 12 to 24 hours after caesarean section, for 2 weeks. **Group 2** (n = 200): placebo, once daily, timing as above. **All women**: received non-pharmacological prophylaxis using graduated compression stockings.
Outcomes	**Review outcomes reported**: maternal death; symptomatic DVT. Other outcomes reported: none
Notes	Information extracted from conference abstracts. Number randomised somewhat unclear, as there appears to be an error in the abstract, which reports that 200 women consented, and also that there were 100 and 200 women in the intervention and comparison groups, respectively. Unable to find a contact email address for author to clarify. Funding sources: not reported. Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized into two groups..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to determine (despite reported use of a placebo).

Algahtani 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to determine.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine. Additionally, "minor and major bleeding events" reported as an outcome of interest in abstract methods, but results not reported for this outcome; trial registration also specifies PE and thrombocytopenia as outcomes of interest, and these outcomes are not reported in the abstracts reporting this study.
Other bias	Unclear risk	Insufficient information to determine.

Burrows 2001

Study characteristics	
Methods	RCT.
Participants	76 women were randomised. Setting: tertiary obstetric centre in Australia. Study dates: June to November 1999. **Inclusion criteria**: women who had undergone an elective or emergency caesarean section. **Exclusion criteria**: history of bleeding disorder; need for anticoagulant therapy; history of thrombotic event; heparin sensitivity; recent GI haemorrhage or peptic ulcer; hepatic encephalopathy; renal dysfunction requiring dialysis; uncontrolled hypertension; refusal to give informed consent; insufficient English to provide consent.
Interventions	**Group 1** (n = 39): LMWH (dalteparin), 2500 IU once daily.The injections, 4 or 5, depending on hospital stay, were given either in the thigh or abdomen, depending on women's preference and the site rotated each day. Enough syringes for 5 days of treatment were provided. **Group 2** (n = 37): matching placebo (saline) once daily for 4 to 5 days. Interventions started 4 to 24 hours after caesarean section, and continued for 4 to 5 days.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion; bleeding episodes (reports major bleeding: 20 g/L fall in Hb, the need for a blood transfusion, a retroperitoneal, intraocular or intracranial bleed; reports major bruising); serious wound complications (reports major wound disruption requiring surgical repair and wound disruption); adverse effects not sufficient to stop treatment (reports major reaction) Other outcomes reported: fever post-operation; antibiotics post-operation; wound infection; minor wound disruption.
Notes	This study was a pilot protocol to inform an intended national level multi-centre RCT. Funding sources: quote: "Pharmacia and Upjohn kindly provided the dalteparin and saline placebo medication but no other intellectual or financial support for this study." Declarations of interest: not reported.

Burrows 2001 *(Continued)*

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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All primary analyses were based on 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	No trial protocol 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

Study characteristics

Methods	RCT
Participants	120 women were randomised. Setting: 9 centres in the USA. Study dates: September 1998 to December 2005. **Inclusion criteria**: women who were candidates for low-dose thromboprophylaxis for the duration of their pregnancy, aged 18 years or more, who could begin therapy < 24 weeks of gestation. **Exclusion criteria**: women with contraindication to anticoagulation.
Interventions	**Group 1** (n = 61): LMWH (enoxaparin sodium). Self-administered subcutaneous 30 mg twice daily from enrolment (women < 24 weeks' GA) until 28 weeks of gestation, then 40 mg twice daily until birth. **Group 2** (n = 59): UFH (heparin sodium). Self-administered subcutaneous 7500 units twice daily until 28 weeks, then 10,000 units twice daily until birth. Baseline bone density test for women in both groups. All women received adjusted-dose coumadin for 6 to 8 weeks after birth.

Casele 2006 *(Continued)*

	All women were asked to take antenatal vitamins and were asked to take calcium supplements (500 mg) daily from enrolment until birth.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events (reports recurrent thrombosis); bleeding episodes (reports bleeding at birth); symptomatic osteoporosis (reports clinically significant bone loss in total femur ≥ 10%); fetal loss (reports spontaneous abortion). Other outcomes reported: other measures of mean bone density (reports bone mineral density change at femoral neck and total proximal femur); gestational age at birth; birthweight.
Notes	The power calculation was based on detecting bone mass changes, the original sample estimate required was 240. 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 before the intended sample size had been reached. Funding sources: not reported. Declarations of interest: not reported.

Risk of bias

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 considering the interventions assessed.
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 (11 women had spontaneous abortions, 7 women were non-compliant, 2 women had allergic reactions, 2 women switched to therapeutic anticoagulation), 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	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No obvious risk of other bias.

Cornette 2002

Study characteristics	
Methods	RCT
Participants	44 women were randomised. Setting: authors from Belgium (no further details provided). Study dates: not reported. **Inclusion criteria**: women with full-term singleton pregnancies admitted for elective caesarean section. **Exclusion criteria**: women with known bleeding or coagulation disorders.
Interventions	**Group 1** (n = 22): preoperative, 0.3 mL nadroparin calcium (LMWH), administered 12 hours before elective caesarean birth. **Group 2** (n = 22): postoperative, 0.3 mL (2850 IU) nadroparin calcium, administered 12 hours after elective caesarean birth. 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	**Review outcomes reported**: none. Other outcomes reported: Hb and haematocrit concentrations 12 hours before and 48 hours after surgery (as a substitute for blood loss).
Notes	No outcomes included in the review analysis as outcomes were not relevant to the review. The power calculation was based on changes in Hb levels. Funding sources: not reported. Declarations of interest: not reported.

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.

Cornette 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trial protocol 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

Study characteristics	
Methods	RCT
Participants	646 women were randomised. Setting: San Cecilio University Hospital, Granada, Spain. Study dates: 1-year period (not further specified). **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	**Group 1** (n = 311): 5 day bemiparin regimen (3500 IU once daily) as post-caesarean section prophylaxis ≥ 8 hours following caesarean. **Group 2** (n = 335): 10 day bemiparin regimen (3500 IU once daily) as post-caesarean section prophylaxis ≥ 8 hours following caesarean.
Outcomes	Review outcomes reported: maternal death; symptomatic thromboembolic events; symptomatic PE; symptomatic DVT (all up to 3 months following caesarean); bleeding episodes; thrombocytopenia; post-caesarean infection and seroma. Other outcomes reported: variables assessed as possible risk factors for a thromboembolic event included hypertension; diabetes; type of caesarean section; type of anaesthesia; week of birth; preterm birth; placental abruption; intrauterine growth restriction. Post-caesarean section risk factors that were measured included anaemia; infection; seroma and hypertension.
Notes	Funding sources: research grant from the Laboratorios Fcos. ROVI, SA. Authors state that the results reported in the manuscript were not influenced by the funding received. Declarations of interest: not reported.

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).

Cruz 2011 *(Continued)*

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 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	No trial protocol to confidently assess selective reporting; further important outcomes such as adverse effects and bleeding episodes were not reported.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

De Veciana 2001

Study characteristics	
Methods	RCT
Participants	121 women were randomised. Setting: authors from the USA. Dates of the study: not reported. **Inclusion criteria**: not reported; though as per results presented, women with prophylactic anticoagulation indicators were included: antiphospholipid syndrome, a history of DVT/embolus, protein C/protein S deficiency, Factor V Leiden mutation, and obesity. **Exclusion criteria**: women with renal/liver disease, bleeding diathesis, pork/heparin sensitivity.
Interventions	**Group 1** (n = 61): dalteparin (LMWH): initial dosing was 2500 IU (5000 IU if > 70 kg) 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 **Group 2** (n = 60): UFH: dosed with the standard 5000 U (8000 U if > 68 kg) subcutaneously twice daily.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports bruises > 2.5 cm); adverse effects sufficient to stop treatment (reports switched from UFH to LMWH due to excess bruising/allergic rashes); adverse effects not sufficient to stop treatment (reports injection burning); thrombocytopenia. Other outcomes reported: gestation at birth; fetal loss (reports stillbirths < 20 weeks); anaesthesia complications.
Notes	Published as abstract only. Timing of intervention not specified further than "during pregnancy". Funding sources: not reported. Declarations of interest: not reported.
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

De Veciana 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Prospective randomized controlled trial".
Allocation concealment (selection bias)	Unclear risk	Quote: "Prospective randomized controlled trial".
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.

de Vries 2012

Study characteristics	
Methods	RCT: ISRCTN87325378
Participants	139 women were randomised. Setting: 13 centres (all university hospitals in the Netherlands, 2 in Australia and 1 in Sweden, and 6 non-university/teaching hospitals in the Netherlands). Study dates: December 2000 to December 2009. **Inclusion criteria**: < 12 weeks' gestation; aged > 18 years; with a history of uteroplacental insufficiency and birth < 34 weeks' gestation (hypertensive disorders of pregnancy (pre-eclampsia or HELLP syndrome or eclampsia); and/or a SGA infant); with a thrombophilic disorder (1 or more of: protein C deficiency; protein S deficiency; activated protein C resistance; factor V Leiden mutation (heterozygous); prothrombin gene G20210A mutation (heterozygous)). If antiphospholipid antibodies (lupus anticoagulant and/or cardiolipin IgG, and/or cardiolipin IgM antibodies) were also present, women were randomised into a separate study (see van Hoorn 2016). **Exclusion criteria**: 1 or more of: antithrombin deficiency; homozygosity for factor V Leiden and prothrombin G20210A mutation; diabetes mellitus; known malignancy; known peptic ulceration; severe renal or hepatic insufficiency; history of VTE; haemorrhagic diathesis; idiopathic thrombocytopenia; earlier participation in the FRUIT trial; LMWH use in an earlier pregnancy.
Interventions	**Group 1** (n = 70): LMWH (dalteparin (Fragmin)) 5000 IU subcutaneously daily commenced between 6 and 12 weeks' gestation, and continued until the onset of labour; together with 80 mg oral aspirin daily, commenced before 12 weeks' gestation, and continued until 36 weeks' gestation (Australian participants received aspirin 100 mg; Swedish participants received aspirin 75 mg). Daily dose of LMWH adjusted for body weight: participants below 50 kg received dalteparin 2500 IU, and those above received 80 kg 7500 IU; further adjusted as the pregnancy proceeded and postpartum.

de Vries 2012 *(Continued)*

	Women received instructions for self-injection; for women with local irritation, dalteparin was changed to enoxaparin (and if irritation persisted, nadroparin). **Group 2** (n = 69): women received 80 mg oral aspirin daily, as above. **All women**: after birth, all women received LMWH for 6 weeks.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic DVT; bleeding episodes (reports placental abruption); adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment (reports skin reaction: pain, itching, swelling, allergy; haematoma; need to convert LMWH prescription; superficial thrombophlebitis); symptomatic osteoporosis (reports complaints suggestive of osteoporosis); fetal loss (reports spontaneous abortion < 16 weeks; and fetal death > 16 weeks) thrombocytopenia. Other outcomes reported: recurrent hypertensive disorders of pregnancy (any of: pre-eclampsia, HELLP syndrome and/or eclampsia) before 34 weeks' gestation, and until term; SGA; preterm birth; duration of maternal and neonatal admissions; pre-eclampsia; HELLP syndrome; eclampsia; termination of pregnancy; gestational age at birth; birthweight; gestational age at hypertensive disorder diagnosis; medications during pregnancy (antihypertensive; magnesium sulphate; corticosteroids); increase in pregnancy duration; measures of fetal growth and uterine and umbilical arterial Doppler.
Notes	Funding sources: quote: "The study was supported by a single 2-year investigator grant period 2000–2001 by Pfizer, formerly Pharmacia grant number 524E-CVD-9101-0001, annual Dutch investigators meetings, a single grant to support a midwife to recruit Australian subjects, and support for a local meeting in Sweden in 2004. Pharmacia was not the sponsor of the study." Declarations of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a computer to select random permuted blocks of four, stratifying by hospital and presence/absence of chronic hypertension."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by an independent center… Block length and randomization codes were concealed from the investigators."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither study personnel nor participants were blinded to treatment assignment, as placebo injections were not considered to be ethically acceptable during pregnancy."
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	Of 70 women in intervention group, 3 stopped LMWH (bleeding from placenta praevia (1) and inconvenience (2)), all analysed; and of 69 in comparison group, 2 stopped aspirin due to stomach complaints; all analysed. See additional protocol deviations below.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Ellison 2001

Study characteristics	
Methods	RCT (3 arms)
Participants	30 women were randomised. Setting: authors from Glasgow, UK (not further specified). Study dates: not reported. **Inclusion criteria**: women undergoing caesarean section, with an additional risk factor for thromboembolism (including: obesity, immobility, maternal age older than 35 years, parity > 4, labour > 4 hours, gross varicose veins, current infection, pre-eclampsia, major current illness, caesarean section performed as an emergency). **Exclusion criteria**: not reported.
Interventions	**Group 1** (n = 10): dalteparin (LMWH) 5000 IU once daily. **Group 2** (n = 10): enoxaparin (LMWH) 4000 IU once daily. **Group 3** 2 (n = 10): tinzaparin (LMWH) 50 IU/kg (based on booking weight) once daily. Drugs started from 6 hours following caesarean section and continued for 5 days.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events (reports "thrombotic... events"); symptomatic PE; symptomatic DVT; bleeding episodes (reports "haemorrhagic events"... "excessive bruising"); adverse effects not sufficient to stop treatment (reports "skin reactions"). Other outcomes reported: women were followed up for 1 day to examine laboratory haemostatic parameters (plasma anti-factor Xa, plasma thrombin-antithrombin (TAT) complex, plasma tissue factor pathway inhibitor (TFPI)).
Notes	Funding sources: not reported. Declarations of interest: not reported. Trial included in the review analysis as 3 pair-wise comparisons of LMWH: dalteparin vs enoxaparin; dalteparin vs tinzaparin; and enoxaparin vs tinzaparin

Risk of bias

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)	Low risk	All women seem to be accounted for in the analysis.

Ellison 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Gates 2004a

Study characteristics	
Methods	RCT ('trial 1').
Participants	16 women were randomised. Setting: 23 hospitals in theUK (women were recruited in only 11 hospitals). Study dates: April 1998 to February 2000 **Inclusion criteria**: pregnant women with clinical uncertainty that antenatal thromboprophylaxis was indicated (women with a history of ≥ 1 previous thromboembolic event, women with a known congenital thrombophilia, or women with other accepted risk factors for which clinicians would consider the use of antenatal heparin (all 16 women recruited had a previous thromboembolic event)); no gestational age limit on recruitment. **Exclusion criteria**: women with a known allergy to heparin.
Interventions	**Group 1** (n = 8): self-administered once-daily subcutaneous 40 mg enoxaparin (LMWH) in 1 mL from antenatal recruitment until a maximum of 6 weeks after birth. **Group 2** (n = 8): self-administered once-daily subcutaneous placebo (normal saline 1 mL) from antenatal recruitment until 6 a maximum of weeks after birth. All trial drugs were packaged identically in packs that contained 7 prefilled syringes, which was enough 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	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion; serious wound complications; adverse events not sufficient to stop treatment (reports "allergic reaction"); symptomatic osteoporosis (reports osteoporotic symptomatic fracture); thrombocytopenia. Other outcomes reported: primary (process) outcome for this pilot was the number of women recruited; also reported bleeding complications, number of hospital admissions, surgical procedures, number of infants admitted to the NICU and number of infants with major bleeding disorders to be secondary outcomes of interest, however no data were reported for these outcomes.
Notes	Pilot study. After birth some clinicians elected to discontinue study drugs and 3 women in both groups were given heparin postnatally. Funding sources: quote: "Supported by the National Health Service Executive South East Region Research and Development (trial 1), and both trials were supported by a donation to the National Perinatal Epidemiology Unit by Rhone-Poulenc Rorer." "Study drugs: Rhone-Poulenc Rorer/Aventis Pharma Ltd, Kent, UK." Declarations of interest: not reported.
Risk of bias	

Gates 2004a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors report that a central telephone randomisation service was used.
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 and for 6 weeks after birth. 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 birth. No attrition.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Gates 2004b

Study characteristics	
Methods	Multi-centre randomised controlled trial ('trial 2')
Participants	141 women were randomised. Setting: 23 hospitals in the UK (women were recruited in only 8 hospitals). Study dates: November 1998 to June 2000. **Inclusion criteria**: women undergoing caesarean section where there was clinical uncertainty that thromboprophylaxis was indicated. **Exclusion criteria**: women with a known allergy to heparin.
Interventions	**Group 1** (n = 70): once-daily self-injected subcutaneous 40 mg enoxaparin (LMWH) in 1 mL. **Group 2** (n = 71): once-daily self-injected subcutaneous placebo (normal saline 1 mL). Treatment with the study drug began within 12 hours of the caesarean section, and its duration was determined by the attending clinician. 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.

Gates 2004b *(Continued)*

	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	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion; bleeding episodes (reports "bleeding/bruising reported at discharge"); serious wound complications (reports wound infections); adverse events sufficient to stop treatment (reports "allergic reactions that were sufficient to stop treatment"). Other outcomes reported: main process outcome for this pilot was the number of women recruited; also reports hospital admissions not for thromboembolic disease; in methods indicates that duration of hospital stay, and number of surgical procedures in 6 months after birth to be secondary outcomes of interest, however no data reported for these outcomes. Data collection at hospital discharge following birth and at 6 months postpartum.
Notes	Pilot study. Funding sources: quote: "both trials were supported by a donation to the National Perinatal Epidemiology Unit by Rhone-Poulenc Rorer." "Study drugs: Rhoˆ ne-Poulenc Rorer/Aventis Pharma Ltd, Kent, UK." Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External randomisation, with a "a pre-randomized 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 < 5%. 141 women randomised, data at discharge for 140, and at 6 months, follow-up for 132.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Gibson 1998

Study characteristics

Gibson 1998 *(Continued)*

Methods	RCT (3 arms).
Participants	17 women were randomised. Setting: authors from Glasgow, UK. Study dates: not reported. **Inclusion criteria**: women undergoing a caesarean section; either an emergency caesarean section or with other risk factors for VTE. **Exclusion criteria**: not reported.
Interventions	**Group 1** (n = 6): LMWH (enoxaparin) 20 mg once daily. **Group 2** (n = 5): LMWH (enoxaparin) 40 mg once daily. **Group 3** (n = 6): UFH 7500 IU every 12 hours. Intervention started after caesarean section, duration of intervention not stated.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports "haemorrhagic event"). Other outcomes reported: anti-Xa activity.
Notes	3-way randomisation (UFH/20 mg enoxaparin/40 mg enoxaparin). 2 enoxaparin groups combined for inclusion in the review analysis. Funding sources: not reported. Declarations of interest: not reported.

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	No trial protocol 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

Study characteristics	
Methods	RCT.
Participants	61 women were randomised. Setting: authors from the USA. Study dates: not reported. **Inclusion criteria**: pregnant women with an underlying diagnosis of either antiphospholipid syndrome, protein S or C deficiency, or idiopathic thrombophilia. **Exclusion criteria**: not reported.
Interventions	**Group 1** (n = 32): LMWH **Group 2** (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 aspirin (81 mg) was also prescribed.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; thrombocytopenia. Other outcomes reported: epidural related complications; physician estimates of blood loss, post-birth haematocrit.
Notes	Published as an abstract only; no further information describing intervention (including when in the antepartum period the intervention commenced) provided; authors contacted, with no response. Funding sources: not reported. Declarations of interest: not reported.

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.

Hamersley 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

Heilmann 1991

Study characteristics	
Methods	RCT
Participants	207 women were randomised. Setting: authors from Germany (setting not further specified). Study dates: not stated. **Inclusion criteria**: women undergoing caesarean section. **Exclusion criteria**: not reported.
Interventions	**Group 1** (n = 103): HES 6%, 3 x 500 mL; first 500 mL during the caesarean section (the first 500 mL), second in the evening of the day of the caesarean, third in the evening of the first postoperative day. **Group 2** (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	**Review outcomes reported**: asymptomatic thromboembolic events (DVT); blood transfusion; bleeding episodes; serious wound complications. Other outcomes reported: a number of laboratory measurements were also taken (relating to blood clotting factors).
Notes	Information obtained from a translation of the manuscript. Funding sources: not reported. Declarations of interest: not reported.

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)	Unclear risk	No detail of blinding of outcome assessors.

Heilmann 1991 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

Heilmann 2007

Study characteristics	
Methods	RCT (3 arms, 1 not randomised).
Participants	100 women were randomised. Setting: authors from Germany (setting not further specified). Study dates: not reported. **Inclusion criteria**: women with uncomplicated pregnancy; following elective caesarean section (for breech presentation or maternal/fetal indications at birth). Quote: "The indication for prophylaxis was the previous diagnosis of a heterozygote factor V-Leiden-mutation." **Exclusion criteria**: not reported.
Interventions	**Group 1** (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-hour intervals). **Group 2** (n = 50): UFH (calciparin 2 x 5000 IU daily, with the first dose 6 hours following caesarean section, and then at 8-hour intervals). Comparison (n = 50, not randomly assigned) Received no pharmacological prophylaxis but compressions stockings according to the guidelines of RCOG (Controls) during hospital days.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports "bleeding complications (blood loss > 500 mL or reoperation)"); adverse effects sufficient to stop treatment (reports "allergy"); thrombocytopenia. Other outcomes reported: osteopenia; a number of outcomes relating to the rheological properties of blood were also assessed.
Notes	50 additional matched controls were assessed in the manuscript. We included data for the 2 treatment groups only in this review. Funding sources: not reported. Declarations of interest: not reported.
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Heilmann 2007 *(Continued)*

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 "The clinical outcome showed no differences in the blood loss for the different prophylaxis groups and thrombocytopenia or Osteopenia.".
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

Heller 2016

Study characteristics	
Methods	RCT: NCT01793194
Participants	44 women were randomised. Setting: authors were from the USA (no further details) Study dates: not reported. **Inclusion criteria**: pregnant women; quote: "Due to the small pilot sample size, ethnicity was limited to Caucasians and African Americans" (unclear if this was an inclusion criterion). Protocol suggests that women with and without varicose veins were included and women age 18-45 years were eligible. **Exclusion criteria**: not reported.
Interventions	**Group 1** (n = 21): compression stockings (20 to 30 mm Hg maternity pantyhose), protocol suggests that women were instructed to wear the stockings daily. **Group 2** (n = 23): no compression stockings. **All women**: timing of interventions unclear, however women were visited 3 times (between 8 to 20 weeks and 32 ± 4 weeks before the birth, and 8 weeks postpartum ± 2 weeks).
Outcomes	**Review outcomes reported**: symptomatic DVT; adverse effects no sufficient to stop treatment (thrombophlebitis). Other outcomes reported: VCSS (Venous Clinical Severity Score); stocking adherence; venous oedema; SF-36 measures (including pain component); thrombophlebitis; superficial axial venin reflux.
Notes	Information extracted from conference abstract.

Heller 2016 *(Continued)*

	Funding sources: not reported. Declarations of interest: Quote: " J. Heller: Consultant/advisory board for BMS/Pfizer, and research grant, principal investigator, collaborator, and consultant for Sigvaris; J. Canner: Nothing to disclose; Y. W. Lum: Nothing to disclose; K. Tsuchiya: Nothing to disclose." DVT not clearly reported as symptomatic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were entered in a consecutive randomized fashion."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine.
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	Insufficient information to determine.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to determine; though abstract suggests no losses: quote: "A total of 44 patients enrolled and completed the study".
Selective reporting (reporting bias)	Unclear risk	Abstract reporting the study describes results of the study, however provides no data.
Other bias	Unclear risk	Insufficient information to determine.

Hill 1988

Study characteristics

Methods	RCT
Participants	50 women were randomised. Setting: authors from the UK (not further specified). Study dates: not reported. **Inclusion criteria**: women undergoing elective caesarean section. **Exclusion criteria**: placenta praevia, multiple pregnancy, pregnancy-induced hypertension, APH, a history off thromboembolic disease, coagulation disorders or peptic ulceration.
Interventions	**Group 1** (n = 25): UFH 1000 units, 1 hour before caesarean, then twice daily for 5 days. **Group 2** (n = 25): saline, 1 hour before caesarean, then twice daily for 5 days.

Hill 1988 *(Continued)*

Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic DVT; symptomatic PE; blood transfusion; serious wound complications; adverse effects not sufficient to stop treatment (reports injection "discomfort"). Other outcomes reported: blood loss; Hb values; abnormalities of plasma clotting factors; defects of platelet function.
Notes	Funding sources: Quote: "We acknowledge the support of Leo Laboratories and the South East Thames Regional Health Authority (grant LORS No 77/19)." Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
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, no information was provided on how blinding was attempted, and it is unlikely considering the interventions assessed that all personnel and participants were blind to treatment assignment.
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	Unable to assessed confidently as high or low risk without access to a trial protocol.
Other bias	Unclear risk	Insufficient information to assess.

Howell 1983

Study characteristics

Methods	RCT
Participants	40 women were randomised. Setting: 1 centre in UK. Study dates: not reported. **Inclusion criteria**: women with a history of thromboembolism treated with anticoagulants for ≥ 6 weeks. Recruitment at time of referral to clinic (8 to 37 weeks' gestational age). **Exclusion criteria**: not reported.

Howell 1983 *(Continued)*

Interventions	**Group 1** (n = 20): subcutaneous calcium heparin antenatally throughout pregnancy (10,000 IU twice daily, started after the first routine antenatal booking) and for 6 weeks postpartum (8000 IU twice daily). **Group 2** (n = 20): calcium heparin for 6 weeks postpartum only.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; bleeding episodes (antenatal vaginal bleeding; postpartum haemorrhage); symptomatic osteopenia (reports "severe debilitating bone demineralization"); fetal loss (reports "complete abortion"). Other outcomes reported: "other fetal or neonatal losses"; threatened abortion; blood loss after birth; preterm labour; admission to special care baby unit and indications; birthweight; gestational age; placental weight.
Notes	Funding sources: not reported. Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "The allocation was randomized".
Allocation concealment (selection bias)	Unclear risk	Described as "by opening sealed envelopes".
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 participants 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 birth. 1 participant 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	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

Krauss 1994

Study characteristics

Methods	RCT
Participants	100 women were randomised.

Krauss 1994 *(Continued)*

	Setting: University Hospital, Gottinghen, Germany. Study dates: not reported. **Inclusion criteria**: women undergoing caesarean section. **Exclusion criteria**: known heparin allergy, GI ulcers, severe kidney, liver or pancreatic disease or previous cerebral haemorrhage, severe hypertension (BP > 180/120), haemorrhagic diathesis.
Interventions	**Group 1** (n = 50): LMWH (fragmin) once daily 2500 to 5000 anti-Xa units. **Group 2** (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	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports "post surgical haemorrhage"); thrombocytopenia. Other outcomes reported: coagulation parameters (including anti-Xa activity; anti-thrombin III; partial thromboplastin time; thrombin time); haematological parameters and liver enzymes.
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 (irritation at site of injection; lasting pain at site of injection; secondary bleeding at site of injection; headaches; minor dizziness) were reported for 75 women in the intervention group and 75 women in the comparison group, and thus we could not include these data. Funding sources: not reported. Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
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 dropouts or withdrawals.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

O'Riordan 2008

Study characteristics	
Methods	RCT
Participants	20 women were randomised. Setting: authors from Ireland. Dates of the study: not reported. **Inclusion criteria**: women following caesarean section. **Exclusion criteria**: none detailed.
Interventions	**Group 1:** enoxaparin 40 mg once daily subcutaneously. **Group 2:** tinzaparin 4500 units once daily subcutaneously. All women: the first dose of LMWH was administered 4 to 6 hours following the caesarean section.
Outcomes	**Review outcomes reported**: none. Other outcomes reported: venous blood samples were taken for: APTT, Factor Xa, Factor II, vWF, platelet count, volume and granularity.
Notes	Published as abstract only. Funding sources: not reported. Declarations of interest: not reported.

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	High 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	No trial protocol to confidently assess selective reporting.

O'Riordan 2008 *(Continued)*

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

Study characteristics	
Methods	RCT
Participants	107 women were randomised. Setting: 8 centres in Finland. Study dates: 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. **Exclusion criteria**: any of the following: surgical procedure within 1 week, surgical procedure in central nervous system, eye or ear within 1 month, intracerebral bleeding within 1 year, platelet count < 100 X 10E9/L twice, hypertension over 150/100 mmHg, S-creatinine over 155 µmol/L, liver disease, septic endocarditis, known hypersensitivity to heparin, known positive HIV or hepatitis B or C, unsuitable for venous sampling, antithrombin deficiency, artifical hear value, placenta praevia or ablation detected, participation in another study, weight < 45 kg before pregnancy, use of acetylsalicylic acid of any strength.
Interventions	**Group 1** (n = 51): subcutaneous LMWH dalteparin (fragmin) once daily (starting dose 5000 IU (women weighing < 85 kg) or 7500 IU (women weighing ≥ 85 kg), dose adjusted based on anti-Xa measurements). During birth, 2500 IU dalteparin was administered 18 hours after the previous dose if the woman had not yet delivered; if she delivered within 18 hours, 5000 IU was given, 24 hours after the previous injection. The daily dose postpartum was 2500 IU lower than during the third trimester; and 2 weeks after birth, if anti-Xa was < 0.20, the dose was increased by 2500 IU. **Group 2** (n = 56): subcutaneous UFH (7500 IU, adjusted according to APTT target values) twice daily. At the time of birth, and on the first day postpartum 7500 IU UFH was given at 12 hour intervals, and then according to APTT target values. All women: treatment started before week 20 of gestation and continued for 6 weeks after birth.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion; bleeding episodes (reports injection-site haemato mas, bleeding during birth, other bleeding); adverse events sufficient to stop treatment; symptomatic osteoporosis; fetal loss (reports spontaneous abortion); thrombocytopenia. Other outcomes reported: lumbosacral compression fractures, fetal outcomes, laboratory values (Hb, platelet count, serum creatinine, serum alanine aminotransferase); birth bleeding (mL); caesarean section; birthweight; Apgar score.
Notes	Funding sources: supported by research funds from Helsinki University Central Hospital and a grant from Pharmacia and Upjohn. Declarations of interest: not reported.
Risk of bias	

Pettila 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation quote: "by means of a computer generated procedure".
Allocation concealment (selection bias)	Low risk	Quote: "Immediately after the inclusion and exclusion criteria were met and informed consent was obtained, a closed envelope was opened"; 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	Low risk	2 randomised participants (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 participants (50 from the dalteparin and 55 from the heparin group) were included in the intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Reddick 2014

Study characteristics	
Methods	RCT
Participants	50 women were randomised. Setting: Duke Obstetrics outpatient clinics or the Duke University Hospital Birthing Center, USA. Study dates: April 2009 to March 2010. **Inclusion criteria**: scheduled (non-labour) caesarean at term (≥ 37 weeks' gestation); no history of thrombophilia; no history of or current venous or arterial thrombosis; aged ≥ 18 years; BMI 18.5 to 35; English literate. **Exclusion criteria**: hypertension (chronic and pregnancy related); diabetes (insulin-dependent, type II and gestational); maternal cardiac disease (valvular heart disease, congenital heart disease, cardiomyopathy); substance use (including tobacco, alcohol, and illicit substances); family history of thrombophilia; multiple gestation; sickle cell disease; and lupus/connective tissue disorder.
Interventions	**Group 1** (n = 25): intermittent pneumatic compression during caesarean birth. Women had compression devices (Aircast Venaflow Calf Cuff—DJO, LLC, Vista, CA) placed on their lower extremities.The intervention started 1 hour before the start of surgery and continued or ≥ 30 minutes following completion of the procedure. **Group 2** (n = 25): women received no compression treatment during the surgery and were placed on bed rest beginning 1 hour before the start of surgery.

Reddick 2014 *(Continued)*

Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion; bleeding: estimated blood loss at birth (mL). Other outcomes reported: gestational age; birthweight; 5-minute Apgar score; operative time; estimated blood loss; use of regional anaesthesia; serum markers of fibrinolysis (tPA, uPA, TAT complex, PAI-1, PAI-2).
Notes	Funding sources: Quote: "This study was funded by Charles B. Hammond Research Fund, Duke University School of Medicine, Durham, NC, and DJO, LLC, Vista, CA." "The authors thank DJO, LLC (Vista, CA) for providing equipment to complete the study." Declarations of interest: "None of the authors reports conflict."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization sequence."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 women randomised, 25 to each group; 1 woman randomised to intervention group withdrew, and thus 24 and 25 women analysed in intervention and control groups, respectively.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Rodger 2014

Study characteristics

Methods	RCT (NCT00967382, ISRCTN87441504)
Participants	292 women were randomised. Setting: initiated in 36 tertiary care centres in Canada, Australia, USA, UK and France; however conducted in 26 of these centres as 10 centres were unable to implement the trial protocol or get referrals to screen potentially eligible participants. Study dates: 28 February 2000 to 14 September 2012. **Inclusion criteria**: pregnant, confirmed thrombophilia (fact V Leiden; prothrombin gene mutation, or 2 abnormal tests and no normal tests for protein C deficiency, protein S deficiency, or antithrombin de-

Rodger 2014 *(Continued)*

	ficiency; or anti-phospholipid antibody confirmed by 2 positive tests) and with raised risk of placenta-mediated pregnancy complications or VTE (previous pre-eclampsia, previous unexplained SGA infant, previous major placental abruption, previous pregnancy loss, 1 or more of: previous provoked proximal VTE, previous calf vein thrombosis, previous superficial phlebitis, 1st degree relative with history of PE or DVT treatment with anticoagulants). **Exclusion criteria**: ≥ 21 weeks or more gestational age at the time of randomisation, contraindication to heparin treatment (history of heparin-induced thrombocytopenia; placental count < 100,000 x 10^6/L; history of osteoporosis or steroid use; actively bleeding; documented peptic ulcer within 6 weeks; heparin, bisulphite or fish allergy; severe hypertension; severe hepatic failure; serum creatinine > 80 umol/L and 24-hour clearance < 30 mL/minute), geographically inaccessible, needed anticoagulant therapy as judged by the local investigator (women with recurrent pregnancy loss and antiphospholipid antibody syndrome; women with unprovoked proximal VTE whose PE or DVT was treated with anticoagulants (> 1 month heparin or warfarin), or IVC interruption; women with mechanical heart valves, women on long-term anticoagulants before pregnancy), had already previously participated in the study, or were younger than the legal lower age limit to provide consent according to country-specific regulations.
Interventions	**Group 1** (n = 148): LMWH: dalteparin 5000 IU once daily by subcutaneous self-injection from the day of randomisation until 20 weeks of gestation, followed by 5000 IU twice daily from 20 weeks until at least 37 weeks gestational age. **Group 2** (n = 144): placebo: during the initial 26 months of the study, the control group received matching, identically supplied and formulated placebo in prefilled syringes. Owing to poor recruitment (only 19 in 26 months), on June 25, 2002, the trial steering committee changed the study design to an open-label trial comparing antepartum open-label dalteparin with no antepartum dalteparin control. **All participants**: postpartum dalteparin (5000 IU once daily, by subcutaneous self-injection); day 1 (started 6–28 hours after birth), to 42.
Outcomes	**Review outcomes reported**: symptomatic VTE; bleeding episodes (minor peripartum haemorrhage, major peripartum haemorrhage, major bleeding, minor bleeding, estimated blood loss at birth, placental abruption); symptomatic osteoporosis (including osteoporotic fracture, and bone mineral density measured at 6 weeks postpartum); adverse events not sufficient to stop treatment (including left parieto-occipital transient Ischaemic attack at 27 weeks with non thrombocytopenia, severe allergic reaction defined as lip/tongue swelling after first dose of postpartum dalteparin, allergic type skin reaction noted antepartum, allergic type skin reaction noted postpartum, raised levels of liver enzymes defined as 2 times normal values of aspartate aminotransferase or alanine transaminase); neonatal death (in infant born prematurely); thrombocytopenia; fetal loss < 20 weeks (pregnancy loss any); fetal anomalies. Other outcomes reported: composite outcome that included any of the following events: objectively documented symptomatic major VTE (DVT proximal to the calf trifurcation, PE, or sudden maternal death); severe early onset (< 32 weeks) pre-eclampsia; birth of SGA infant; preterm birth; and symptomatic fracture.
Notes	Funding sources: Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada. Drugs supplied by Pharmacia and Upjohn. Declarations of interest: 1 author (Clement, AM) reported receiving honoraria for educational activities from Leo Pharma, Sanofi, and Bayer. The other authors declared no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computer-generated randomisation schedule was stratified by country and gestational age at randomization day (<8 weeks, 8-12 weeks, and 12-20 weeks) and had a permuted block design (block sizes 4 and 8)".

Rodger 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Web-based randomisation system used to conceal allocation. At the time of the assignment, site pharmacists or other delegates received a randomisation number and treatment allocation from the central web randomisation system (by fax and/or email). The site pharmacist or delegate then dispenses the study drug to the local coordinator who taught the study participant how to administer the assigned treatment and explained the trial procedures to be followed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and study personnel were not masked but outcome adjudicators were masked to treatment assignment".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected primary and secondary outcome events were adjudicated independently and blindly by at least two physicians in a panel that included experts in obstetrics and thrombosis".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/148 and 1/144 women assigned to the intervention and control groups respectively were excluded from analyses due to ineligibility. Therefore 146 women in the intervention group, and 143 women in the control group were included in 'on treatment' analysis, which was reported for the safety outcomes. 26 women crossed over within 10 days of randomisation: 12 from dalteparin to no dalteparin, and 14 from no dalteparin to dalteparin.
Selective reporting (reporting bias)	Unclear risk	Multiple trial registrations, including study web site.
Other bias	Low risk	Aspirin was used slightly more by women in the control group than women in the intervention group, and analgesic was used slightly more frequently by women in the intervention group than in the control group during the study. However, data presented show that neither of these differences were statistically significant.

Rodger 2015

Study characteristics	
Methods	RCT: NCT01274637
Participants	25 women were randomised. Setting: 6 centres in Canada and the USA. Study dates: May 2011 to March 2012. **Inclusion criteria**: women at higher VTE risk due to known low risk thrombophilia (heterozygous factor V Leiden or prothrombin gene variant or protein C deficiency or protein S deficiency) or immobilisation (90% of waking hours in bed, of a week or more at any point in the antepartum period); or with any 2 of the following: postpartum infection; postpartum haemorrhage (> 1000 mL); pre-pregnancy BMI > 25 kg/m^2, emergency caesarean birth; smoking > 5 cigarettes per day prior to pregnancy; pre-eclampsia; IUGR. **Exclusion criteria**: < 6 hours or > 36 hours since birth; need for anticoagulation; LMWH started antenatally, contraindication to heparin, received a dose of heparin or LMWH since birth; below the age of legal majority; prior trial participation; no informed consent.

Rodger 2015 *(Continued)*

Interventions	**Group 1** (n = 14): LMWH. Women received daily prophylactic dalteparin (5000 IU), by subcutaneous injection for 3 weeks following birth, starting approximately 36 hours after delivery of the placenta. **Group 2** (n = 11): placebo. Women received daily placebo, by subcutaneous injections, for 3 weeks following birth, starting approximately 36 hours after delivery of the placenta.
Outcomes	**Review outcomes reported**: maternal death; symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; asymptomatic thromboembolic events (detected by screening); bleeding episodes (reports major bleeding events); adverse effects not sufficient to stop treatment (reports unexpected serious adverse events related to the interventions); thrombocytopenia.
Notes	Funding sources: Quote: "National Institutes of Health Research grant # NIH 1R34HL107725–01 and Canadian Institutes of Health Research grant #MOP 106641. Dr. Rodger is supported by a Heart and Stroke Foundation Career Investigator Award and a University of Ottawa, Faculty of Medicine Chair in Venous Thrombosis and Thrombophilia. Dr. Kahn is supported by a National Research Scholar award from the Fonds de recherche santé Québec. The funders played no role in the design, conduct, analysis or interpretation for the pilot trial." Declarations of interest: "None declared." Pilot trial to determine feasibility.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was in permuted blocks of eight, prepared by the trial statistician using random number tables and stratified by centre."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible consenting women were randomised via central web randomisation by a study coordinator within 36 h after delivery of the placenta."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "They were equally and blindly allocated to the treatment group (prophylactic-dose dalteparin 5,000 IU) or matching placebo saline, administered subcutaneously once daily for 21 days;" and see quote below.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome adjudicators were blinded to the treatment allocation, as were the participants, care providers and all trial personnel."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/14 woman in intervention group excluded from analyses; all 11 women in placebo group included in analyses.
Selective reporting (reporting bias)	Unclear risk	While trial registration available, limited detail, and no full protocol available. Results for clinical outcomes reported incompletely in text.
Other bias	Unclear risk	No data provided on key characteristics of the 2 groups of women compared, and therefore it is not possible to confidently assess other bias.

Rodger 2016

Study characteristics

Methods	RCT: NCT01274637

Rodger 2016 *(Continued)*

Participants	37 women were randomised. Setting: 6 Canadian teaching hospitals and 2 teaching hospitals in the USA. Study dates: November 2012 to November 2013 (follow-up to February 2014). **Inclusion criteria**: women at higher VTE risk due to known low-risk thrombophilia or immobilisation; or with any 2 of the following: 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 < 3rd percentile. **Exclusion criteria**: women < 6 hours or > 36 hours since birth; need for anticoagulation; contraindication to heparin; received > 1 dose of heparin or LMWH since birth; below the age of legal majority; prior trial participation; no informed consent.
Interventions	**Group 1** (n = 16):LMWH. Women received daily prophylactic dalteparin 5000 IU subcutaneous injections for 10 days following birth, starting 36 hours after delivery of the placenta. **Group 2** (n = 21): no treatment. Women received no treatment for 10 days following birth, starting 36 hours after delivery of the placenta.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; asymptomatic thromboembolic events; bleeding episodes (reports: major bleeding event (> 4 g/dL drop in Hb with excessive vaginal blood loss in early postpartum period); reports 'clinically relevant bleeding events'; reports 'minor bleeding events'); serious wound complications (serious adverse event - wound dehiscence with wound haematoma). Other outcomes reported: number of participants randomised per centre per month; other indicators of feasibility (proportion of referred participants who meet eligibility criteria (> 20%); proportion of eligible participants who provide consent (> 30%); withdrawals/losses to follow-up (< 10%); and level of compliance with study drug (> 60%).
Notes	Funding sources: Quote: "National Institutes of Health research grant # NIH 1R34HL107725-01 and Canadian Institutes of Health Research grant # MOP 106641. Dr. Rodger is supported by a Heart and Stroke Foundation Career Investigator Award and a University of Ottawa, Faculty of Medicine Chair in Venous Thrombosis and Thrombophilia. Dr. Kahn is supported by a National Research Scholar award from the Fonds de recherche santé Québec. The funders played no role in the design, conduct, analysis or interpretation for the pilot trial." Declarations of interest: not reported. Pilot trial to determine feasibility.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was in permuted blocks of eight, prepared by the trial statistician using random number tables and stratified by centre."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible consenting women were randomized via central web randomization by a study coordinator within 36 h after delivery of the placenta."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial with a no treatment arm.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Outcome adjudicators were blinded to the treatment allocation."

Rodger 2016 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 16 women in intervention group, all analysed; of 21 women in intervention group, 19 analysed (1 withdrew and 1 lost to follow-up).
Selective reporting (reporting bias)	Unclear risk	While trial registration available, limited detail, and no full protocol available.
Other bias	Low risk	No other obvious risk of bias identified.

Salim 2016

Study characteristics	
Methods	RCT: NCT01068795
Participants	144 women were randomised. Setting: 1 university teaching hospital and 3 specialised community clinics in Israel. Study dates: October 2009 to January 2015. **Inclusion criteria**: singleton pregnancies at ≤ 14 weeks' gestation, prior placenta-mediated pregnancy complications or a lower leg thrombotic event (documental calf vein thrombosis), and testing positive for any thrombophilia (homozygous or heterozygous for prothrombin-20210A or factor V Leiden mutations; homozygous for the mutation of cytosine to thymine at nucleotide 677 in the gene encoding methylenetetrahydrofolate reductase accompanied with homocysteine elevated serum levels; and tested positive for anti-thrombin III, protein C and S deficiencies, lupus anticoagulant, anti-cardiolipin IgG and/or IgM and anti-β2 glycoprotein IgG and/or IgM) (prior placenta-mediated pregnancy complications included: prior severe pre-eclampsia; prior birth of SGA infant; with placenta related antepartum signs; prior placental abruption; or prior unexplained pregnancy loss (3 losses < 13 weeks, 2 losses 14-22 weeks, any loss > 23 weeks)). Women were categorised as having low-risk thrombophilia (factor V Leiden heterozygous; prothrombin gene mutation heterozygous; protein C deficiency; protein S deficiency; anti-phospholipid antibody) or high-risk thrombophilia (antithrombin III deficiency; homozygous for factor V Leiden; homozygous for prothrombin mutation; combined thrombophilias). **Exclusion criteria**: women who had previous pregnancy complications that could be attributed to multiple gestations; having fetuses with major congenital anomalies or chromosomal abnormalities, fetal infection, or hydrops fetalis; women with pre-gestational diabetes; or women who required therapeutic dosage of LMWH or had a contraindication to LMWH therapy.
Interventions	**Group 1** (n = 74): LMWH adjusted dose: starting around 14 weeks GA, adjusted dose of antepartum enoxaparin according to the results of anti-FXa levels until birth. The initial dose was 40 mg and increased by fractions of 20 mg, according to anti-FXa level. The targeted prophylactic level was 0.2 IU/mL or more 3.5 to 4 hours post-injection. Quote: "All women had levels of anti-FXa examined approximately every 8–10 weeks… A blood sample was taken from all women 3.5-4 h after the injection of enoxaparin at the central laboratory. Subsequently, the results were computerised and enoxaparin dose was then adjusted in the next visit among women in the adjusted-dose group. Women attended follow-up visits every 3–4 weeks." **Group 2** (n = 70): LMWH fixed dose. starting around 14 weeks GA, maintained fixed dose of 40 mg enoxaparin, once daily by subcutaneous self-injection, until birth regardless of the results of anti-factor Xa.

Salim 2016 *(Continued)*

	Women in both groups with antiphospholipid antibodies were given low dose aspirin in addition to enoxaparin. Postpartum, all women were prescribed enoxaparin 40 mg once daily by subcutaneous injection from day 1 until day 42.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports placental abruption; postpartum haemorrhage; and side effects - bleeding); adverse effects sufficient to stop treatment; adverse effects not sufficient to stop treatment (reports skin allergy); fetal loss (reports spontaneous abortion, assumed to be < 23 weeks; and reports intrauterine fetal death > 23 weeks); thrombocytopenia. Other outcomes reported: composite outcome (1 or more of the following events: any pregnancy loss, pre-eclampsia, SGA, placental abruption, and VTE); components of the composite outcome; gestational age at birth; preterm birth; mode of birth; birthweight; Apgar score < 7 at 5 minutes; cord pH < 7,1; and anti-FXa levels (and < 0.2 IU/mL); maternal placental vascular lesions; fetal placental vascular lesions.
Notes	Funding sources: not reported. Declarations of interest: "None declared."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using a computer randomisation sequence generation program."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation sequence results were kept in the delivery ward in a closed study box. The site investigator enrolled participants after confirming eligibility. The sequence was concealed until intervention was assigned (and after obtaining a signed informed consent)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Women and providers were not masked to the treatment arm."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	For secondary analyses: "Placentas were examined by the same pathologist who was blinded to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 74 women in intervention group, all included in intention to treat analyses; of 70 women in control group 4 excluded from intention to treat analyses (2 lost to follow-up, and 2 discontinued intervention – 1 due to side effects, and 1 due to ineligibility).
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Segal 1975

Study characteristics

Methods	RCT

Segal 1975 *(Continued)*

Participants	210 women were randomised. Setting: Jerusalem, Israel. Study dates: 1973. **Inclusion criteria**: women identified with varicose veins before birth. **Exclusion criteria**: a history of thrombosis, and thus treatment with heparin.
Interventions	**Group 1** (n = 116): UFH 50 mg (5000 IU) subcutaneous UFH every 12 hours for 4 to 5 days after birth (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 giving birth; for women having a caesarean section UFH was given 2 hours before the caesarean, at the end of the caesarean, and at 12-hour intervals; for women having an emergency caesarean, the initial dose was immediately following the decision). **Group 2** (n = 94): care in the comparison group was not described, there did not seem to be a placebo (routine care/no heparin).
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT. Other outcomes reported: superficial venous thrombosis.
Notes	Very little information on methods was provided. There appeared to be a baseline imbalance between groups with 16/94 in the control group having a caesarean section versus 6/116 in the intervention group. Funding sources: not reported. Declarations of interest: not reported.

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	High risk	Not stated. No placebo use reported.
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".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women followed up.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.

Segal 1975 *(Continued)*

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.

Stephenson 2016

Study characteristics

Methods	RCT: NCT02070237
Participants	90 women were randomised. Setting: Memorial Care Center for Women at Miller Children's Hospital, Long Beach Memorial Medical Center, Long Beach, California, USA. Study dates: August 2013 to February 2014. **Inclusion criteria**: BMI ≥ 35 at admission for birth, undergone a caesarean section (elective or performed during labour) within the previous 12 hours, and scheduled to receive enoxaparin thromboprophylaxis. **Exclusion criteria**: previous VTE, already receiving anticoagulation of any type (including LMWH or UFH), allergy to enoxaparin, renal impairment (creatinine > 1.2), or contraindications to treatment with enoxaparin, such as active bleeding or thrombocytopenia (platelets < 150).
Interventions	**Group 1** (n = 45): weight-based LMWH: twice daily dose of 0.5 mg/kg enoxaparin every 12 hours (dose not capped and rounded to the nearest 5 mg unit), by subcutaneous injection (in abdomen). **Group 2** (n = 45): fixed-dose LMWH: once daily dose of 40 mg, by subcutaneous injection (in abdomen). **All women**: enoxaparin was started between 8 and 12 hours after the caesarean, and continued until hospital discharge at which time it was discontinued. A peak anti-Xa activity level was drawn 3.5 to 4 hours after the third dose of each regimen.The result was not available to the care team.
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; blood transfusion (reports bleeding events requiring transfusion); bleeding episodes (reports bleeding events requiring reoperation); serious wound complications (reports caesarean wound dehiscence or reoperation; caesarean wound infection; caesarean wound haematoma); adverse events not sufficient to stop treatment (reports heparin-induced skin necrosis). Other outcomes reported: achievement of the desired prophylactic anti-Xa level of 0.2 to 0.6 IU/,L; mean anti-Xa levels; highest peak anti-Xa levels; anti-Xa levels reaching therapeutic or supra prophylactic levels of 0.6 to 1.0 IU/mL;
Notes	Funding sources: "funded by a grant from the Long Beach Memorial Medical Center Foundation." Declarations of interest: "The authors declare no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were randomized… using computer-generated block sizes of 20."
Allocation concealment (selection bias)	Unclear risk	Not reported.

Stephenson 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Assumed that blinding not possible due to nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 women randomised, 45 to each group. 3 women withdrew from each group, thus 42 were analysed in each group.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	No other obvious risk of bias identified.

van Hoorn 2016

Study characteristics	
Methods	RCT: ISRCTN87325378
Participants	32 women were randomised. Setting: 13 hospital centres in (5 university and 6 non-university/teaching hospitals in the Netherlands, 2 hospitals in Australia, and 1 hospital in Sweden. Study dates: December 2000 to December 2009. **Inclusion criteria**: < 12 weeks' gestation, aged ≥ 18 years, history of uteroplacental insufficiency and birth < 34 weeks' gestation (hypertensive disorders of pregnancy (including pre-eclampsia, HELLP syndrome, eclampsia) and/or SGA infant), and antiphospholipid antibodies (anticardiolipin antibodies present and/or lupus anticoagulant present) [women without antiphospholipid antibodies were included in de Vries 2012) **Exclusion criteria**: women with 1 or more antithrombin deficiency, homozygosity for factor V Leiden and prothrombin G20210A mutations, diabetes mellitus, known malignancy, known peptic ulceration, severe renal or hepatic insufficiency, history of VTE, haemorrhagic diathesis, idiopathic thrombocytopenia, earlier participation in the FRUIT trial, or LMWH use in earlier pregnancy.
Interventions	**Group 1** (n = 16): LMWH and aspirin: once-daily dalteparin (5000 IU, by subcutaneous self-administration), starting at 6-12 weeks' gestation until the onset of labour or prior to the caesarean section, plus once-daily aspirin (80 mg, oral), stating at < 12 weeks and continued to 36 weeks' gestation. The daily dose of dalteparin was adjusted for body weight: women < 50 kg received dalteparin 2500 IU, those > 80 kg 7500 IU. Dalteparin injections started at 6 to 12 weeks' gestation, and stopped at the onset of labour or prior to caesarean section. Aspirin was commenced at < 12 weeks' gestation and stopped at 36 weeks' gestation (women in Australia were treated with aspirin 100 mg daily as the standard dose). In women who developed local skin reactions, treatment with dalteparin was altered to enoxaparin and, if the reaction was persistent, to nadroparin. **Group 2** (n = 16): aspirin alone: daily aspirin (80 mg, orally), commencing at < 12 weeks' gestation, until 36 weeks' gestation (women in Australia were treated with aspirin 100 mg daily as the standard dose). **All women**: educated on self-injection, and after birth weight-adjusted dalteparin (for 6 weeks) was prescribed.

van Hoorn 2016 *(Continued)*

Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes (reports placental abruption); adverse effects not sufficient to stop treatment (reports skin reactions, pain, itching, swelling, allergy; reports need for an alternate LMWH; reports haematoma); fetal loss (reports spontaneous miscarriage < 16 weeks; reports fetal death > 16 weeks (miscarriage excluded)); thrombocytopenia. Other outcomes reported: hypertensive disorders of pregnancy (pre-eclampsia and/or eclampsia and/or HELLP syndrome) onset before 34 weeks' gestation and irrespective of gestational age; SGA; miscarriage; preterm birth; length of maternal and neonatal admission; pre-eclampsia; eclampsia; HELLP syndrome; termination of pregnancy; gestational age at miscarriage; gestational age at birth; birthweight.
Notes	Funding sources: Quote: "The study was supported by a single 2-year investigator grant period 2000–2001 by Pfizer, formerly Pharmacia, grant number 524E-CVD-9101-0001, annual Dutch investigators meetings, a single grant to support a midwife to recruit Australian women, and support for a local meeting in Sweden in 2004. Pharmacia was not the sponsor of the study. A follow-up study of the trial received a 1-year investigator grant period in 2014 by Pfizer." Declarations of interest: Quote: "All authors have declared that they have no conflicts of interest." "After the completion of recruitment to the inheritable thrombophilia group of the trial, and given the slow inclusion rate of women with acquired thrombophilia, an interim analysis was performed after delivery of 29 women. The Data Monitoring committee advised cessation of recruitment since accrual was slow and the incidence… of early onset HD (3.4%) was far lower than expected (60%), and the decision was taken by the trial management group to halt the study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a computer to select random permuted blocks of four, with stratification for hospital and presence/absence of chronic hypertension."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was carried out by an independent centre."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither study personnel nor participants were blinded to treatment assignment, as placebo injections during pregnancy were at that time not considered to be ethically acceptable."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The adjudication of the study endpoints was not blinded, but was performed by the chief researcher (JdeV) using absolute values of blood pressure, proteinuria and appropriate laboratory tests in the adjudication, after an initial local assessment at each centre."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or exclusions.
Selective reporting (reporting bias)	Unclear risk	No trial protocol to confidently assess selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Welti 1981

Study characteristics	
Methods	RCT
Participants	580 women were randomised Setting: not clear, authors from Switzerland. Study dates: not reported. Inclusion criteria: women undergoing surgery for gynaecological indications (with 580 women undergoing caesarean section (both emergency and elective)).
Interventions	**Group 1** (n = 272): physiotherapy and twice-daily subcutaneous 5000 IU heparin (UFH). **Group 2** (n = 308): physiotherapy alone (no heparin).
Outcomes	**Review outcomes reported**: symptomatic thromboembolic events; symptomatic PE; symptomatic DVT; bleeding episodes. Other outcomes: unclear (not translated)
Notes	Data extraction from translation notes and tables in the paper (original paper in French). Limited description of interventionand other (non review) outcomes. No information on timing of the intervention. Funding sources: not reported. Declarations of interest: not reported.

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 quote: "selon le principle de la randomisation fermee".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely considering the interventions assessed.
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	No trial protocol to confidently assess selective reporting.
Other bias	Unclear risk	Insufficient information to assess other potential sources of bias.

Abbreviations: **APH**: antepartum haemorrhage; **APTT**: activated partial thromboplastin time; **BMI**: body mass index;**BP:** blood pressure; **DVT**: deep vein thrombosis; **FRUIT**: Fractionated heparin in pregnant women with a history of uteroplacental insufficiency and thrombophilia (randomised trial); **HELLP:** Hemolysis, Elevated Liver enzyme levels, and low platelet levels;**GA:** gestational age; **GI**: gastrointestinal; **Hb:** haemoglobin; **HES**: hydroxyethyl starch;**IgG:** immunoglobulin g; **IgM:** immunoglobulin M; **IU**: international units;**IUGR:** intrauterine growth retardation; **LMWH**: low molecular weight heparin; **NICU**: neonatal intensive care unit; **PAI:** plasminogen activator inhibitor; **PE**: pulmonary embolism; **RCT:** randomised controlled trial; **SGA**: small-for-gestational age; **tPA:** tissue plasminogen activator (abbreviate; **UFH**: unfractionated heparin; **VTE**: venous thromboembolism;**vWF**: von Willebrand factor

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

Study	Reason for exclusion
Aina 2006	Trial terminated (principal investigator assigned to a different hospital; difficulty recruiting participants).
Alalaf 2015	Excluded based on study design: sequential, not random, assignment.
Badawy 2008	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Blomback 1998	Excluded based on study design: not a randomised trial.
Brenner 2005	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
de Jong 2015	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Dendrinos 2007	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Farquharson 2002	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Giancotti 2012	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Gris 2010	Excluded based on types of participants: women with abruptio placentae; women at high risk of VTE (e.g. who had a previous DVT or antiphospholipid antibodies) explicitly excluded.
Gris 2011	Excluded based on types of participants: women with pre-eclampsia; women at high risk of VTE (e.g. who had a previous DVT or antiphospholipid antibodies) explicitly excluded.
Guven 2014	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Harenberg 1993	Excluded based on types of participants: healthy pregnant women; not women at high risk of VTE.
Kaandorp 2010	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Kamin 2008	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Kutteh 1996a	Excluded based on study design: not a randomised trial; the first 25 women were allocated to 1 arm, and the next 25 to other arm; and types of participants: women with recurrent miscarriage/pregnancy loss.
Kutteh 1996b	Excluded based on study design: allocation was by alternation, not by random assignment: and types of participants: women with recurrent miscarriage/pregnancy loss.
Langer 2013	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Laskin 2007	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Milic 2018	Excluded based on types of participants: women were at low risk of VTE.

Study	Reason for exclusion
Noble 2005	Excluded based on study design: not a randomised trial; and types of participants: women with recurrent miscarriage/pregnancy loss.
Pyregov 2012	Excluded based on study design: not a randomised trial; trial was quasi-randomised (allocation based on day of the week).
Rai 1997	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Ratiu 2009	Excluded based on study design; not a randomised trial; and types of participants: women with acute stage proximal DVT in pregnancy.
Rey 2009	Excluded based on types of participants: women with 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 a previous thromboembolic event) were specifically excluded.
Rodger 2017	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Samantha 2013	Excluded based on study design: not a randomised trial.
Schleussner 2015	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Stephenson 2004	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Thaler 2004	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Tulppala 1997	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.
Visser 2011	Excluded based on types of participants: women with recurrent miscarriage/pregnancy loss.

Abbreviations: **DVT**: deep venous thrombosis; **VTE**: venous thromboembolism.

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

Abdolvand 2019

Methods	Randomised controlled trial.
Participants	220 patients older than 18 years undergoing major obstetric-gynecological surgeries (e.g. total abdominal hysterectomy, total vaginal hysterectomy, cesarean section, cesarean hysterectomy with or without colporrhaphy) with risk factors for VTE (prolonged immobility, obesity or previous history of VTE).
Interventions	LHMW types: PDxane versus Clexane.
Outcomes	DVT, PE, bleeding, adverse effects (including injection site reactions, confusion, and hematuria).
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

Dittmer 1991

Methods	Randomised controlled trial.

Dittmer 1991 *(Continued)*

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

Ganer 2020

Methods	Randomised controlled trial.
Participants	256 women aged 18–54 years, who underwent cesarean delivery during the study period, with one or more risk factors for thromboembolism.
Interventions	Pedometer around the wrist starting 24 hours after delivery, for 48 hours and personalised feedback versus pedometer around the wrist starting 24 hours after delivery and standard care.
Outcomes	Serious wound complications.
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

Movahedi 2020

Methods	Randomised controlled trial.
Participants	31 pregnant women with mechanical heart valves at their first trimester (0-14 weeks) of pregnancy.
Interventions	LMWH versus UFH.
Outcomes	Fetal loss.
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

Nagornaya 2012

Methods	Unclear. The abstract states in the methods that the "study was prospective and randomized" but this design was not clear.
Participants	Quote: "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 dependent on the woman's weight and risk).
Outcomes	Risk factors for VTE; quote: "thrombohaemorrhagic complications during 6 months of follow-up".

Nagornaya 2012 *(Continued)*

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.

NCT02856295

Methods	Randomised controlled trial.
Participants	116 postpartum women (estimated to be enrolled, not yet recruiting)
Interventions	Weight-based versus fixed-dose LMWH.
Outcomes	Symptomatic thromboembolic events, bleeding.
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

NCT04305756

Methods	Randomised controlled trial.
Participants	Post-caesarian delivery women.
Interventions	Weight-based versus fixed-dose LMWH.
Outcomes	Symptomatic thromboembolic events, wound complications.
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

NCT04635839

Methods	Randomised controlled trial.
Participants	46 hospitalised antepartum women (estimated enrolment, still recruiting).
Interventions	Gestational age-based versus standard dose UFH.
Outcomes	Symptomatic thromboembolic events, blood transfusion, bleeding.
Notes	This study was identified in the updated search (18 Feb 2021) and will be incorporated into this review at the next update.

Abbreviations: **DVT**: deep vein thrombosis;**LMWH**: low molecular weight heparin; **UFH**: unfractionated heparin; **VTE**: venous thromboembolism.

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

Dargaud 2018

Study name	NCT03659708: Pregnancy and Risk of Venous Thromboembolism (PRESCOT)
Methods	Randomised controlled trial (4 arms)
Participants	Pregnant women 18 to 50 years at high risk of VTE (personal history of VTE and/or known thrombophilia).
Interventions	Intervention (n = 300), 3 groups informed by Lyon-VTE score management. The Lyon score classifies patients into 3 risk categories that directs the preventive LMWH prescription. Group 1: women with a score strictly less than 3 (moderate thrombotic risk) will receive no LMWH in ante-partum; Group 2: women with a score between 3 and 5 (high thrombotic risk) will receive a preventive dose of LMWH, introduced in the third trimester (from the beginning of the 7th month); Group 3: women with a score greater than or equal to 6 (very high thrombotic risk) will receive LMWH at a preventive dose throughout the antepartum. Women in all the 3 intervention groups will also receive: an elasto-compression prescription, and exercise advice (daily physical activity recommended throughout pregnancy (except obstetric contraindication); and systematic preventive LMWH treatment postpartum for 6 weeks (not further specified in trial protocol). Control (n = 300): management according to relevant study centre guidelines (e.g. ACCP)
Outcomes	Primary: cost-utility ratio Secondary: venous thromboembolism; bleeding complications; quality of life of women (EQ-5D-3L), all collected until 12 months after birth
Starting date	November 2018
Contact information	Yesim Dargaud (Principal Investigator), Hôpital Cardiologique L. Pradel Bron, France, 69677 email: ydargaud@univ-lyon1.fr
Notes	Last updated posted: September 2018

Heller 2016b

Study name	Compression stocking use in multiparous women during pregnancy & its effects on chronic venous insufficiency
Methods	Randomised controlled trial
Participants	Unclear other than: aged 18-45 years and between 8 to 20 weeks' gestation (although the title of the included abstract reporting this protocol suggests multiparous women).
Interventions	Intervention group: compression stockings (20–30 mmg Hg maternity pantyhose); women were "requested to use the knee high stockings until they reach the second trimester and then switch to the pantyhose for the remainder of the pregnancy". Control group: no compression stockings
Outcomes	Loosely defined in the objective statement: Objective "Primary 1) To quantify and compare the incidence of symptoms of venous insufficiency in pregnant women between the treatment and control groups. 2) To quantify and compare the incidence of varicose veins between participants ran-

Heller 2016b *(Continued)*

	domized to the compression stocking use group and those randomized to the no compression stocking use group. Secondary: 1) To quantify and compare the incidence of superficial thrombophlebitis and DVT".
Starting date	
Contact information	Unclear. No information provided other than "J Heller Institution JHVC, Baltimore, MD"
Notes	

NCT00225108

Study name	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, Ontario, Canada.
Notes	

NCT00878826

Study name	NCT00878826: Prophylactic enoxaparin dosing forpPrevention of venous thromboembolism in pregnancy.
Methods	Randomised controlled trial (open-label). Estimated enrolment: 64 women.
Participants	Women > 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.
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.

NCT00878826 *(Continued)*

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	

NCT01019655

Study name	NCT01019655: Heparin for pregnant women with thrombophilia.
Methods	Randomised controlled trial (open-label).
Participants	Pregnant women with thrombophilia. Estimated enrolment: 300 women.
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 restriction.
Starting date	January 2010.
Contact information	Dr Clemens B Tempfer, University of Vienna, Austria.
Notes	

NCT01828697

Study name	NCT01828697: Comparison of low and intermediate dose low-molecular-weight heparin to prevent recurrent venous thromboembolisms in pregnancy.
Methods	Randomised controlled trial (open-label).
Participants	Women 18 years or older; < 14 weeks' gestational age; previously objectively 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.

NCT01828697 *(Continued)*

Starting date	April 2013.
Contact information	Dr S Middeldorp, Acadmic Medical Centre, Amsterdam.
Notes	Estimated study completion date: December 2020

NCT04153760

Study name	NCT04153760: Pilot PARTUM Trial: Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity (PARTUM)
Methods	Randomised controlled trial (multicentre, placebo-controlled, trial to determine feasibility)
Participants	Women with 1 (or more) specified first order criterion or 2 (or more) specified second order criteria. First order criteria: known inherited thrombophilia diagnosed prior to enrolment; and immobilisation (90% of waking hours spent in bed) for ≥ 7 days anytime during the antepartum period. Second order criteria; postpartum infection; postpartum haemorrhage (> 1000 mL of blood loss, regardless of delivery mode); pre-pregnancy BMI ≥30kg/$m^{2;}$ emergency or unplanned caesarean; smoking ≥ 5 cigarettes/day before pregnancy; pre-eclampsia; current pregnancy ending in stillbirth (pregnancy loss > 20 weeks' gestation; SGA infant; and previous history of superficial vein thrombosis. A woman is eligible if they have multiple criteria met, at the discretion of the local investigator. Exclusions: > 48 hours since delivery; received more than 2 doses of LMWH since birth; need for postpartum LMWH prophylaxis or systemic anticoagulation as judged by local investigator; need for postpartum aspirin as judged by the local investigator; contraindication to aspirin; < 18 years of age; unable or refused consent. Estimated enrolment: 336 women
Interventions	Intervention: aspirin 81 mg daily for 6 weeks post-randomisation (postpartum) Comparator: placebo daily for 6 weeks post-randomisation (postpartum)
Outcomes	Primary outcome: recruitment rate (at 6 months). Secondary outcomes: consent rate (at 6 months); withdrawals/loss to follow-up (at 6 months); level of compliance with study drug (at 6 months); time required to obtain site institutional approvals (timeframe 24 months); VTE events (up to 6 months postpartum); bleeding events(up to 6 months postpartum)
Starting date	January 2020 (planned, not yet recruiting)
Contact information	Dr L Skeith, University of Calgary, Canada. email: laskeith@ucalgary.ca
Notes	First posted: November 6, 2019. Estimated completion date: December 2021

Abbreviations: **AT-II**: antithrombin II; **BMI**: body mass index;**DVT**: deep vein thrombosis; **IU**: international units; **LMWH**: low molecular weight heparin; **PE**: pulmonary embolism; **SGA**: small for gestational age; **VTE**: venus thromboembolism.

DATA AND ANALYSES

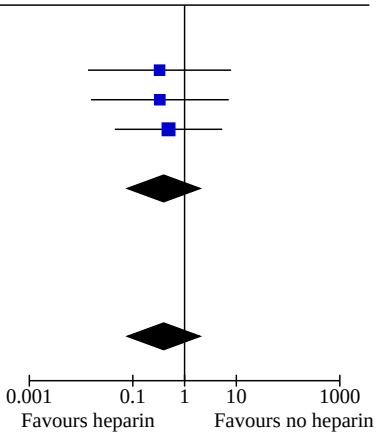
Comparison 1. Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Symptomatic thromboembolic events	4	476	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.98]
1.1.1 LMWH	4	476	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.98]
1.2 Symptomatic pulmonary embolism	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
1.2.1 LMWH	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
1.3 Symptomatic deep vein thrombosis	4	227	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.10]
1.3.1 LMWH	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.93]
1.3.2 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.72]
1.4 Blood transfusion	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5 Bleeding episodes	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 LMWH: placental abruption	3	463	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.31, 3.20]
1.5.2 LMWH: peripartum haemorrhage	1	289	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.79]
1.5.3 LMWH non-major/minor bleeding	1	284	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.15, 3.93]
1.5.4 LMWH: major bleeding	1	284	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.25, 8.72]
1.5.5 UFH: antenatal vaginal bleeding	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.16, 6.42]
1.5.6 UFH: postpartum haemorrhage	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 69.52]
1.6 Serious wound complications	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.6.1 LMWH	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.7 Adverse effects sufficient to stop treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 LMWH	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Adverse effects not sufficient to stop treatment	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 LMWH: skin/allergic reactions	4	476	Risk Ratio (M-H, Fixed, 95% CI)	5.11 [2.00, 13.08]
1.8.2 LMWH: raised liver enzymes	1	289	Risk Ratio (M-H, Fixed, 95% CI)	22.53 [1.34, 378.78]
1.8.3 LMWH: haematoma	2	171	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [0.46, 34.23]
1.8.4 Superficial thrombophlebitis	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.93]
1.8.5 LMWH: other	1	289	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.51]
1.9 Symptomatic osteoporosis	4	479	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 69.52]
1.9.1 LMWH	3	439	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.9.2 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 69.52]
1.10 Fetal loss	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 LMWH or UFH: gestation unclear	2	329	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.54, 2.51]
1.10.2 LMWH: < 20 weeks	2	171	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.50, 9.41]
1.10.3 LMWH: ≥ 20 weeks	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.12]
1.11 Thrombocytopenia	5	511	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 64.26]
1.11.1 LMWH	4	471	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 64.26]
1.11.2 UFH	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.12 Fetal anomalies	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 LMWH	1	289	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.60, 14.32]

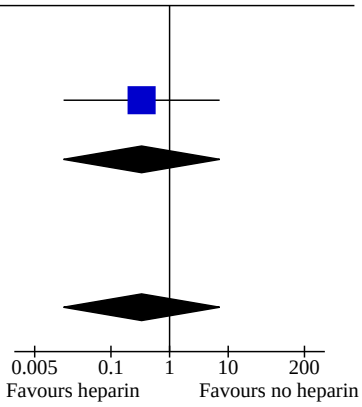
Analysis 1.1. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 LMWH						
de Vries 2012	0	70	1	69	30.0%	0.33 [0.01 , 7.93]
Gates 2004a	0	8	1	8	29.8%	0.33 [0.02 , 7.14]
Rodger 2014	1	146	2	143	40.2%	0.49 [0.04 , 5.34]
van Hoorn 2016	0	16	0	16		Not estimable
Subtotal (95% CI)		**240**		**236**	**100.0%**	**0.39 [0.08 , 1.98]**
Total events:	1		4			
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**240**		**236**	**100.0%**	**0.39 [0.08 , 1.98]**
Total events:	1		4			
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Not applicable						



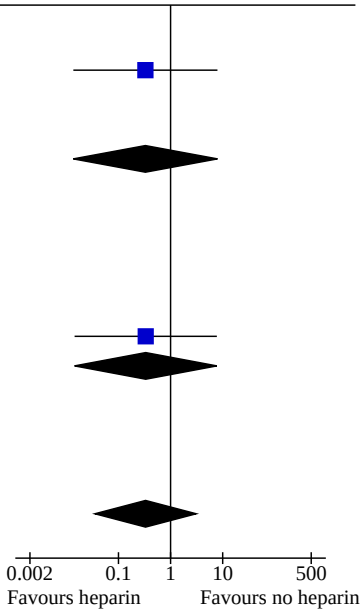
Analysis 1.2. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 LMWH						
de Vries 2012	0	70	0	69		Not estimable
Gates 2004a	0	8	1	8	100.0%	0.33 [0.02 , 7.14]
van Hoorn 2016	0	16	0	16		Not estimable
Subtotal (95% CI)		**94**		**93**	**100.0%**	**0.33 [0.02 , 7.14]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**94**		**93**	**100.0%**	**0.33 [0.02 , 7.14]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						



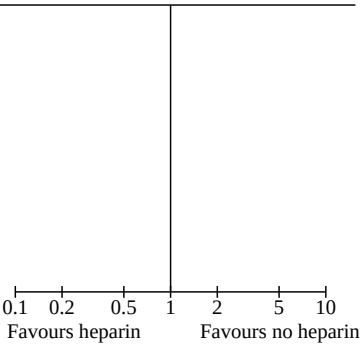
Analysis 1.3. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 LMWH						
de Vries 2012	0	70	1	69	50.2%	0.33 [0.01 , 7.93]
Gates 2004a	0	8	0	8		Not estimable
van Hoorn 2016	0	16	0	16		Not estimable
Subtotal (95% CI)		**94**		**93**	**50.2%**	**0.33 [0.01 , 7.93]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.3.2 UFH						
Howell 1983	0	20	1	20	49.8%	0.33 [0.01 , 7.72]
Subtotal (95% CI)		**20**		**20**	**49.8%**	**0.33 [0.01 , 7.72]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**114**		**113**	**100.0%**	**0.33 [0.04 , 3.10]**
Total events:	0		2			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



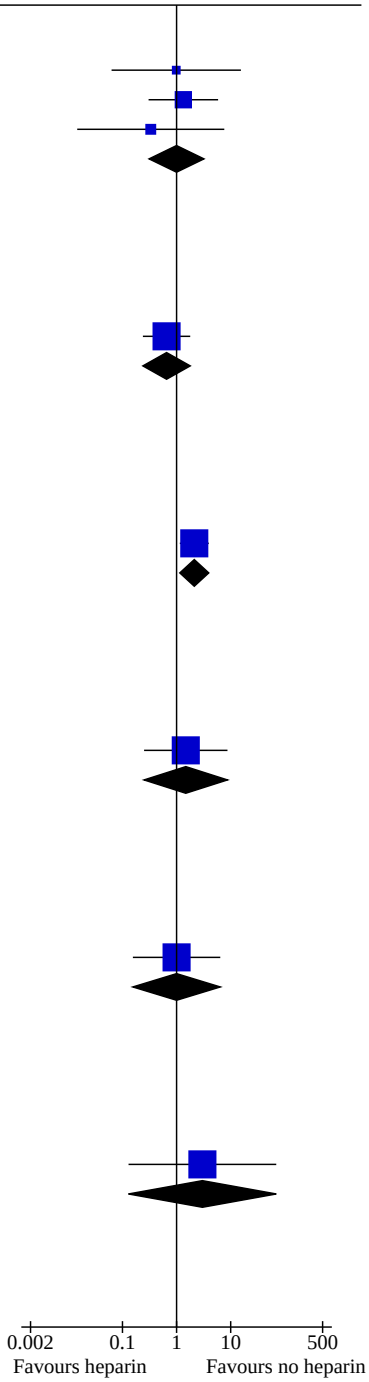
Analysis 1.4. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 4: Blood transfusion

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 LMWH						
Gates 2004a	0	8	0	8		Not estimable
Subtotal (95% CI)		**8**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**8**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.5. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 5: Bleeding episodes

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 LMWH: placental abruption						
de Vries 2012	1	70	1	69	18.3%	0.99 [0.06 , 15.45]
Rodger 2014	4	146	3	146	54.5%	1.33 [0.30 , 5.85]
van Hoorn 2016	0	16	1	16	27.2%	0.33 [0.01 , 7.62]
Subtotal (95% CI)		**232**		**231**	**100.0%**	**1.00 [0.31 , 3.20]**
Total events:	5		5			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.5.2 LMWH: peripartum haemorrhage						
Rodger 2014 (1)	6	146	9	143	100.0%	0.65 [0.24 , 1.79]
Subtotal (95% CI)		**146**		**143**	**100.0%**	**0.65 [0.24 , 1.79]**
Total events:	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.5.3 LMWH non-major/minor bleeding						
Rodger 2014 (2)	28	143	13	141	100.0%	2.12 [1.15 , 3.93]
Subtotal (95% CI)		**143**		**141**	**100.0%**	**2.12 [1.15 , 3.93]**
Total events:	28		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
1.5.4 LMWH: major bleeding						
Rodger 2014 (2)	3	143	2	141	100.0%	1.48 [0.25 , 8.72]
Subtotal (95% CI)		**143**		**141**	**100.0%**	**1.48 [0.25 , 8.72]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.5.5 UFH: antenatal vaginal bleeding						
Howell 1983 (3)	2	20	2	20	100.0%	1.00 [0.16 , 6.42]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.16 , 6.42]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.5.6 UFH: postpartum haemorrhage						
Howell 1983 (4)	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		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						

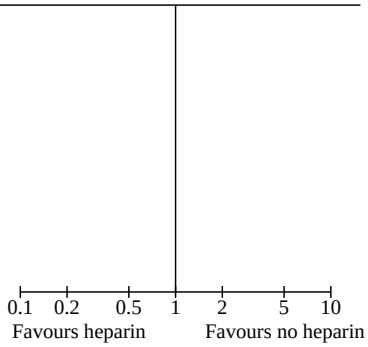


Footnotes

(1) >40 g/L decrease in haemoglobin at 24 h post-partum
(2) On treatment analysis
(3) Antenatal vaginal bleeding
(4) Postpartum haemorrhage of 700 mL

Analysis 1.6. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 6: Serious wound complications

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 LMWH						
Gates 2004a (1)	0	8	0	8		Not estimable
Subtotal (95% CI)		**8**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**8**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

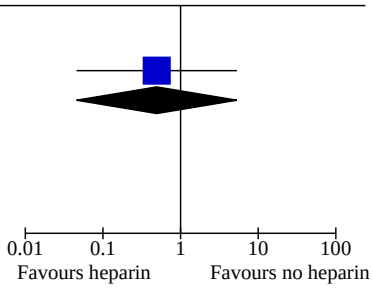


Footnotes

(1) "serious wound complications (hematoma, wound infection, or wound breakdown)"

Analysis 1.7. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 7: Adverse effects sufficient to stop treatment

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 LMWH						
de Vries 2012 (1)	1	70	2	69	100.0%	0.49 [0.05 , 5.31]
Subtotal (95% CI)		**70**		**69**	**100.0%**	**0.49 [0.05 , 5.31]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Not applicable						

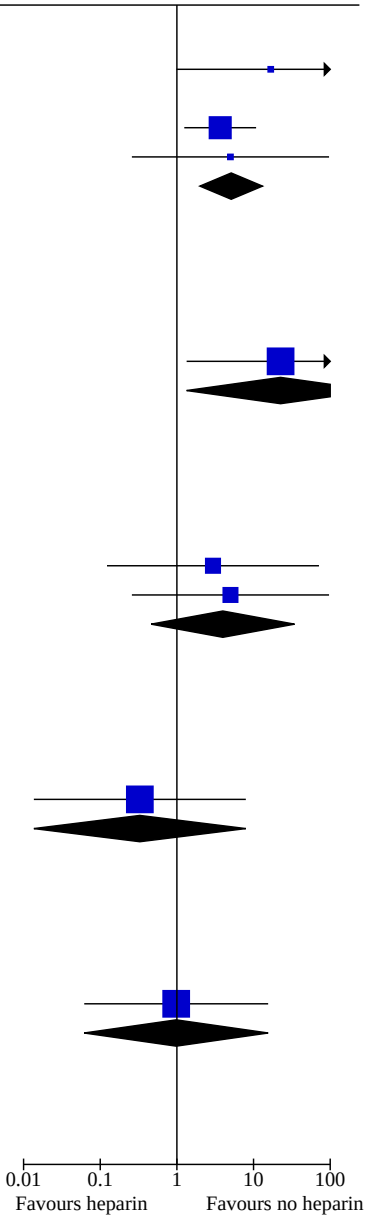


Footnotes

(1) Intervention group reason: "bleeding from placental praevia"; no treatment group reason: stomach complaints

Analysis 1.8. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 8: Adverse effects not sufficient to stop treatment

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 LMWH: skin/allergic reactions						
de Vries 2012 (1)	8	70	0	69	10.0%	16.76 [0.99 , 284.87]
Gates 2004a (2)	0	8	0	8		Not estimable
Rodger 2014 (3)	15	146	4	143	80.1%	3.67 [1.25 , 10.80]
van Hoorn 2016 (4)	2	16	0	16	9.9%	5.00 [0.26 , 96.59]
Subtotal (95% CI)		**240**		**236**	**100.0%**	**5.11 [2.00 , 13.08]**
Total events:	25		4			
Heterogeneity: Chi² = 1.04, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 3.40 (P = 0.0007)						
1.8.2 LMWH: raised liver enzymes						
Rodger 2014 (5)	11	146	0	143	100.0%	22.53 [1.34 , 378.78]
Subtotal (95% CI)		**146**		**143**	**100.0%**	**22.53 [1.34 , 378.78]**
Total events:	11		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						
1.8.3 LMWH: haematoma						
de Vries 2012	1	70	0	69	50.2%	2.96 [0.12 , 71.38]
van Hoorn 2016	2	16	0	16	49.8%	5.00 [0.26 , 96.59]
Subtotal (95% CI)		**86**		**85**	**100.0%**	**3.98 [0.46 , 34.23]**
Total events:	3		0			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
1.8.4 Superficial thrombophlebitis						
de Vries 2012	0	70	1	69	100.0%	0.33 [0.01 , 7.93]
Subtotal (95% CI)		**70**		**69**	**100.0%**	**0.33 [0.01 , 7.93]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.8.5 LMWH: other						
Rodger 2014 (6)	1	146	1	143	100.0%	0.98 [0.06 , 15.51]
Subtotal (95% CI)		**146**		**143**	**100.0%**	**0.98 [0.06 , 15.51]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						

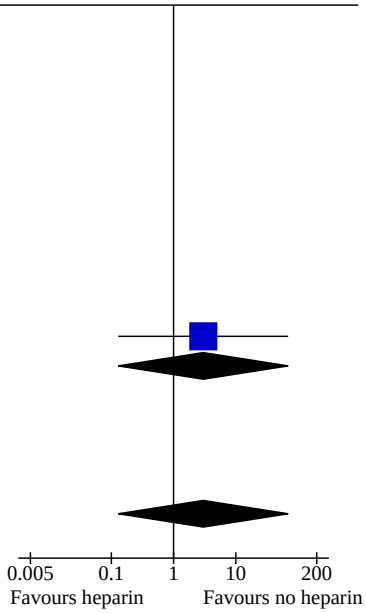


Footnotes

(1) "Skin reaction: pain, itching, swelling, allergy"
(2) "allergic reactions"
(3) "Allergic-type skin reactions"
(4) "Skin reaction, pain, itching, swelling, allergy" " women were prescribed an alternative LMWH, after which the reaction disappeared"
(5) "Raised levels of liver enzymes (aspartate aminotransferase or alanine transaminase) — defined as two-times normal values"
(6) 1 transient ischaemic attack (heparin); 1 allergic reaction (no heparin)

Analysis 1.9. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 9: Symptomatic osteoporosis

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 LMWH						
de Vries 2012 (1)	0	70	0	69		Not estimable
Gates 2004a (2)	0	8	0	8		Not estimable
Rodger 2014 (3)	0	143	0	141		Not estimable
Subtotal (95% CI)		**221**		**218**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.9.2 UFH						
Howell 1983 (4)	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		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**241**		**238**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						

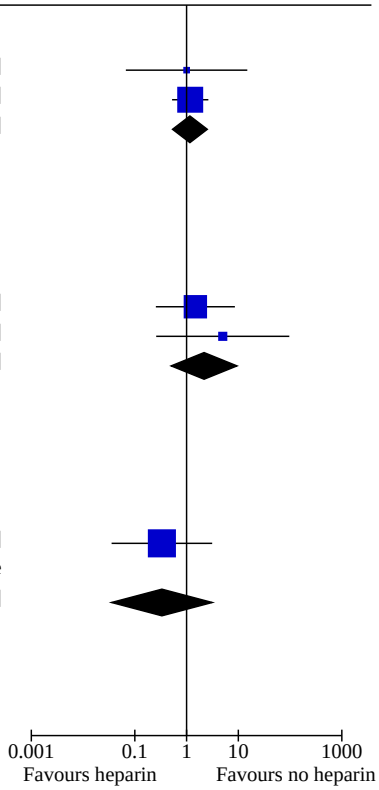


Footnotes

(1) "Complaints suggestive of osteoporosis"
(2) "Osteoporotic symptomatic fracture"
(3) "Osteoporotic fracture"
(4) "severe debilitating bone demineralization"

Analysis 1.10. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 10: Fetal loss

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 LMWH or UFH: gestation unclear						
Howell 1983 (1)	1	20	1	20	9.0%	1.00 [0.07 , 14.90]
Rodger 2014 (2)	12	146	10	143	91.0%	1.18 [0.52 , 2.63]
Subtotal (95% CI)		**166**		**163**	**100.0%**	**1.16 [0.54 , 2.51]**
Total events:	13		11			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.71)						
1.10.2 LMWH: < 20 weeks						
de Vries 2012 (3)	3	70	2	69	80.1%	1.48 [0.25 , 8.58]
van Hoorn 2016 (4)	2	16	0	16	19.9%	5.00 [0.26 , 96.59]
Subtotal (95% CI)		**86**		**85**	**100.0%**	**2.18 [0.50 , 9.41]**
Total events:	5		2			
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.10.3 LMWH: ≥ 20 weeks						
de Vries 2012 (5)	1	67	3	67	100.0%	0.33 [0.04 , 3.12]
van Hoorn 2016 (6)	0	16	0	16		Not estimable
Subtotal (95% CI)		**83**		**83**	**100.0%**	**0.33 [0.04 , 3.12]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						

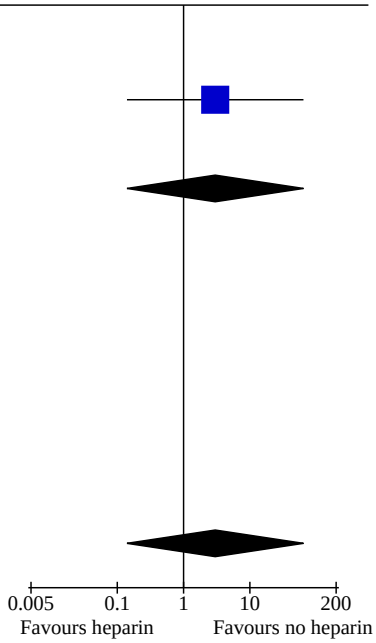


Footnotes

(1) "Complete abortion"
(2) "Pregnancy loss (any)"
(3) "Spontaneous abortion < 16 weeks gestation"
(4) "Spontaneous miscarriage <16 weeks"
(5) "Fetal death >16 weeks gestation"
(6) "Foetal death >16 weeks (miscarriage excluded)"

Analysis 1.11. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 11: Thrombocytopenia

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 LMWH						
de Vries 2012	0	70	0	69		Not estimable
Gates 2004a (1)	1	8	0	8	100.0%	3.00 [0.14 , 64.26]
Rodger 2014 (2)	0	143	0	141		Not estimable
van Hoorn 2016	0	16	0	16		Not estimable
Subtotal (95% CI)		**237**		**234**	**100.0%**	**3.00 [0.14 , 64.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.11.2 UFH						
Howell 1983	0	20	0	20		Not estimable
Subtotal (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**257**		**254**	**100.0%**	**3.00 [0.14 , 64.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						



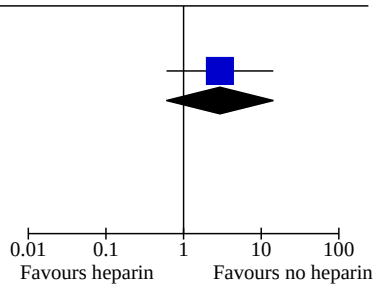
Footnotes

(1) Described as mild thrombocytopenia

(2) on treatment anlaysis

Analysis 1.12. Comparison 1: Antenatal (± postnatal) prophylaxis: Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 12: Fetal anomalies

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 LMWH						
Rodger 2014 (1)	6	146	2	143	100.0%	2.94 [0.60 , 14.32]
Subtotal (95% CI)		**146**		**143**	**100.0%**	**2.94 [0.60 , 14.32]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Heparin group: ankyloglossia (2), ectopic kidney, trisomy, strawberry haemangioma and cataract); no heparin group: hemivertebrae/scoliosis, and duı

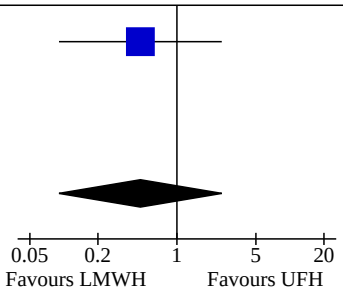
Comparison 2. Antenatal (± postnatal) prophylaxis: LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Symptomatic thromboembolic events	4	404	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.49]
2.2 Symptomatic pulmonary embolism	3	287	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Symptomatic deep vein thrombosis	3	287	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4 Blood transfusion	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.47]
2.5 Bleeding episodes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 Bruises > 1 inch	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.09, 0.36]
2.5.2 Bleeding at birth	1	117	Risk Ratio (M-H, Fixed, 95% CI)	3.80 [0.44, 32.99]
2.5.3 Bleeding complications	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.53]
2.6 Adverse effects sufficient to stop treatment	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
2.7 Adverse effects not sufficient to stop treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 Injection burning	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.53, 1.18]
2.8 Symptomatic osteoporosis	2	188	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.06, 2.98]
2.9 Fetal loss	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.9.1 Gestation unclear	2	222	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.21, 1.77]
2.9.2 < 20 weeks	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.00]
2.10 Thrombocytopenia	3	287	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.64]

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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Casele 2006 (1)	2	60	4	57	100.0%	0.47 [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%**	**0.47 [0.09 , 2.49]**
Total events:	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

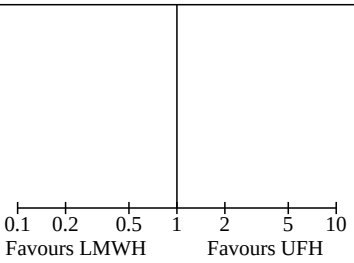


Footnotes
(1) Not clear if events were symptomatic, described as "recurrent thrombosis".

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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	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
Pettila 1999	0	50	0	55		Not estimable
Total (95% CI)		**143**		**144**		**Not estimable**
Total events:	0		0			

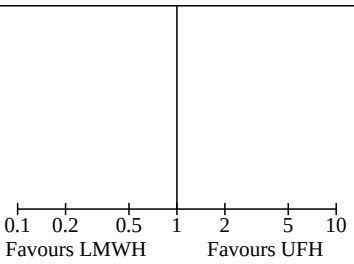
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	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
Pettila 1999	0	50	0	55		Not estimable
Total (95% CI)		**143**		**144**		**Not estimable**
Total events:	0		0			

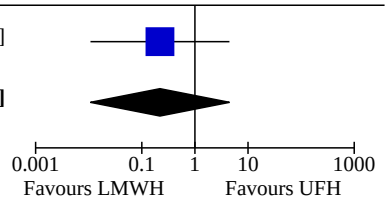
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pettila 1999 (1)	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		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Footnotes
(1) "major delivery bleedings requiring blood transfusions"

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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 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		39			

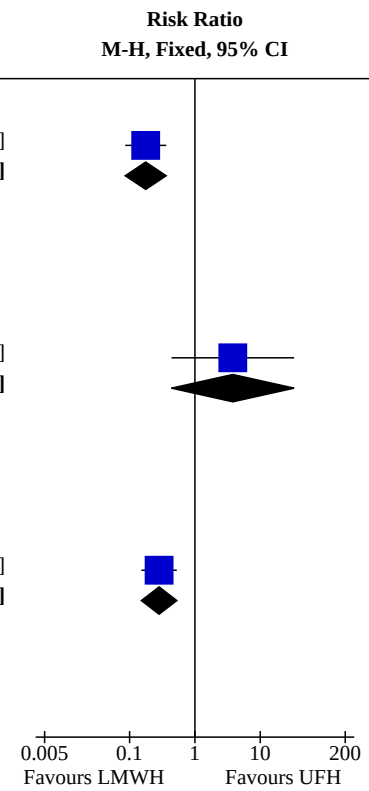
Heterogeneity: Not applicable
Test for overall effect: Z = 4.71 (P < 0.00001)

2.5.2 Bleeding at birth						
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		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)

2.5.3 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		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.96 (P < 0.0001)

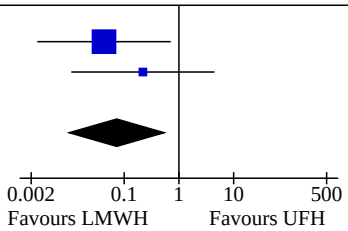


Footnotes
(1) Bleeding complications: injection-site haematoma (≥ 2 cm), bleeding during delivery and other bleeding

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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Veciana 2001 (1)	0	61	11	60	82.9%	0.04 [0.00 , 0.71]
Pettila 1999 (2)	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		13			

Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Not applicable

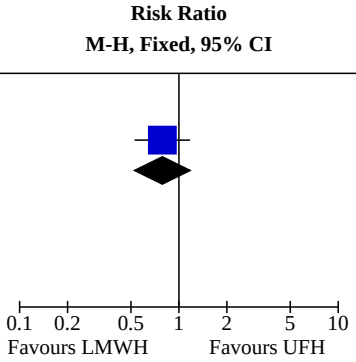


Footnotes
(1) "switched to dalteparin due to excess bruising/allergic rashes which resolved"
(2) "due to an allergic reaction... due to mild anaemia with no confirmed bleeding"

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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Injection burning						
De Veciana 2001	24	61	30	60	100.0%	0.79 [0.53 , 1.18]
Subtotal (95% CI)		**61**		**60**	**100.0%**	**0.79 [0.53 , 1.18]**
Total events:	24		30			

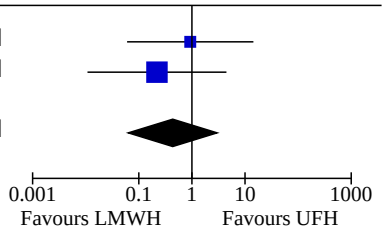
Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)



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

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Casele 2006 (1)	1	43	1	40	30.3%	0.93 [0.06 , 14.38]
Pettila 1999 (2)	0	50	2	55	69.7%	0.22 [0.01 , 4.47]
Total (95% CI)		**93**		**95**	**100.0%**	**0.43 [0.06 , 2.98]**
Total events:	1		3			

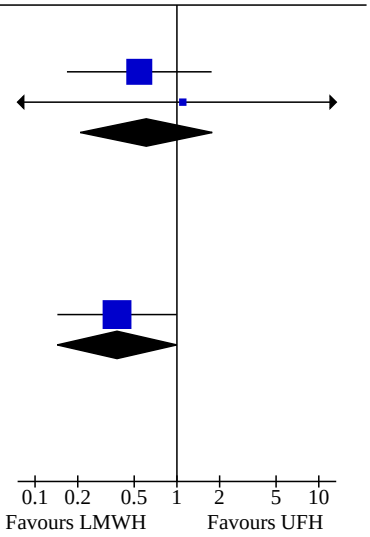
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable



Footnotes
(1) "clinically significant bone loss (>10%) in the femur"
(2) "Osteoporotic fractures"

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

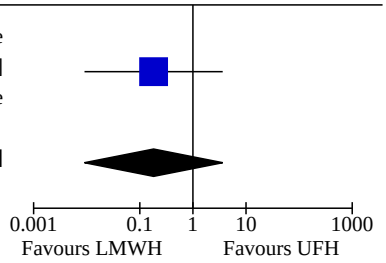
Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.9.1 Gestation unclear						
Casele 2006 (1)	4	60	7	57	88.3%	0.54 [0.17 , 1.76]
Pettila 1999 (1)	1	50	1	55	11.7%	1.10 [0.07 , 17.12]
Subtotal (95% CI)		**110**		**112**	**100.0%**	**0.61 [0.21 , 1.77]**
Total events:	5		8			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
2.9.2 < 20 weeks						
De Veciana 2001 (2)	5	61	13	60	100.0%	0.38 [0.14 , 1.00]
Subtotal (95% CI)		**61**		**60**	**100.0%**	**0.38 [0.14 , 1.00]**
Total events:	5		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



Footnotes
(1) "Spontaneous abortion"
(2) "SAB <20wk"

Analysis 2.10. Comparison 2: Antenatal (± postnatal) prophylaxis: LMWH versus UFH, Outcome 10: Thrombocytopenia

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	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		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Not applicable						



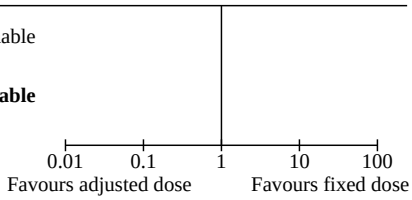
Comparison 3. Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptomatic thromboembolic events	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Symptomatic pulmonary embolism	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Symptomatic deep vein thrombosis	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Asymptomatic thromboembolic events	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5 Bleeding episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 Placental abruption	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.03, 1.95]
3.5.2 Postpartum haemorrhage	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
3.5.3 Side effects: bleeding	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.6 Adverse effects sufficient to stop treatment	1	144	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.50]
3.7 Adverse effects not sufficient to stop treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.7.1 Skin allergy	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.19]
3.8 Fetal loss	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.8.1 < 20 weeks	1	140	Risk Ratio (M-H, Fixed, 95% CI)	4.47 [0.22, 91.38]
3.8.2 ≥ 20 weeks	1	140	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.11, 64.68]
3.9 Thrombocytopenia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 3.1. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 1: Symptomatic thromboembolic events

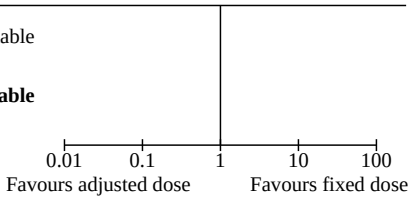
Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016	0	74	0	66		Not estimable
Total (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 3.2. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016	0	74	0	66		Not estimable
Total (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			

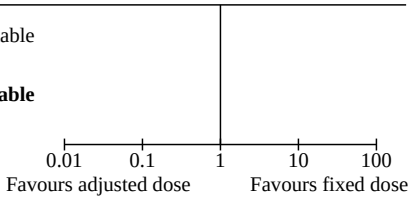
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016	0	74	0	66		Not estimable
Total (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			

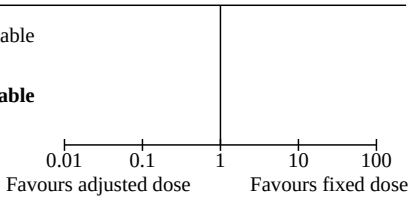
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 4: Asymptomatic thromboembolic events

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016 (1)	0	74	0	66		Not estimable
Total (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

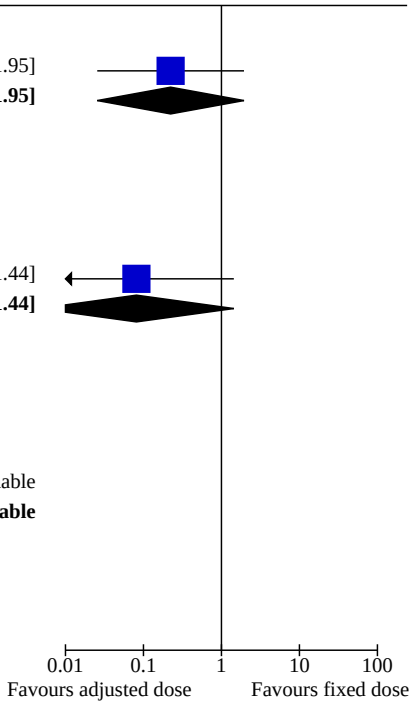


Footnotes

(1) "objectively documented VTE"

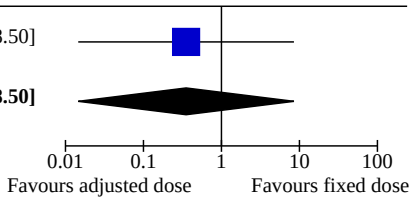
Analysis 3.5. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 5: Bleeding episodes

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Placental abruption						
Salim 2016	1	74	4	66	100.0%	0.22 [0.03 , 1.95]
Subtotal (95% CI)		**74**		**66**	**100.0%**	**0.22 [0.03 , 1.95]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
3.5.2 Postpartum haemorrhage						
Salim 2016	0	74	5	66	100.0%	0.08 [0.00 , 1.44]
Subtotal (95% CI)		**74**		**66**	**100.0%**	**0.08 [0.00 , 1.44]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
3.5.3 Side effects: bleeding						
Salim 2016	0	74	0	66		Not estimable
Subtotal (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 3.6. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 6: Adverse effects sufficient to stop treatment

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016 (1)	0	70	1	74	100.0%	0.35 [0.01 , 8.50]
Total (95% CI)		**70**		**74**	**100.0%**	**0.35 [0.01 , 8.50]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						

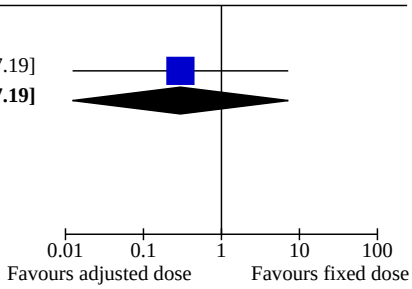


Footnotes

(1) Discontinued intervention due to "enoxaparin side effects"

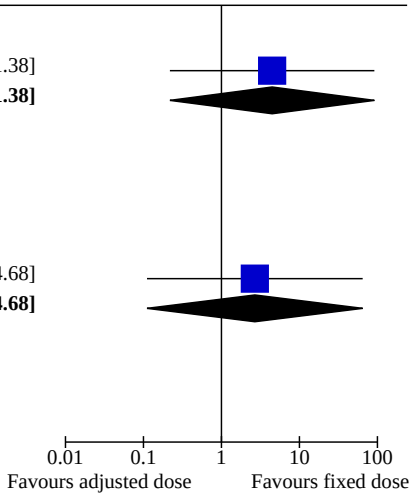
Analysis 3.7. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 7: Adverse effects not sufficient to stop treatment

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Skin allergy						
Salim 2016	0	74	1	66	100.0%	0.30 [0.01 , 7.19]
Subtotal (95% CI)		**74**		**66**	**100.0%**	**0.30 [0.01 , 7.19]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.46)						



Analysis 3.8. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 8: Fetal loss

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 < 20 weeks						
Salim 2016 (1)	2	74	0	66	100.0%	4.47 [0.22 , 91.38]
Subtotal (95% CI)		**74**		**66**	**100.0%**	**4.47 [0.22 , 91.38]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
3.8.2 ≥ 20 weeks						
Salim 2016 (2)	1	74	0	66	100.0%	2.68 [0.11 , 64.68]
Subtotal (95% CI)		**74**		**66**	**100.0%**	**2.68 [0.11 , 64.68]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						



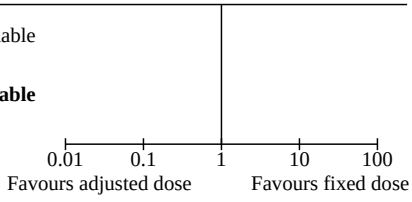
Footnotes

(1) "Spontaneous abortion"

(2) "Intra-uterine fetal death (>23 weeks)"

Analysis 3.9. Comparison 3: Antenatal (±postnatal) prophylaxis: Adjusted-dose versus fixed-dose LMWH, Outcome 9: Thrombocytopenia

Study or Subgroup	Adjusted dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salim 2016	0	74	0	66		Not estimable
Total (95% CI)		**74**		**66**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

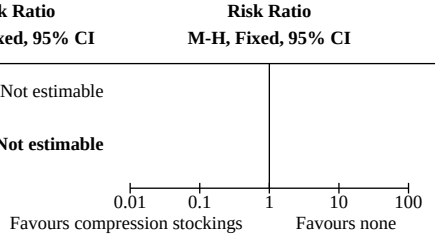


Comparison 4. Antenatal (± postnatal) prophylaxis: Compression stockings versus none

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Symptomatic deep vein thrombosis	1	44	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Adverse effects not sufficient to stop treatment	1	44	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

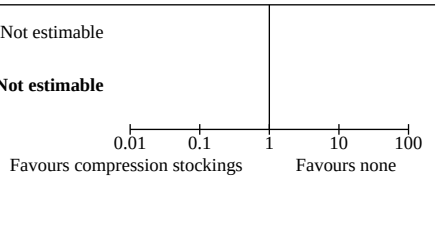
Analysis 4.1. Comparison 4: Antenatal (± postnatal) prophylaxis: Compression stockings versus none, Outcome 1: Symptomatic deep vein thrombosis

Study or Subgroup	Compression stockings Events	Compression stockings Total	No compression stockings Events	No compression stockings Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heller 2016	0	21	0	23		Not estimable
Total (95% CI)		**21**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 4.2. Comparison 4: Antenatal (± postnatal) prophylaxis: Compression stockings versus none, Outcome 2: Adverse effects not sufficient to stop treatment

Study or Subgroup	Compression stockings Events	Compression stockings Total	No compression stockings Events	No compression stockings Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heller 2016	0	21	0	23		Not estimable
Total (95% CI)		**21**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



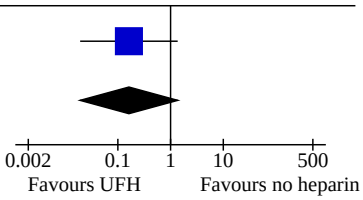
Comparison 5. Peripartum/postnatal prophylaxis: UFH versus no treatment

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

Analysis 5.1. Comparison 5: Peripartum/postnatal prophylaxis: UFH versus no treatment, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	UFH Events	UFH Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Segal 1975	1	116	5	94	100.0%	0.16 [0.02 , 1.36]
Total (95% CI)		**116**		**94**	**100.0%**	**0.16 [0.02 , 1.36]**
Total events:	1		5			

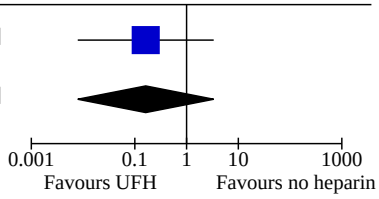
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Peripartum/postnatal prophylaxis: UFH versus no treatment, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	UFH Events	UFH Total	No heparin Events	No heparin Total	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		2			

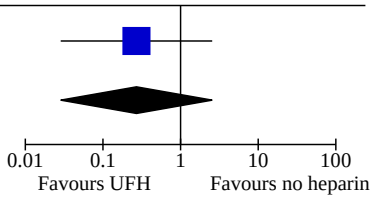
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Peripartum/postnatal prophylaxis: UFH versus no treatment, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	UFH Events	UFH Total	No heparin Events	No heparin Total	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		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



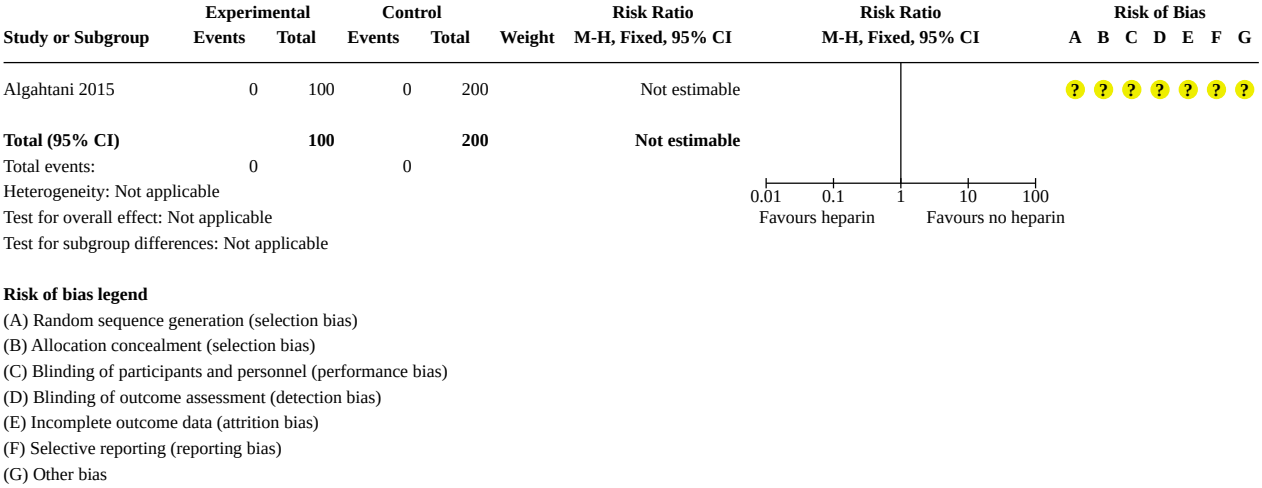
Comparison 6. Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/ placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Maternal death	1	300	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Symptomatic thromboembolic events	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.39, 4.27]
6.2.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.31, 28.03]
6.2.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.19, 3.76]
6.3 Symptomatic pulmonary embolism	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.25, 4.87]
6.3.1 LMWH	2	210	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.51]
6.3.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.13, 4.48]
6.4 Symptomatic deep vein thrombosis	5	1140	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.24, 6.94]
6.4.1 LMWH	3	510	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.17, 11.55]
6.4.2 UFH	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 18.02]
6.5 Blood transfusion	3	266	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.13]
6.5.1 LMWH	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.54]
6.5.2 UFH	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 3.97]
6.6 Bleeding episodes (variously defined)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.6.1 Major bleeding	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.6.2 Major bruising	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.6.3 Bleeding complications	2	714	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [2.49, 10.18]
6.6.4 Bleeding/bruising reported at discharge	1	140	Risk Ratio (M-H, Fixed, 95% CI)	6.17 [0.76, 49.96]
6.6.5 Blood loss < 500 mL	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.63, 3.59]
6.6.6 Blood loss 500-1000 mL	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
6.6.7 Blood loss 1000-1500 mL	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.17]
6.6.8 Blood loss 1500-2000 mL	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.19, 20.67]
6.7 Serious wound complications	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.7.1 Major wound disruption	2	126	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.2 Wound infection	2	216	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.34, 15.53]
6.8 Adverse effects sufficient to stop treatment	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.9 Adverse effects not sufficient to stop treatment	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

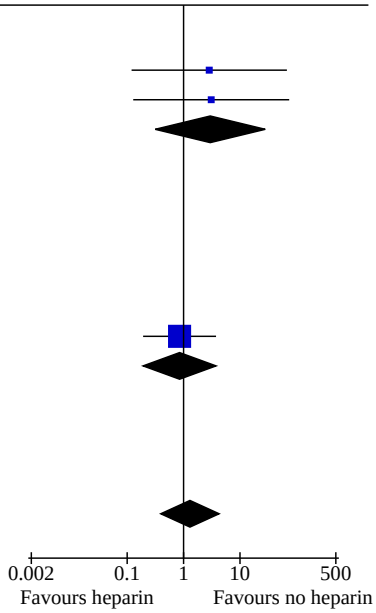
Analysis 6.1. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 1: Maternal death



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.2. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 2: Symptomatic thromboembolic events

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 LMWH						
Burrows 2001	1	39	0	37	10.8%	2.85 [0.12 , 67.83]
Gates 2004b	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		0			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
6.2.2 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		4			
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		4			
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%						

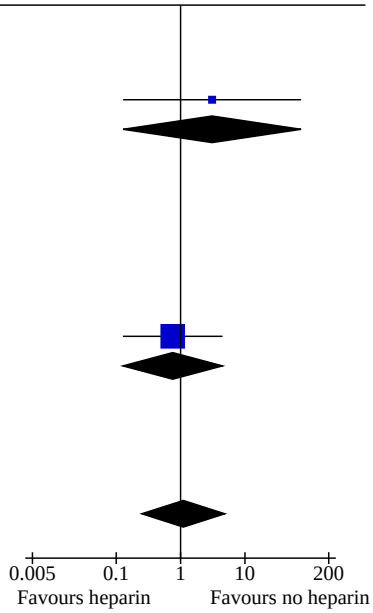


Footnotes

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

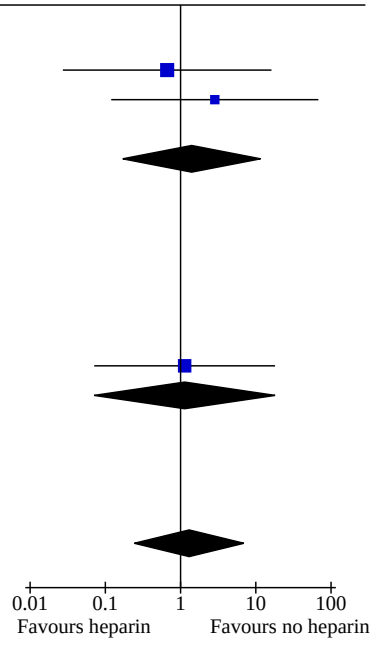
Analysis 6.3. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 3: Symptomatic pulmonary embolism

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 LMWH						
Burrows 2001	0	39	0	37		Not estimable
Gates 2004b	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		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
6.3.2 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		3			
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		3			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						



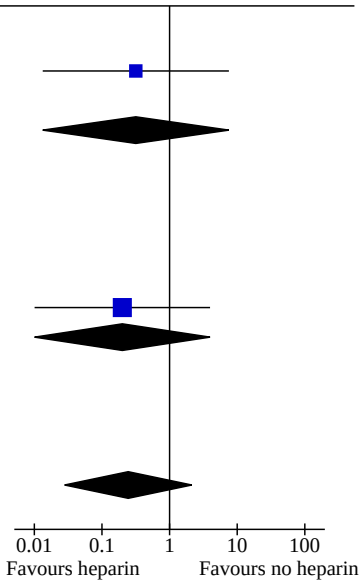
Analysis 6.4. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 4: Symptomatic deep vein thrombosis

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.1 LMWH						
Algahtani 2015	0	100	1	200	40.9%	0.66 [0.03 , 16.14]
Burrows 2001	1	39	0	37	20.9%	2.85 [0.12 , 67.83]
Gates 2004b	0	66	0	68		Not estimable
Subtotal (95% CI)		**205**		**305**	**61.8%**	**1.40 [0.17 , 11.55]**
Total events:	1		1			
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.75)						
6.4.2 UFH						
Hill 1988	0	25	0	25		Not estimable
Welti 1981	1	272	1	308	38.2%	1.13 [0.07 , 18.02]
Subtotal (95% CI)		**297**		**333**	**38.2%**	**1.13 [0.07 , 18.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**502**		**638**	**100.0%**	**1.30 [0.24 , 6.94]**
Total events:	2		2			
Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.90), I² = 0%						



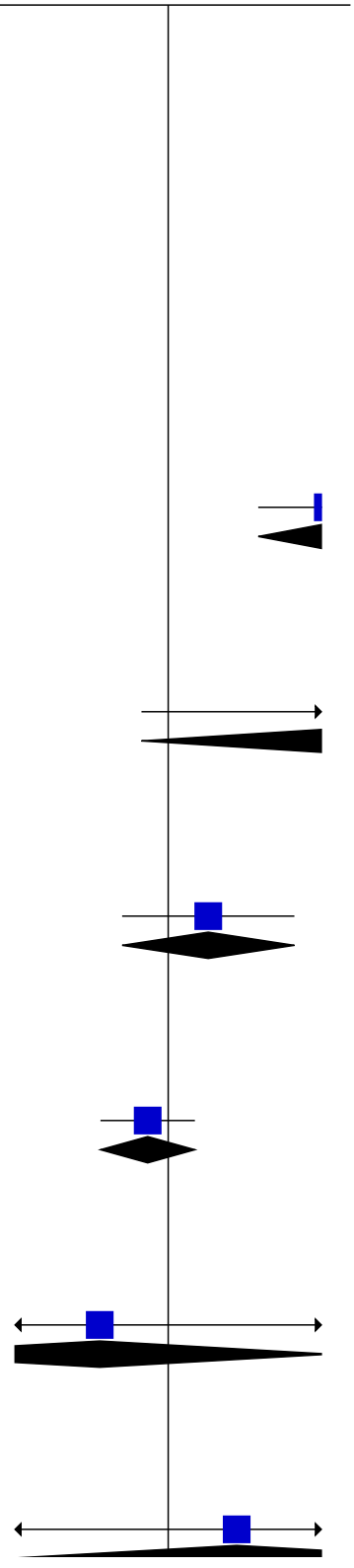
Analysis 6.5. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 5: Blood transfusion

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.5.1 LMWH						
Burrows 2001	0	39	1	37	38.1%	0.32 [0.01 , 7.54]
Gates 2004b	0	69	0	71		Not estimable
Subtotal (95% CI)		**108**		**108**	**38.1%**	**0.32 [0.01 , 7.54]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
6.5.2 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		2			
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		3			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



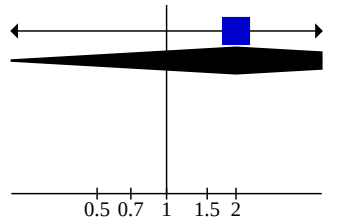
Analysis 6.6. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 6: Bleeding episodes (variously defined)

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.6.1 Major bleeding						
Burrows 2001	0	39	0	37		Not estimable
Subtotal (95% CI)		**39**		**37**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.6.2 Major bruising						
Burrows 2001	0	39	0	37		Not estimable
Subtotal (95% CI)		**39**		**37**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.6.3 Bleeding complications						
Gates 2004b	0	66	0	68		Not estimable
Welti 1981 (1)	40	272	9	308	100.0%	5.03 [2.49 , 10.18]
Subtotal (95% CI)		**338**		**376**	**100.0%**	**5.03 [2.49 , 10.18]**
Total events:	40		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.50 (P < 0.00001)						
6.6.4 Bleeding/bruising reported at discharge						
Gates 2004b	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		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
6.6.5 Blood loss < 500 mL						
Hill 1988	9	25	6	25	100.0%	1.50 [0.63 , 3.59]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**1.50 [0.63 , 3.59]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
6.6.6 Blood loss 500-1000 mL						
Hill 1988	13	25	16	25	100.0%	0.81 [0.50 , 1.31]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**0.81 [0.50 , 1.31]**
Total events:	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
6.6.7 Blood loss 1000-1500 mL						
Hill 1988	1	25	2	25	100.0%	0.50 [0.05 , 5.17]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**0.50 [0.05 , 5.17]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
6.6.8 Blood loss 1500-2000 mL						
Hill 1988	2	25	1	25	100.0%	2.00 [0.19 , 20.67]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.19 , 20.67]**



Analysis 6.6. (Continued)

Hill 1988	2	25	1	25	100.0%	2.00 [0.19 , 20.67]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.19 , 20.67]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

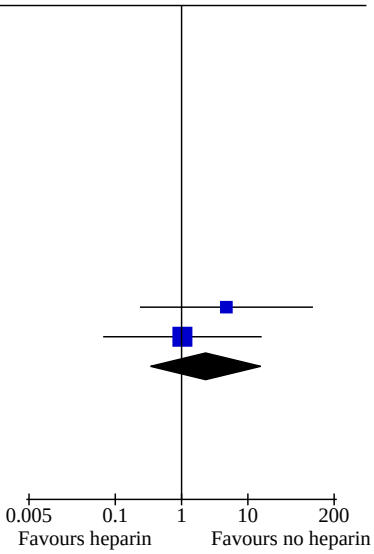


Footnotes

(1) "Complications hémorragiques"

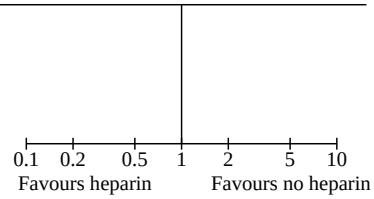
Analysis 6.7. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 7: Serious wound complications

	Heparin		No heparin			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
6.7.1 Major wound disruption							
Burrows 2001	0	39	0	37		Not estimable	
Hill 1988	0	25	0	25		Not estimable	
Subtotal (95% CI)		**64**		**62**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.7.2 Wound infection							
Burrows 2001	2	39	0	37	34.2%	4.75 [0.24 , 95.76]	
Gates 2004b	1	69	1	71	65.8%	1.03 [0.07 , 16.13]	
Subtotal (95% CI)		**108**		**108**	**100.0%**	**2.30 [0.34 , 15.53]**	
Total events:	3		1				
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%							
Test for overall effect: Z = 0.86 (P = 0.39)							



Analysis 6.8. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 8: Adverse effects sufficient to stop treatment

	Heparin		No heparin			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Gates 2004b (1)	0	69	0	71		Not estimable	
Total (95% CI)		**69**		**71**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



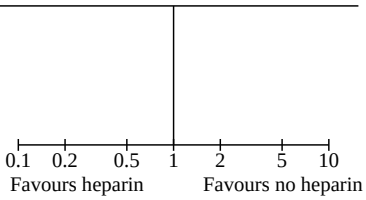
Footnotes

(1) "No women had intrapartum or postnatal blood transfusion, bleeding complications, or allergic reactions that were sufficient to stop treatment"

Analysis 6.9. Comparison 6: Peripartum/postnatal prophylaxis (caesarean): Heparin (LMWH or UFH) versus no treatment/placebo, Outcome 9: Adverse effects not sufficient to stop treatment

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burrows 2001 (1)	0	39	0	37		Not estimable
Total (95% CI)		**39**		**37**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes
(1) "Major reaction"

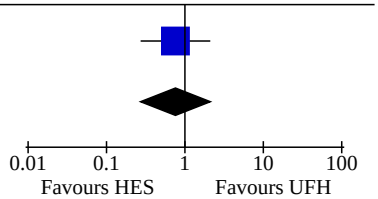
Comparison 7. Peripartum/postnatal prophylaxis (caesarean): HES versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Asymptomatic thromboembolic events	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.11]
7.2 Blood transfusion	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.48]
7.3 Bleeding episodes	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.03]
7.4 Serious wound complications	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.82]

Analysis 7.1. Comparison 7: Peripartum/postnatal prophylaxis (caesarean): HES versus UFH, Outcome 1: Asymptomatic thromboembolic events

Study or Subgroup	HES Events	HES Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heilmann 1991 (1)	6	103	8	104	100.0%	0.76 [0.27 , 2.11]
Total (95% CI)		**103**		**104**	**100.0%**	**0.76 [0.27 , 2.11]**
Total events:	6		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable

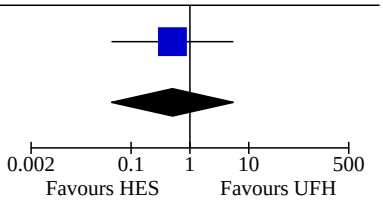


Footnotes
(1) DVT

Analysis 7.2. Comparison 7: Peripartum/postnatal prophylaxis (caesarean): HES versus UFH, Outcome 2: Blood transfusion

Study or Subgroup	HES Events	HES Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heilmann 1991	1	103	2	104	100.0%	0.50 [0.05 , 5.48]
Total (95% CI)		**103**		**104**	**100.0%**	**0.50 [0.05 , 5.48]**
Total events:	1		2			

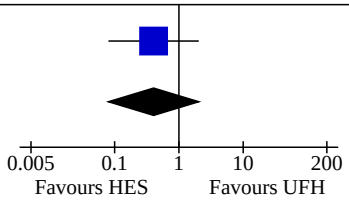
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Peripartum/postnatal prophylaxis (caesarean): HES versus UFH, Outcome 3: Bleeding episodes

Study or Subgroup	HES Events	HES Total	UFH Events	UFH Total	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		5			

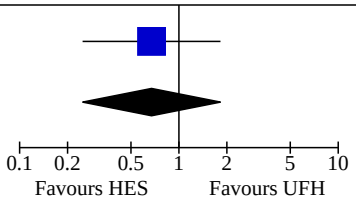
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Peripartum/postnatal prophylaxis (caesarean): HES versus UFH, Outcome 4: Serious wound complications

Study or Subgroup	HES Events	HES Total	UFH Events	UFH Total	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		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



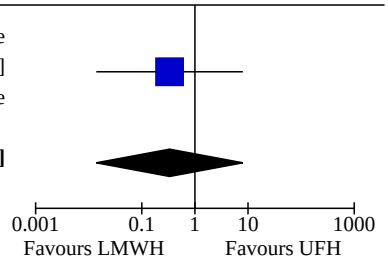
Comparison 8. Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Symptomatic thromboembolic events	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
8.2 Symptomatic pulmonary embolism	3	217	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 Symptomatic deep vein thrombosis	3	217	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
8.4 Bleeding episodes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.4.1 "haemorrhagic event"	1	17	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.4.2 Major bleeding	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.4.3 Post surgical haemorrhage	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.5 Adverse effects not sufficient to stop treatment	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.6 Thrombocytopenia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 8.1. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 1: Symptomatic thromboembolic events

	LMWH		UFH			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**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		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
Test for subgroup differences: Not applicable							



Footnotes

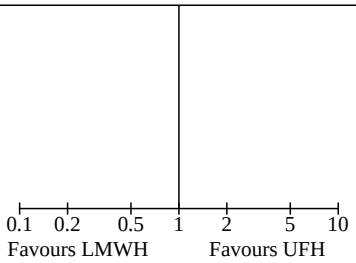
(1) Not clear whether symptomatic

(2) "clinical signs of thrombosis"

Analysis 8.2. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gibson 1998	0	11	0	6		Not estimable
Heilmann 2007	0	50	0	50		Not estimable
Krauss 1994	0	50	0	50		Not estimable
Total (95% CI)		**111**		**106**		**Not estimable**
Total events:	0		0			

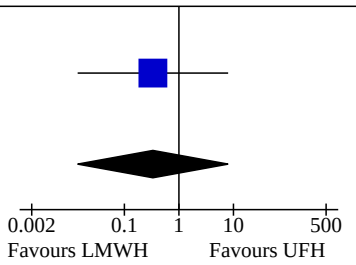
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	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		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

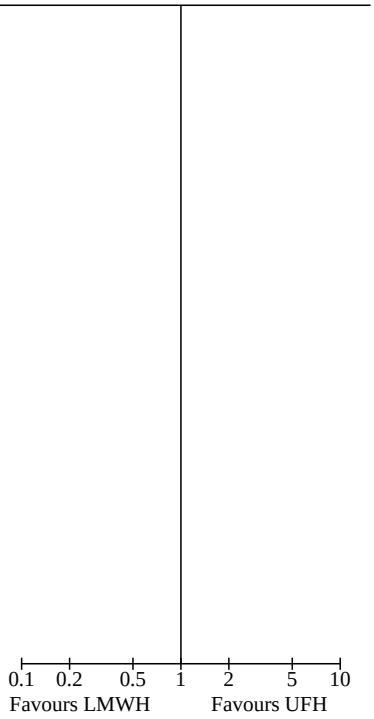


Footnotes

(1) Not clear whether symptomatic
(2) "clinical signs of thrombosis"

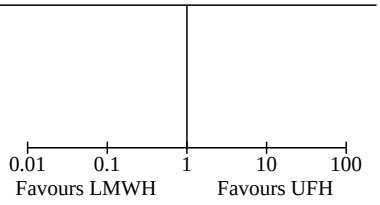
Analysis 8.4. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 4: Bleeding episodes

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.4.1 "haemorrhagic event"						
Gibson 1998	0	11	0	6		Not estimable
Subtotal (95% CI)		**11**		**6**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.4.2 Major bleeding						
Heilmann 2007	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.4.3 Post surgical haemorrhage						
Krauss 1994	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 8.5. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 5: Adverse effects not sufficient to stop treatment

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heilmann 2007 (1)	0	50	0	50		Not estimable
Total (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



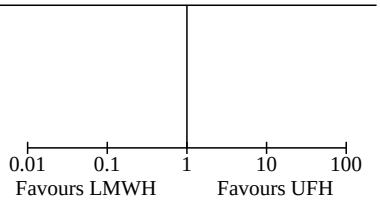
Footnotes

(1) "osteopenia or allergy"

Analysis 8.6. Comparison 8: Peripartum/postnatal prophylaxis (caesarean): LMWH versus UFH, Outcome 6: Thrombocytopenia

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krauss 1994	0	50	0	50		Not estimable
Total (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



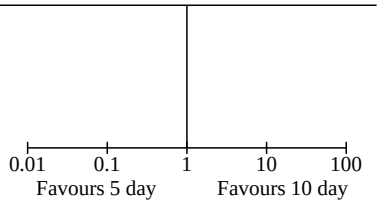
Comparison 9. Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Maternal death	1	646	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Symptomatic thromboembolic events	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
9.3 Symptomatic pulmonary embolism	1	646	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
9.4 Symptomatic deep vein thrombosis	1	646	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.5 Bleeding episodes	1	646	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.6 Serious wound complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.6.1 Post caesarean infection	1	646	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.05]
9.6.2 Post caesarean seroma	1	646	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.59, 2.23]
9.7 Thrombocytopenia	1	646	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 9.1. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 1: Maternal death

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	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		0			

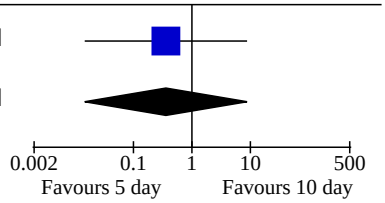
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 2: Symptomatic thromboembolic events

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	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		1			

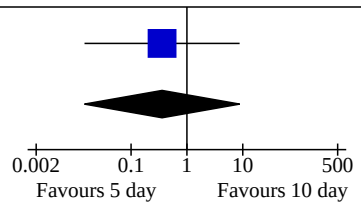
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 3: Symptomatic pulmonary embolism

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	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		1			

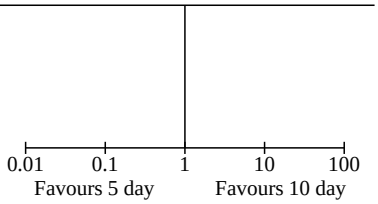
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 4: Symptomatic deep vein thrombosis

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	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		0			

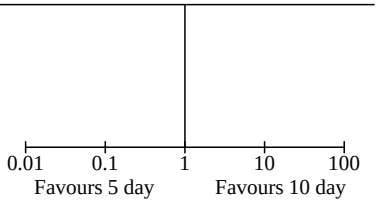
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 9.5. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 5: Bleeding episodes

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cruz 2011 (1)	0	311	0	335		Not estimable
Total (95% CI)		**311**		**335**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes

(1) Reports "adverse effects from the administration of LMWH (bleeding.."

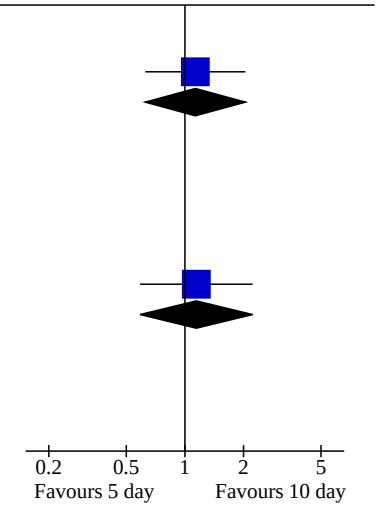
Analysis 9.6. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 6: Serious wound complications

Study or Subgroup	5 day LMWH Events	Total	10 day LMWH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.6.1 Post caesarean infection						
Cruz 2011	21	311	20	335	100.0%	1.13 [0.63 , 2.05]
Subtotal (95% CI)		**311**		**335**	**100.0%**	**1.13 [0.63 , 2.05]**
Total events:	21		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

9.6.2 Post caesarean seroma						
Cruz 2011	17	311	16	335	100.0%	1.14 [0.59 , 2.23]
Subtotal (95% CI)		**311**		**335**	**100.0%**	**1.14 [0.59 , 2.23]**
Total events:	17		16			

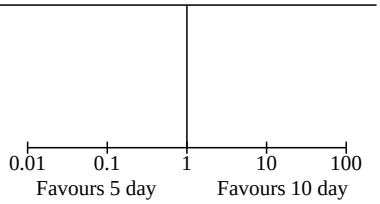
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



Analysis 9.7. Comparison 9: Peripartum/postnatal prophylaxis (caesarean): 5-day versus 10-day LMWH, Outcome 7: Thrombocytopenia

Study or Subgroup	5 day LMWH Events	5 day LMWH Total	10 day LMWH Events	10 day LMWH Total	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		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



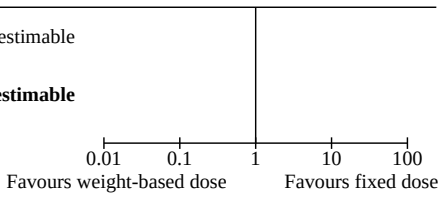
Comparison 10. Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Symptomatic thromboembolic events	1	84	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Symptomatic pulmonary embolism	1	84	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3 Symptomatic deep vein thrombosis	1	84	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.4 Blood transfusion	1	84	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.5 Serious wound complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.5.1 Wound dehiscence or reoperation	1	84	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.5.2 Wound infection	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.04]
10.5.3 Wound haematoma	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.08]

Analysis 10.1. Comparison 10: Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	Weight-based dose Events	Weight-based dose Total	Fixed dose Events	Fixed dose Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stephenson 2016	0	42	0	42		Not estimable
Total (95% CI)		**42**		**42**		**Not estimable**
Total events:	0		0			

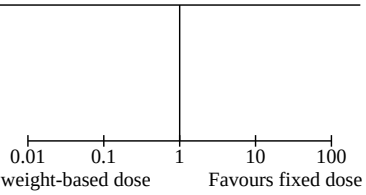
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	Weight-based dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stephenson 2016	0	42	0	42		Not estimable
Total (95% CI)		**42**		**42**		**Not estimable**
Total events:	0		0			

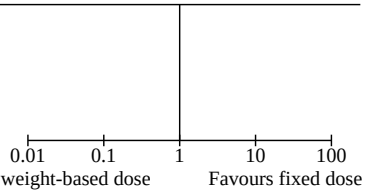
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Weight-based dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stephenson 2016	0	42	0	42		Not estimable
Total (95% CI)		**42**		**42**		**Not estimable**
Total events:	0		0			

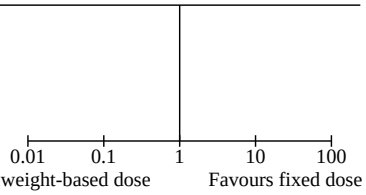
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10: Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH, Outcome 4: Blood transfusion

Study or Subgroup	Weight-based dose Events	Total	Fixed dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stephenson 2016 (1)	0	42	0	42		Not estimable
Total (95% CI)		**42**		**42**		**Not estimable**
Total events:	0		0			

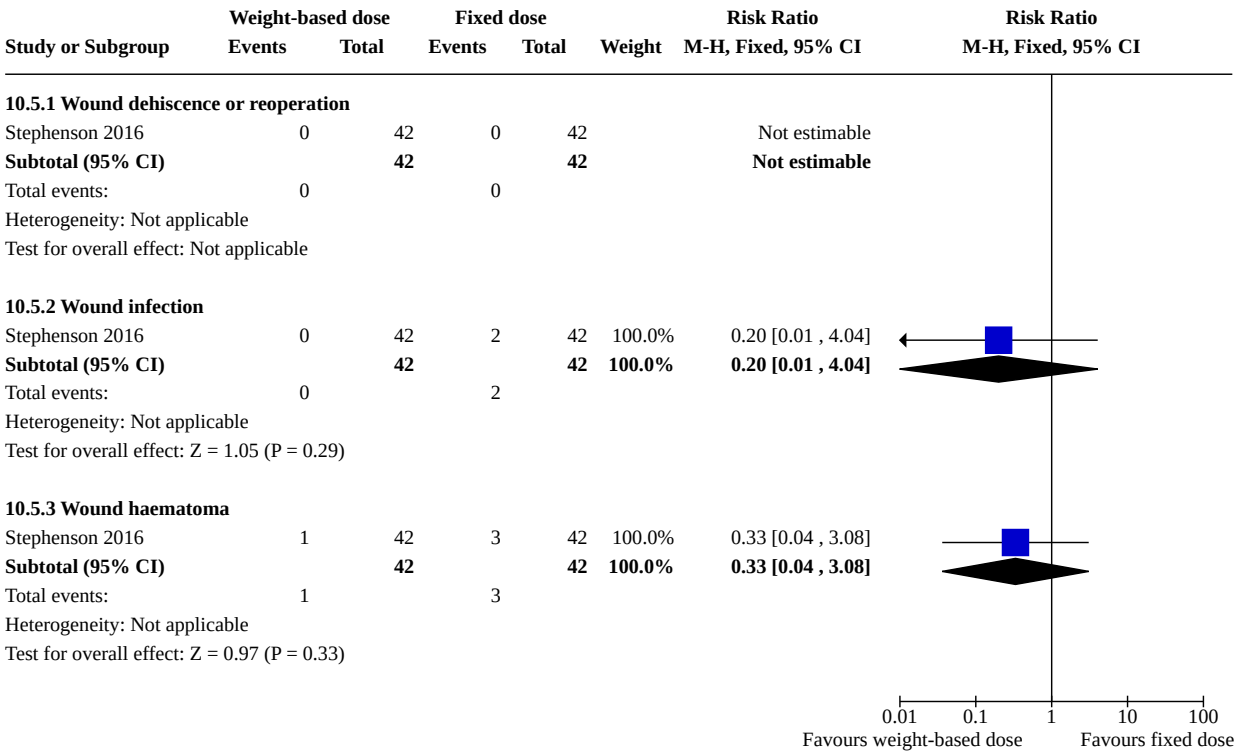
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes

(1) "bleeding events requiring reoperation or transfusion in either group"

Analysis 10.5. Comparison 10: Peripartum/postnatal prophylaxis (caesarean): Weight-based versus fixed-dose LMWH, Outcome 5: Serious wound complications



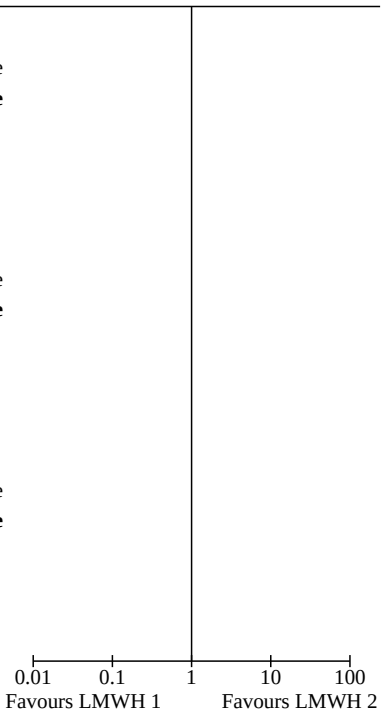
Comparison 11. Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Symptomatic thromboembolic events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1.1 Dalteparin versus enoxaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.1.2 Dalteparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.1.3 Enoxaparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 Symptomatic pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.2.1 Dalteparin versus enoxaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2.2 Dalteparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2.3 Enoxaparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3 Symptomatic deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.3.1 Dalteparin versus enoxaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3.2 Dalteparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3.3 Enoxaparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.4 Bleeding episodes (excessive bruising)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.4.1 Dalteparin versus enoxaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.4.2 Dalteparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.4.3 Enoxaparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.5 Adverse effects not sufficient to stop treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.5.1 Dalteparin versus enoxaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.5.2 Dalteparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.5.3 Enoxaparin versus tinzaparin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

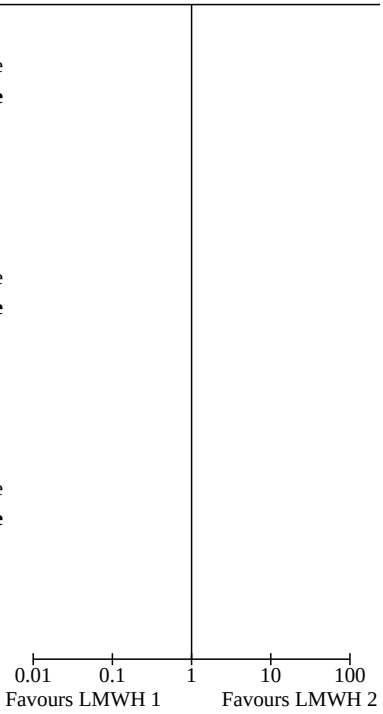
Analysis 11.1. Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types), Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	LMWH 1 Events	LMWH 1 Total	LMWH 2 Events	LMWH 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Dalteparin versus enoxaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.1.2 Dalteparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.1.3 Enoxaparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



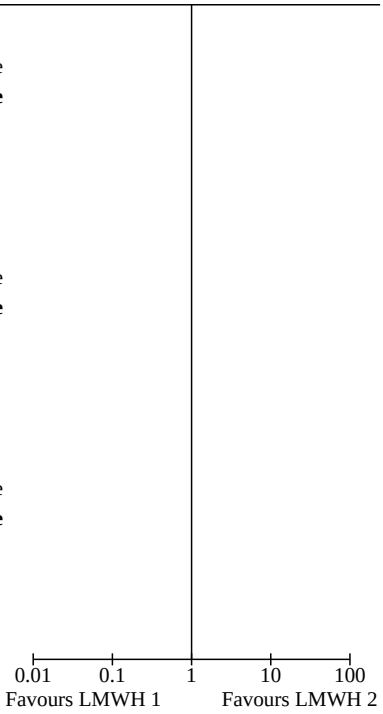
Analysis 11.2. Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types), Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	LMWH 1 Events	LMWH 1 Total	LMWH 2 Events	LMWH 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.2.1 Dalteparin versus enoxaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.2.2 Dalteparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.2.3 Enoxaparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



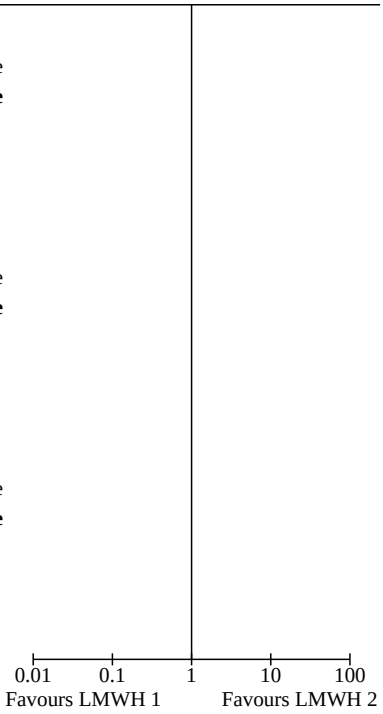
Analysis 11.3. Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types), Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	LMWH 1 Events	LMWH 1 Total	LMWH 2 Events	LMWH 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 Dalteparin versus enoxaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.2 Dalteparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.3 Enoxaparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



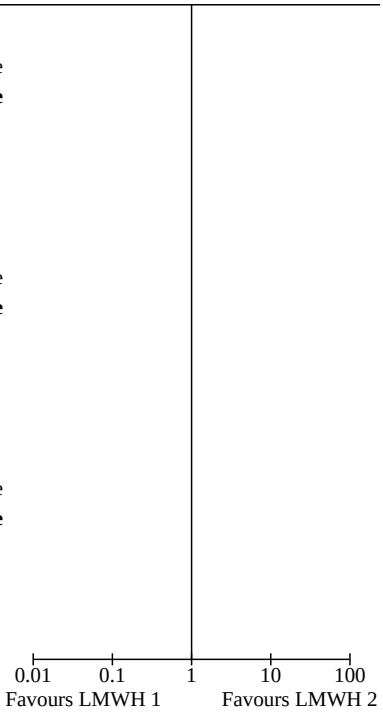
Analysis 11.4. Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types), Outcome 4: Bleeding episodes (excessive bruising)

Study or Subgroup	LMWH 1 Events	LMWH 1 Total	LMWH 2 Events	LMWH 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.4.1 Dalteparin versus enoxaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.4.2 Dalteparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.4.3 Enoxaparin versus tinzaparin						
Ellison 2001	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 11.5. Comparison 11: Peripartum/postnatal prophylaxis (caesarean): LMWH versus LMWH (different types), Outcome 5: Adverse effects not sufficient to stop treatment

Study or Subgroup	LMWH 1 Events	LMWH 1 Total	LMWH 2 Events	LMWH 2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.5.1 Dalteparin versus enoxaparin						
Ellison 2001 (1)	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.5.2 Dalteparin versus tinzaparin						
Ellison 2001 (1)	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.5.3 Enoxaparin versus tinzaparin						
Ellison 2001 (1)	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Footnotes
(1) Skin reactions

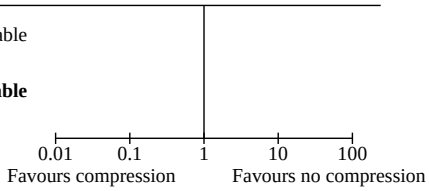
Comparison 12. Peripartum/postnatal prophylaxis (caesarean): Compression devices versus bed rest

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Symptomatic thromboembolic events	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 Symptomatic pulmonary embolism	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3 Symptomatic deep vein thrombosis	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.4 Blood transfusion	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 12.1. Comparison 12: Peripartum/postnatal prophylaxis (caesarean): Compression devices versus bed rest, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	Compression Events	Compression Total	No compression Events	No compression Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reddick 2014	0	24	0	25		Not estimable
Total (95% CI)		**24**		**25**		**Not estimable**
Total events:	0		0			

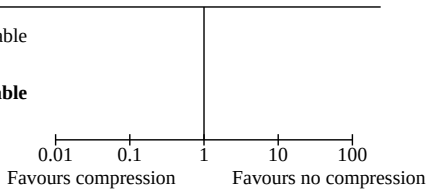
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Peripartum/postnatal prophylaxis (caesarean): Compression devices versus bed rest, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	Compression Events	Compression Total	No compression Events	No compression Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reddick 2014	0	24	0	25		Not estimable
Total (95% CI)		**24**		**25**		**Not estimable**
Total events:	0		0			

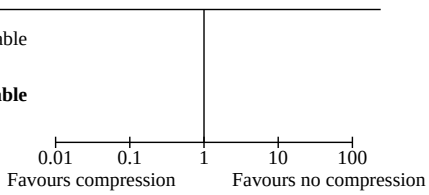
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 12.3. Comparison 12: Peripartum/postnatal prophylaxis (caesarean): Compression devices versus bed rest, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Compression Events	Compression Total	No compression Events	No compression Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reddick 2014	0	24	0	25		Not estimable
Total (95% CI)		**24**		**25**		**Not estimable**
Total events:	0		0			

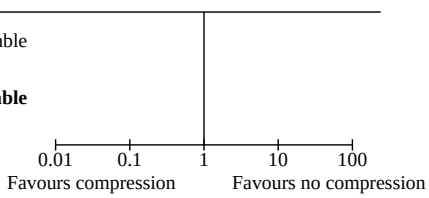
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 12.4. Comparison 12: Peripartum/postnatal prophylaxis (caesarean): Compression devices versus bed rest, Outcome 4: Blood transfusion

Study or Subgroup	Compression Events	Compression Total	No compression Events	No compression Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reddick 2014	0	24	0	25		Not estimable
Total (95% CI)		**24**		**25**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



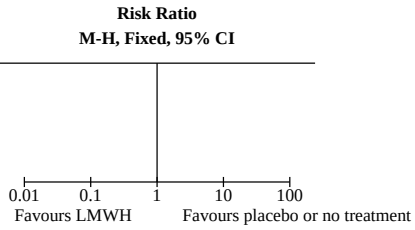
Comparison 13. Postnatal prophylaxis: LMWH versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Maternal death	1	24	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 Symptomatic thromboembolic events	2	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.3 Symptomatic pulmonary embolism	2	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.4 Symptomatic deep vein thrombosis	2	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.5 Asymptomatic thromboembolic events	2	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.6 Bleeding episodes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.6.1 Major bleeding event	2	59	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [0.15, 81.11]
13.6.2 Clinically relevant bleeding event	1	35	Risk Ratio (M-H, Fixed, 95% CI)	5.88 [0.30, 114.28]
13.6.3 Minor bleeding event	1	35	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [0.15, 81.11]
13.7 Adverse effects not sufficient to stop treatment	2	59	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [0.15, 81.11]
13.8 Thrombocytopenia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 13.1. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 1: Maternal death

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015 (1)	0	13	0	11		Not estimable
Total (95% CI)		**13**		**11**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

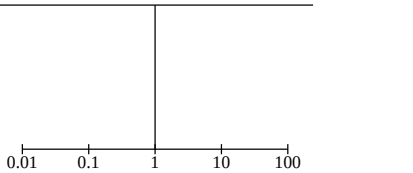


Footnotes
(1) "no… other unexpected serious adverse events related to the intervention during follow-up"

Analysis 13.2. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 2: Symptomatic thromboembolic events

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015	0	13	0	11		Not estimable
Rodger 2016	0	15	0	19		Not estimable
Total (95% CI)		**28**		**30**		**Not estimable**
Total events:	0		0			

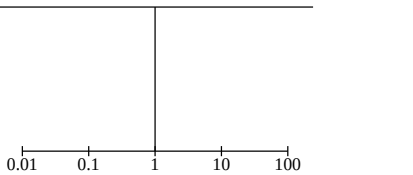
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 3: Symptomatic pulmonary embolism

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015	0	13	0	11		Not estimable
Rodger 2016	0	15	0	19		Not estimable
Total (95% CI)		**28**		**30**		**Not estimable**
Total events:	0		0			

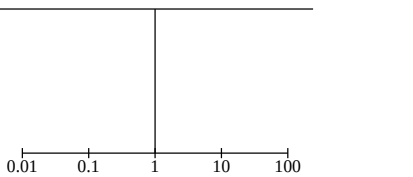
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 13.4. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 4: Symptomatic deep vein thrombosis

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015	0	13	0	11		Not estimable
Rodger 2016	0	15	0	19		Not estimable
Total (95% CI)		**28**		**30**		**Not estimable**
Total events:	0		0			

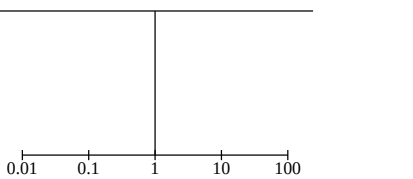
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 13.5. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 5: Asymptomatic thromboembolic events

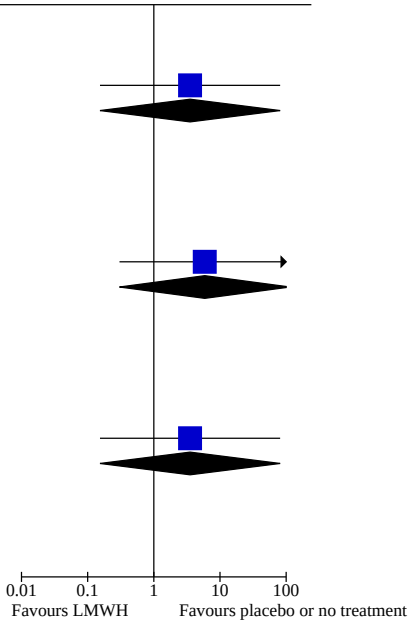
Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015	0	13	0	11		Not estimable
Rodger 2016	0	15	0	19		Not estimable
Total (95% CI)		**28**		**30**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 13.6. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 6: Bleeding episodes

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.6.1 Major bleeding event						
Rodger 2015 (1)	0	13	0	11		Not estimable
Rodger 2016 (2)	1	16	0	19	100.0%	3.53 [0.15 , 81.11]
Subtotal (95% CI)		**29**		**30**	**100.0%**	**3.53 [0.15 , 81.11]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
13.6.2 Clinically relevant bleeding event						
Rodger 2016	2	16	0	19	100.0%	5.88 [0.30 , 114.28]
Subtotal (95% CI)		**16**		**19**	**100.0%**	**5.88 [0.30 , 114.28]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
13.6.3 Minor bleeding event						
Rodger 2016	1	16	0	19	100.0%	3.53 [0.15 , 81.11]
Subtotal (95% CI)		**16**		**19**	**100.0%**	**3.53 [0.15 , 81.11]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						



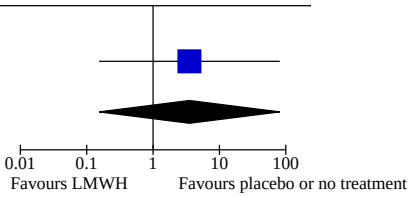
Footnotes

(1) "major bleeding events"

(2) "(>4 g/dl drop in haemoglobin with excessive vaginal blood loss in the early postpartum period)"

Analysis 13.7. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 7: Adverse effects not sufficient to stop treatment

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015 (1)	0	13	0	11		Not estimable
Rodger 2016 (2)	1	16	0	19	100.0%	3.53 [0.15 , 81.11]
Total (95% CI)		**29**		**30**	**100.0%**	**3.53 [0.15 , 81.11]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Not applicable						



Footnotes

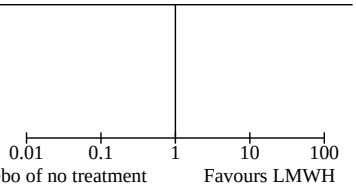
(1) "other unexpected serious adverse events related to the intervention during follow-up"

(2) "one related and unexpected serious adverse event (hospitalization for a clinically relevant non-major bleeding event (wound dehiscence with wound hematoma on post-partum

Analysis 13.8. Comparison 13: Postnatal prophylaxis: LMWH versus no treatment/placebo, Outcome 8: Thrombocytopenia

Study or Subgroup	LMWH Events	LMWH Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodger 2015	0	13	0	11		Not estimable
Total (95% CI)		**13**		**11**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



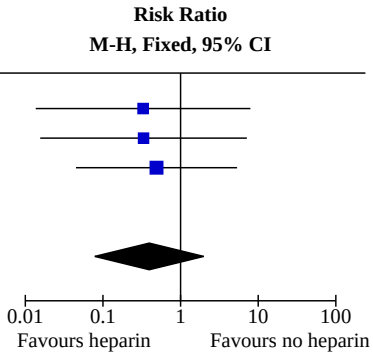
Comparison 14. Sensitivity analysis: antenatal (± postnatal) prophylaxis with heparin versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Symptomatic thromboembolic events	4	476	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.98]
14.2 Symptomatic pulmonary embolism	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
14.3 Symptomatic deep vein thrombosis	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.93]

Analysis 14.1. Comparison 14: Sensitivity analysis: antenatal (± postnatal) prophylaxis with heparin versus no treatment/placebo, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Vries 2012	0	70	1	69	30.0%	0.33 [0.01 , 7.93]
Gates 2004a	0	8	1	8	29.8%	0.33 [0.02 , 7.14]
Rodger 2014	1	146	2	143	40.2%	0.49 [0.04 , 5.34]
van Hoorn 2016	0	16	0	16		Not estimable
Total (95% CI)		**240**		**236**	**100.0%**	**0.39 [0.08 , 1.98]**
Total events:	1		4			

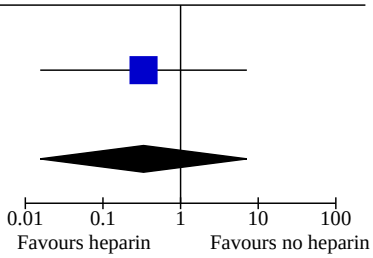
Heterogeneity: $Chi^2 = 0.06$, df = 2 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 14.2. Comparison 14: Sensitivity analysis: antenatal (± postnatal) prophylaxis with heparin versus no treatment/placebo, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Vries 2012	0	70	0	69		Not estimable
Gates 2004a	0	8	1	8	100.0%	0.33 [0.02 , 7.14]
van Hoorn 2016	0	16	0	16		Not estimable
Total (95% CI)		**94**		**93**	**100.0%**	**0.33 [0.02 , 7.14]**
Total events:	0		1			

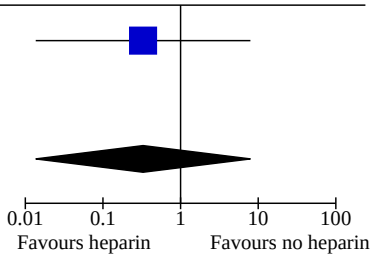
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 14.3. Comparison 14: Sensitivity analysis: antenatal (± postnatal) prophylaxis with heparin versus no treatment/placebo, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Vries 2012	0	70	1	69	100.0%	0.33 [0.01 , 7.93]
Gates 2004a	0	8	0	8		Not estimable
van Hoorn 2016	0	16	0	16		Not estimable
Total (95% CI)		**94**		**93**	**100.0%**	**0.33 [0.01 , 7.93]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



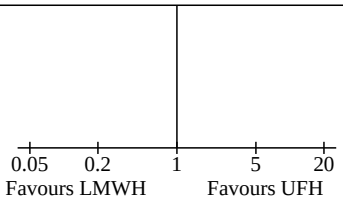
Comparison 15. Sensitivity analysis: antenatal (± postnatal) prophylaxis with LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Symptomatic thromboembolic events	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 Symptomatic pulmonary embolism	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 Symptomatic deep vein thrombosis	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 15.1. Comparison 15: Sensitivity analysis: antenatal (± postnatal) prophylaxis with LMWH versus UFH, Outcome 1: Symptomatic thromboembolic events

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pettila 1999	0	50	0	55		Not estimable
Total (95% CI)		**50**		**55**		**Not estimable**
Total events:	0		0			

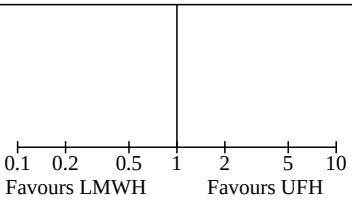
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 15.2. Comparison 15: Sensitivity analysis: antenatal (± postnatal) prophylaxis with LMWH versus UFH, Outcome 2: Symptomatic pulmonary embolism

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pettila 1999	0	50	0	55		Not estimable
Total (95% CI)		**50**		**55**		**Not estimable**
Total events:	0		0			

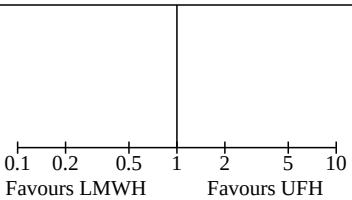
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 15.3. Comparison 15: Sensitivity analysis: antenatal (± postnatal) prophylaxis with LMWH versus UFH, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pettila 1999	0	50	0	55		Not estimable
Total (95% CI)		**50**		**55**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



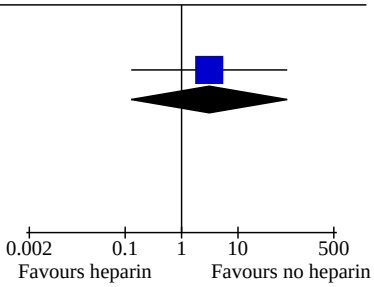
Comparison 16. Sensitivity analysis: peripartum/postnatal prophylaxis (caesarean) with LMWH versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Symptomatic thromboembolic events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1.1 LMWH	1	134	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Symptomatic pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.2.1 LMWH	1	134	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.51]
16.3 Symptomatic deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.3.1 LMWH	1	134	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

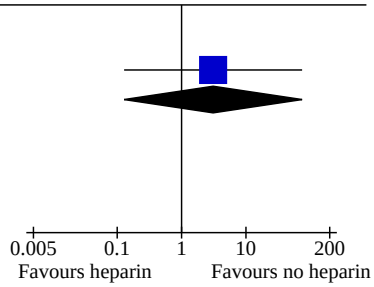
Analysis 16.1. Comparison 16: Sensitivity analysis: peripartum/postnatal prophylaxis (caesarean) with LMWH versus no treatment/placebo, Outcome 1: Symptomatic thromboembolic events

	Heparin		No heparin			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.1.1 LMWH							
Gates 2004b	1	66	0	68	100.0%	3.09 [0.13 , 74.51]	
Subtotal (95% CI)		**66**		**68**	**100.0%**	**3.09 [0.13 , 74.51]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: Not applicable							



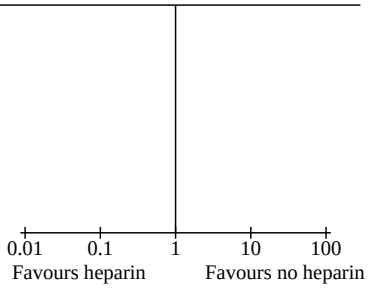
Analysis 16.2. Comparison 16: Sensitivity analysis: peripartum/postnatal prophylaxis (caesarean) with LMWH versus no treatment/placebo, Outcome 2: Symptomatic pulmonary embolism

	Heparin		No heparin			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
16.2.1 LMWH							
Gates 2004b	1	66	0	68	100.0%	3.09 [0.13 , 74.51]	
Subtotal (95% CI)		**66**		**68**	**100.0%**	**3.09 [0.13 , 74.51]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: Not applicable							



Analysis 16.3. Comparison 16: Sensitivity analysis: peripartum/postnatal prophylaxis (caesarean) with LMWH versus no treatment/placebo, Outcome 3: Symptomatic deep vein thrombosis

Study or Subgroup	Heparin Events	Heparin Total	No heparin Events	No heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
16.3.1 LMWH						
Gates 2004b	0	66	0	68		Not estimable
Subtotal (95% CI)		**66**		**68**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Interventions and studies in each comparison

Antenatal (± postnatal) **prophylaxis** (n = 11 RCTs)
Comparison 1 - Heparin (LMWH or UFH) versus no treatment or placebo
de Vries 2012; Gates 2004a; Howell 1983; Rodger 2014; van Hoorn 2016
Comparison 2 - LMWH versus UFH
Casele 2006; De Veciana 2001; Hamersley 1998; Pettila 1999
Comparison 3 - Adjusted- versus fixed-dose LMWH
Salim 2016
Comparison 4 - Compression stockings versus none
Heller 2016
Peripartum/postnatal **prophylaxis** (n = 14 RCTs)
Vaginal birth or caesarean
Comparison 5 - UFH versus no heparin treatment
Segal 1975
Caesarean
Comparison 6 - Heparin (LMWH or UFH) versus no treatment or placebo
Algahtani 2015; Burrows 2001; Gates 2004b; Hill 1988; Welti 1981
Comparison 7 - HES versus UFH
Heilmann 1991
Comparison 8 - LMWH versus UFH

Table 1. Interventions and studies in each comparison *(Continued)*

Gibson 1998*; Heilmann 2007*; Krauss 1994
Comparison 9 - 5-day versus 10-day LMWH
Cruz 2011
Comparison 10 - Weight-based versus fixed-dose LMWH
Stephenson 2016
Comparison 11 - LMWH versus LMWH (different types)
Ellison 2001*
Comparison 12 - Compression devices versus bed rest
Reddick 2014
Postnatal prophylaxis (n = 2 RCTs)
Comparison 13 - LMWH versus no treatment or placebo
Rodger 2015; Rodger 2016

*Trial had three arms. Ellison 2001 assessed three different types of heparin, and we included all three groups in the review analysis as pair-wise comparisons; Gibson 1998 included two separate LMWH groups and an UFH group, and for this trial we combined the two LMWH groups in the review meta-analysis. Heilmann 2007 included two randomised treatment groups, and a non-randomised control (no treatment group), so for this trial we included only the two treatment groups.
Two additional studies are included in the review (Cornette 2002; O'Riordan 2008), both of which assessed intrapartum (+ postnatal) prophylaxis (pharmacologic), although are not included in the review comparisons as they contributed no outcomes for analysis.
Abbreviations: **RCT**: randomised controlled trial; **LMWH**: low molecular weight heparin; **UF**: unfractionated heparin

Table 2. Participant characteristics

Study	Personal history of VTE (all/none/mixed NR)	Known acquired or inherited thrombophilia (all/none/mixed/NR)	Obesity (BMI ≥ 30 kg/m^2) (all/none/mixed/NR)	Advanced age (e.g. ≥ 35 years) (all/none/mixed/NR)	Pre-eclampsia (all/none/mixed/NR)	If post caesarean prophylaxis (emergency/elective/mixed/NR)
Algahtani 2015	None	None	None	None	None	Mixed
Burrows 2001	None	NR (though "Need of therapy with an anticoagulant" was listed as an exclusion)	Mixed	Mixed	Mixed	Mixed
Casele 2006	NR (only reports that "Any patient who was a candidate for low-dose thromboprophylaxis" were included)	NR (see left)	NR	Mixed	NR	NA

Table 2. Participant characteristics *(Continued)*

Cornette 2002*	NR	None (women with known coagulation or bleeding disorders were excluded)	NR	NR	None (based on discussion, and apparent exclusion of women with pre-eclampsia)	Elective
Cruz 2011	NR (only reports that "women... who had not required prophylaxis or treatment with any type of LMWH during pregnancy (low risk of VTE during pregnancy)" were included)	NR (see left)	Mixed	Mixed	Mixed (based on baseline characteristics reported - only reported pregnancy-induced hypertension)	Mixed
De Veciana 2001	Mixed	Mixed	Mixed	NR	NR	NA
de Vries 2012	None	All	Mixed	Mixed	None	NA
Ellison 2001	NR	NR	Mixed	Mixed	Mixed	Mixed
Gates 2004a	All	Mixed	NR/mixed (only reports booking weight ≥ 80 kg)	Mixed	NR	NA
Gates 2004b	None	Mixed	NR/mixed (only reports booking weight ≥ 80 kg)	Mixed	Mixed	Mixed
Gibson 1998	NR (women "undergoing caesarean section were recruited to the study if this procedure was performed as an emergency... or if they had 1 or more of the other defined risk factors for thromboembolic disease"; "Additional risk factors include advanced maternal age, high parity, obesity, pre-eclampsia and prolonged bed rest before delivery"; however, no baseline characteristics detailed).	NR	NR (see left)	NR (see left)	NR (see left)	Mixed
Hamersley 1998	NR	All	NR	NR	NR	NA
Heilmann 1991	Mixed (1 woman in HES group)	NR	Mixed	Mixed	NR	NR
Heilmann 2007	NR	All	NR/mixed/none (1 woman in LMWH group had	Mixed	NR	Elective

Table 2. Participant characteristics *(Continued)*

			BMI > 26 kg/m^2)			
Heller 2016	NR	NR	Mixed	Mixed	NR	NA
Hill 1988	None	None (women with coagulation disorders were excluded)	NR	NR	NR/none (women with pregnancy-induced hypertension were excluded)	Elective
Howell 1983	All	NR	NR	Mixed	NR	NA
Krauss 1994	NR	NR	NR	Mixed	NR	NR
O'Riordan 2008*	NR	NR	NR	NR	NR	NR
Pettila 1999	Mixed	Mixed	Mixed	Mixed	NR/none? (reported as an outcome)	NA
Reddick 2014	None	None	Mixed	Mixed	None	Elective
Rodger 2014	Mixed	All	Mixed	Mixed	NR/none? (reported as an outcome)	NA
Rodger 2015	NR	Mixed	Mixed	NR	Mixed	Mixed (vaginal births also included)
Rodger 2016	NR	Mixed	Mixed	NR	Mixed	Mixed
Salim 2016	Mixed	All	Mixed	Mixed	None	NA
Segal 1975	Mixed	NR	NR	NR	NR	Mixed (vaginal births also included)
Stephenson 2016	None	NR	All	Mixed	Mixed	Mixed
van Hoorn 2016	None	All	Mixed	Mixed	Mixed	NA
Welti 1981	NR	NR	NR	Mixed	NR	Mixed

Abbreviations: **BMI**: body mass index;**HES**: hydroxyethyl starch; **LMWH:** low molecular weight heparin; **NR**: not reported; **NA**: not applicable; **VTE**: venous thromboembolism
*No outcomes included in the review analyses.

APPENDICES

Appendix 1. Search methods for ICTRP and ClinicalTrials.gov

thromboembolism AND pregnan*

thromboembolism AND postpartum

thromboembolism AND c(a)eserean

thromboembolic AND pregnan*

thromboembolic AND postpartum

thromboembolic AND c(a)eserean

anticoagulant AND pregnan*

anticoagulant AND postpartum

anticoagulant AND c(a)esarean

DVT AND pregnan*

DVT AND postpartum

DVT AND c(a)esarean

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

Date	Event	Description
18 October 2019	New search has been performed	Search updated and 10 new trials included. We have updated the methods in line with the standard methods used by Cochrane Pregnancy and Childbirth, including the use of GRADE to assess the certainty of the body of evidence. We updated the search on 18th February 2021 and identified 10 trial reports. Two of these are additional reports of an ongoing study (NCT01828697), one is an additional report of Gris 2011, and six trials (seven reports) are awaiting further classification to be assessed at the next update (Abdolvand 2019; Ganer 2020; Movahedi 2020; NCT02856295; NCT04305756; NCT04635839).
18 October 2019	New citation required but conclusions have not changed	No changes to conclusions.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 2, 2002

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.
26 June 2009	New search has been performed	Search updated. Data from seven new trials have been included (Casele 2006; Gates 2004b; Gates 2004a; 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.

Date	Event	Description
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

For this updated review, Judith Gomersall (JG) and Emily Shepherd (ES) applied the selection criteria, extracted data for included studies, assessed risk of bias, carried out GRADE assessments and prepared SoF tables. All three authors (Philippa Middleton, JG and ES) contributed to the drafting and editing of this update.

DECLARATIONS OF INTEREST

Judith Gomersall: none known.

Philippa Middleton: none known.

Emily Shepherd: none known.

SOURCES OF SUPPORT

Internal sources

- SAHMRI Women and Kids, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2020 update of this review

- We have updated the methods in line with those in the standard template used by Cochrane Pregnancy and Childbirth.
- We have used the GRADE approach to assess the certainty of the body of evidence and we have included 'Summary of findings' tables.
- We have added in an additional search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).
- We previously excluded trials specifically focused on the role of heparin for pregnant women with known thrombophilias to prevent adverse pregnancy outcomes, as this was the focus of a related Cochrane Review (Walker 2003); however, in this update we have removed known thrombophilias from our exclusion criteria, as the relevant review has not since been updated.

2014 update of this review

- We updated the background and the methods section, including 'Risk of bias' assessment.
- We clarified that we would include studies reported only as abstracts in analyses where it was possible to extract relevant data from the text.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [therapeutic use]; Bias; Cesarean Section; Heparin [therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Pregnancy Complications, Hematologic [*prevention & control]; Puerperal Disorders [*prevention & control]; Randomized Controlled Trials as Topic; Venous Thrombosis [*prevention & control]

MeSH check words

Female; Humans; Pregnancy