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Techniques for preventing hypotension during spinal anaesthesia for caesarean section (Review)

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[Intervention Review]

Techniques for preventing hypotension during spinal anaesthesia for caesarean section

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ABSTRACT

Background

Maternal hypotension is the most frequent complication of spinal anaesthesia for caesarean section. It can be associated with nausea or vomiting and may pose serious risks to the mother (unconsciousness, pulmonary aspiration) and baby (hypoxia, acidosis, neurological injury).

Objectives

To assess the effects of prophylactic interventions for hypotension following spinal anaesthesia for caesarean section.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (9 August 2016) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials, including full texts and abstracts, comparing interventions to prevent hypotension with placebo or alternative treatment in women having spinal anaesthesia for caesarean section. We excluded studies if hypotension was not an outcome measure.

Data collection and analysis

Two review authors independently assessed study quality and extracted data from eligible studies. We report 'Summary of findings' tables using GRADE.

Main results

We included 125 studies involving 9469 women. Interventions were to prevent maternal hypotension following spinal anaesthesia only, and we excluded any interventions considered active treatment. All the included studies reported the review's primary outcome. Across 49 comparisons, we identified three intervention groups: intravenous fluids, pharmacological interventions, and physical interventions. Authors reported no serious adverse effects with any of the interventions investigated. Most trials reported hypotension requiring intervention and Apgar score of less than 8 at five minutes as the only outcomes. None of the trials included in the comparisons we describe reported admission to neonatal intensive care unit.

Crystalloid versus control (no fluids)

Fewer women experienced hypotension in the crystalloid group compared with no fluids (average risk ratio (RR) 0.84, 95% confidence interval (CI) 0.72 to 0.98; 370 women; 5 studies; *low-quality evidence*). There was no clear difference between groups in numbers of women with nausea and vomiting (average RR 0.19, 95% CI 0.01 to 3.91; 1 study; 69 women; *very low-quality evidence*). No baby had an Apgar score of less than 8 at five minutes in either group (60 babies, *low-quality evidence*).

Colloid versus crystalloid

Fewer women experienced hypotension in the colloid group compared with the crystalloid group (average RR 0.69, 95% CI 0.58 to 0.81; 2009 women; 27 studies; *very low-quality evidence*). There were no clear differences between groups for maternal hypertension requiring intervention (average RR 0.64, 95% CI 0.09 to 4.46, 3 studies, 327 women; *very low-quality evidence*), maternal bradycardia requiring intervention (average RR 0.98, 95% CI 0.54 to 1.78, 5 studies, 413 women; *very low-quality evidence*), nausea and/or vomiting (average RR 0.89, 95% CI 0.66 to 1.19, 14 studies, 1058 women, I^2 = 29%; *very low-quality evidence*), neonatal acidosis (average RR 0.83, 95% CI 0.15 to 4.52, 6 studies, 678 babies; *very low-quality evidence*), or Apgar score of less than 8 at five minutes (average RR 0.24, 95% CI 0.03 to 2.05, 10 studies, 730 babies; *very low-quality evidence*).

Ephedrine versus phenylephrine

There were no clear differences between ephedrine and phenylephrine groups for preventing maternal hypotension (average RR 0.92, 95% CI 0.71 to 1.18; 401 women; 8 studies; *very low-quality evidence*) or hypertension (average RR 1.72, 95% CI 0.71 to 4.16, 2 studies, 118 women, *low-quality evidence*). Rates of bradycardia were lower in the ephedrine group (average RR 0.37, 95% CI 0.21 to 0.64, 5 studies, 304 women, *low-quality evidence*). There was no clear difference in the number of women with nausea and/or vomiting (average RR 0.76, 95% CI 0.39 to 1.49, 4 studies, 204 women, I^2 = 37%, *very low-quality evidence*), or babies with neonatal acidosis (average RR 0.89, 95% CI 0.07 to 12.00, 3 studies, 175 babies, *low-quality evidence*). No baby had an Apgar score of less than 8 at five minutes in either group (321 babies; *low-quality evidence*).

Ondansetron versus control

Ondansetron administration was more effective than control (placebo saline) for preventing hypotension requiring treatment (average RR 0.67, 95% CI 0.54 to 0.83; 740 women, 8 studies, *low-quality evidence*), bradycardia requiring treatment (average RR 0.49, 95% CI 0.28 to 0.87; 740 women, 8 studies, *low-quality evidence*), and nausea and/or vomiting (average RR 0.35, 95% CI 0.24 to 0.51; 653 women, 7 studies, *low-quality evidence*). There was no clear difference between the groups in rates of neonatal acidosis (average RR 0.48, 95% CI 0.05 to 5.09; 134 babies; 2 studies, *low-quality evidence*) or Apgar scores of less than 8 at five minutes (284 babies, *low-quality evidence*).

Lower limb compression versus control

Lower limb compression was more effective than control for preventing hypotension (average RR 0.61, 95% CI 0.47 to 0.78, 11 studies, 705 women, I^2 = 65%, *very low-quality evidence).* There was no clear difference between the groups in rates of bradycardia (RR 0.63, 95% CI 0.11 to 3.56, 1 study, 74 women, *very low-quality evidence*) or nausea and/or vomiting (average RR 0.42, 95% CI 0.14 to 1.27, 4 studies, 276 women, I^2 = 32%, *very-low quality evidence*). No baby had an Apgar score of less than 8 at five minutes in either group (130 babies, *very low-quality evidence*).

Walking versus lying

There was no clear difference between the groups for women with hypotension requiring treatment (RR 0.71, 95% CI 0.41 to 1.21, 1 study, 37 women, *very low-quality evidence*).

Many included studies reported little to no information that would allow an assessment of their risk of bias, limiting our ability to draw meaningful conclusions. GRADE assessments of the quality of evidence ranged from very low to low. We downgraded evidence for limitations in study design, imprecision, and indirectness; most studies assessed only women scheduled for elective caesarean sections.

External validity also needs consideration. Readers should question the use of colloids in this context given the serious potential side effects such as allergy and renal failure associated with their administration.

Authors' conclusions

While interventions such as crystalloids, colloids, ephedrine, phenylephrine, ondansetron, or lower leg compression can reduce the incidence of hypotension, none have been shown to eliminate the need to treat maternal hypotension in some women. We cannot draw any conclusions regarding rare adverse effects associated with use of the interventions (for example colloids) due to the relatively small numbers of women studied.

PLAIN LANGUAGE SUMMARY

Techniques for preventing a decrease in blood pressure during spinal anaesthesia for caesarean section

What is the issue?

Spinal anaesthesia is a commonly used technique for caesarean birth as the mother is able to be awake for the birth and usually remains comfortable afterwards. In addition, the technique avoids the risks of general anaesthesia. The most common adverse effect of spinal anaesthesia is a fall in blood pressure (hypotension).

This study reviews the evidence for preventing hypotension following spinal anaesthesia for caesarean birth.

Why is this important?

Hypotension following spinal anaesthesia for caesarean birth occurs frequently. When it occurs, the mother may feel faint or nauseous and may vomit. If her blood pressure falls excessively, the mother runs serious risks (such as loss of consciousness), as does the baby (such as lack of oxygen and brain damage). Hypotension may be prevented by administering intravenous fluids, giving medications (such as ephedrine, phenylephrine, and ondansetron), by leg compression, or by the mother either lying down or walking around before the spinal anaesthesia.

What evidence did we find?

We searched the evidence in August 2016 and found a total of 125 studies involving 9469 women. Included studies investigated 49 different comparisons, which we split into three groups: intravenous fluid therapy, medications, and physical methods. Here we describe the results of the six main comparisons (crystalloid versus control; colloid versus crystalloid; ephedrine versus phenylephrine; ondansetron versus control; leg compression versus control; walking versus lying).

Fluid therapy (crystalloid versus control; colloid versus crystalloid)

It is uncertain whether crystalloids prevent hypotension because the quality of the evidence is very low. Giving colloids instead of crystalloids may mean that fewer women have low blood pressure after having spinal anaesthesia.

We cannot be certain due to the very low quality evidence whether crystalloid or colloid are better at preventing maternal low heart rate (bradycardia), high blood pressure, nausea and vomiting, neonatal acidosis, or low Apgar scores. Whether women received crystalloids or no fluids did not affect the number of women who experienced nausea and/or vomiting.

Medications (ephedrine versus phenylephrine; ondansetron versus control)

Lower rates of bradycardia occurred in women receiving ephedrine versus phenylephrine, and with ondansetron versus no ondansetron, but the evidence is low quality. Ondansetron may prevent low blood pressure and nausea/vomiting but made little or no difference to neonatal acidosis or Apgar scores. There was little difference between ephedrine and phenylephrine for low or high blood pressure, nausea and vomiting, neonatal acidosis, or Apgar scores. We cannot be certain of these results due to the low or very low quality of the evidence.

Physical methods (leg compression versus control; walking versus lying)

It is uncertain whether leg compression reduces the number of women with hypotension compared with no leg compression because the quality of evidence is very low. Similarly, we cannot be certain whether leg compression made any difference to women experiencing bradycardia or nausea and vomiting, or to babies' Apgar scores. It is also uncertain whether walking or lying down before the spinal anaesthesia reduces low blood pressure.

What does this mean?

We found that no single method completely prevents hypotension in women receiving spinal anaesthesia during caesarean birth. Administering intravenous fluids or certain medications, and compressing the legs with bandages, stockings, or inflatable devices may reduce the incidence of hypotension. However, we found the quality of the evidence to be low or very low, so there is still a need for large, high-quality studies using these clinically relevant interventions, either alone or in combination.

Future research in this setting could focus on combinations of these effective strategies or on new innovative strategies.

SUMMARY OF FINDINGS

Summary of findings 1. Techniques for preventing hypotension during spinal anaesthesia for caesarean section: key interventions for the primary outcome (women with hypotension requiring intervention)

Techniques for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section

Setting: hospital (inpatient)

Outcome: maternal hypotension requiring intervention

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with Intervention			
Crystalloid vs control	**Control**	**Crystalloid**	average RR 0.84 (0.72 to 0.98)	370 (5 RCTs)	⊕⊕⊖⊖ Low[a,b]
	535 per 1000	449 per 1000 (385 to 524)			
Colloid vs crystalloid	**Crystalloid**	**Colloid**	average RR 0.68 (0.58 to 0.80)	2105 (28 RCTs)	⊕⊖⊖⊖ Very low[a,c,d]
	586 per 1000	398 per 1000 (340 to 468)			
Ephedrine vs phenylephrine	**Phenylephrine**	**Ephedrine**	average RR 0.92 (0.71 to 1.18)	401 (8 RCTs)	⊕⊖⊖⊖ Very low[a,d,e]
	465 per 1000	428 per 1000 (330 to 549)			
Ondansetron vs control	**Control**	**Ondansetron**	average RR 0.67 (0.54 to 0.83)	740 (8 RCTs)	⊕⊕⊖⊖ Low[a,f]
	579 per 1000	388 per 1000 (313 to 481)			
Lower limb compression vs control	**Control**	**Lower limb compression**	average RR 0.61 (0.47 to 0.78)	705 (11 RCTs)	⊕⊖⊖⊖ Very low[a,c,d]
	663 per 1000	404 per 1000 (312 to 517)			
Walking vs lying	**Lying**	**Walking**	RR 0.71	37	⊕⊖⊖⊖

	706 per 1000	501 per 1000 (289 to 854)	(0.41 to 1.21)	(1 RCT)	Very low[f,g]

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Inclusion criteria not representative of wider population (e.g. only elective caesarean sections) (−1).
[b]Confidence interval includes potential for benefit or no benefit from the intervention (−1).
[c]Downgraded one level for serious risk of bias (due to unclear risk of selection bias in most included studies (−1).
[d]Substantial heterogeneity (−1).
[e]Inadequate sample size (−1).
[f]Participants and anaesthetists not blinded in 1 study with 100% weight in analysis (−1).
[g]Wide CI that includes potential for benefit or no benefit from the intervention. Small sample size (−2).

Summary of findings 2. Crystalloid versus control

Crystalloid versus control for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital settings in Europe, North America, India, and the Middle East
Intervention: crystalloid
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with crystalloid			
Maternal hypotension requiring intervention	Study population		RR 0.84 (0.72 to 0.98)	370 (5 RCTs)	⊕⊕⊖⊖ Low[a,b]
	535 per 1000	449 per 1000 (385 to 524)			
Maternal hypertension requiring intervention	No studies reported this outcome.				

Maternal bradycardia requiring intervention	No studies reported this outcome.				
Maternal nausea and/or vomiting	Study population		RR 0.19 (0.01 to 3.91)	69 (1 RCT)	⊕⊖⊖⊖ Very low[a,c]
	59 per 1000	11 per 1000 (1 to 230)			
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	No studies reported this outcome.				
Neonatal Apgar score < 8 at 5 minutes	Study population		Not estimable	60 (1 RCT)	⊕⊕⊖⊖ Low[a,d]
	0 per 1000	0 per 1000 (0 to 0)			
Admission to neonatal intensive care unit	No studies reported this outcome.				

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Only elective caesarean sections included (−1).
[b]Small sample size and CI includes potential for benefit or no benefit from the intervention (−1).
[c]One study with small sample size, few events, and wide confidence intervals that cross the line of no effect (−2).
[d]No events and small sample size (−1).

Summary of findings 3. Colloid versus crystalloid

Colloid versus crystalloid for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital settings in Europe, North America, India, and the Middle East
Intervention: colloid

Comparison: crystalloid

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with crystalloid	Risk with colloid			
Maternal hypotension requiring intervention	Study population		RR 0.69 (0.58 to 0.81)	2009 (27 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]
	595 per 1000	411 per 1000 (345 to 484)			
Maternal hypertension requiring intervention	Study population		RR 0.64 (0.09 to 4.46)	327 (3 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]
	55 per 1000	35 per 1000 (5 to 246)			
Maternal bradycardia requiring intervention	Study population		RR 0.98 (0.54 to 1.78)	413 (5 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]
	87 per 1000	86 per 1000 (47 to 156)			
Maternal nausea and/or vomiting	Study population		RR 0.89 (0.66 to 1.19)	1058 (14 RCTs)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
	230 per 1000	205 per 1000 (152 to 274)			
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	Study population		RR 0.83 (0.15 to 4.52)	678 (6 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]
	26 per 1000	21 per 1000 (4 to 116)			
Neonatal Apgar score < 8 at 5 minutes	Study population		RR 0.24 (0.03 to 2.05)	730 (10 RCTs)	⊕⊖⊖⊖ Very low[c,d,e,f]
	10 per 1000	3 per 1000 (0 to 22)			
Admission to neonatal intensive care unit	No studies reported this outcome.				

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for serious risk of bias (due to unclear risk of selection bias in most included studies) (−1).
[b]Substantial heterogeneity (−1).
[c]Inclusion criteria not representative of wider population (e.g. elective caesarean section only) (−1).
[d]Wide CI (−1).
[e]Inadequate sample size (−1).
[f]Multiple studies did not report method of randomisation (−1).

Summary of findings 4. Ephedrine versus phenylephrine

Ephedrine versus phenylephrine for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital setting in Europe, North America, India, and the Middle East
Intervention: ephedrine
Comparison: phenylephrine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with phenylephrine	Risk with ephedrine				
Maternal hypotension requiring intervention	Study population		RR 0.92 (0.71 to 1.18)	401 (8 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	—
	465 per 1000	428 per 1000 (330 to 549)				
Maternal hypertension requiring intervention	Study population		RR 1.72 (0.71 to 4.16)	118 (2 RCT)	⊕⊕⊖⊖ Low[b,d]	—
	113 per 1000	194 per 1000 (80 to 470)				
Maternal bradycardia requiring intervention	Study population		RR 0.37 (0.21 to 0.64)	304 (5 RCTs)	⊕⊕⊖⊖ Low[b,c]	—
	243 per 1000	90 per 1000 (51 to 156)				

Maternal nausea and/or vomiting	Study population		RR 0.76 (0.39 to 1.49)	204 (4 RCTs)	⊕⊖⊖⊖ Very low[a,b,e]	—
	216 per 1000	164 per 1000 (84 to 321)				
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	Study population		RR 0.89 (0.07 to 12.00)	175 (3 RCTs)	⊕⊕⊖⊖ Low[b,f]	—
	11 per 1000	10 per 1000 (1 to 133)				
Neonatal Apgar score < 8 at 5 minutes	Study population		Not estimable	321 (6 RCTs)	⊕⊕⊖⊖ Low[b,c]	No events observed in any studies. Relative effect could not be estimated.
	Not pooled	Not pooled				
Admission to neonatal intensive care unit	No studies reported this outcome.					

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Substantial heterogeneity (−1).
[b]Inclusion criteria not representative of wide population (e.g. elective caesarean section only) (−1).
[c]Inadequate sample size (−1).
[d]Sample size inadequate and wide CI (−1).
[e]Wide CI (−1).
[f]CI includes potential for ephedrine to cause either increased or decreased incidence of outcome compared to phenylephrine (−1).

Summary of findings 5. Ondansetron versus control

Ondansetron versus saline placebo for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital setting in Europe, North America, India, and the Middle East
Intervention: ondansetron
Comparison: saline placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with ondansetron			
Maternal hypotension requiring intervention	Study population		RR 0.67 (0.54 to 0.83)	740 (8 RCTs)	⊕⊕⊖⊖ Low[a,b]
	579 per 1000	388 per 1000 (313 to 481)			
Maternal hypertension requiring intervention	No studies reported this outcome.				
Maternal bradycardia requiring intervention	Study population		RR 0.49 (0.28 to 0.87)	740 (8 RCTs)	⊕⊕⊖⊖ Low[a,b]
	100 per 1000	49 per 1000 (28 to 87)			
Maternal nausea and/or vomiting	Study population		RR 0.35 (0.24 to 0.51)	653 (7 RCTs)	⊕⊕⊖⊖ Low[a,b]
	296 per 1000	103 per 1000 (71 to 151)			
Neonatal Apgar score < 8 at 5 minutes	Study population		Not estimable	284 (3 RCTs)	⊕⊕⊖⊖ Low[a,b]
	Not pooled	Not pooled			
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	Study population		RR 0.48 (0.05 to 5.09)	134 (2 RCT)	⊕⊕⊖⊖ Low[a,b]
	30 per 1000	15 per 1000 (2 to 154)			
Admission to neonatal care unit	No studies reported this outcome.				

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Inclusion criteria not representative of wider population (e.g. elective caesarean section only) (−1).
[b] Inadequate sample size (−1).

Summary of findings 6. Lower limb compression versus control

Leg compression versus control for preventing hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital setting in Europe, North America, India, and the Middle East
Intervention: lower limb compression
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with lower limb compression				
Maternal hypotension requiring intervention	Study population		RR 0.61 (0.47 to 0.78)	705 (11 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	—
	663 per 1000	404 per 1000 (312 to 517)				
Maternal hypertension requiring intervention	No studies reported this outcome.					
Maternal bradycardia requiring intervention	Study population		RR 0.63 (0.11 to 3.56)	74 (1 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]	—
	83 per 1000	53 per 1000 (9 to 297)				
Maternal nausea and/or vomiting	Study population		RR 0.42 (0.14 to 1.27)	276 (4 RCTs)	⊕⊖⊖⊖ Very low[a,b,c,d]	—
	162 per 1000	68 per 1000 (23 to 205)				
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	No studies reported this outcome.					
Neonatal Apgar score < 8 at 5 minutes	Study population		Not estimable	130 (3 RCTs)	⊕⊖⊖⊖ Very low[a,c,e]	No events observed in any

	Not pooled	Not pooled		studies. Relative effect could not be estimated.
Admission to neonatal intensive care unit	No studies reported this outcome.			

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for serious risk of bias (due to unclear risk of selection bias in the majority of included studies (−1).
[b]Substantial heterogeneity (−1).
[c]Inclusion criteria not representative of wider population (e.g. elective caesarean sections only) (−1).
[d]Wide CI that includes potential benefit or no benefit from the intervention (−1).
[e]Inadequate sample size (−1).

Summary of findings 7. Walking versus lying

Walking versus lying for reducing risk of maternal hypotension during spinal anaesthesia for caesarean section

Patient or population: women having spinal anaesthesia for caesarean section
Setting: hospital setting in Australia
Intervention: walking
Comparison: lying

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with lying	Risk with walking			
Maternal hypotension requiring intervention	Study population		RR 0.71 (0.41 to 1.21)	37 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]
	706 per 1000	501 per 1000 (289 to 854)			

Maternal hypertension requiring intervention	No studies reported this outcome.
Maternal bradycardia requiring intervention	No studies reported this outcome.
Maternal nausea and/or vomiting	No studies reported this outcome.
Neonatal acidosis as defined by cord or neonatal blood with a pH < 7.2	No studies reported this outcome.
Neonal Apgar score < 8 at 5 minutes	No studies reported this outcome.
Admission to neonatal intensive care unit	No studies reported this outcome.

*__The risk in the intervention group__ (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; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Participants and anaesthetists not blinded in 1 study with 100% weight in analysis (−1).
[b]Wide CI that includes potential for benefit or no benefit from the intervention. Small sample size (−2).

BACKGROUND

The choice of anaesthesia for caesarean birth is made by balancing women's preferences with the risks and benefits of a particular technique to the mother and her baby (Glosten 2000).

Anaesthesia-related maternal mortality occurs most frequently when using general anaesthesia for caesarean delivery (Hawkins 1997; Hibbard 1996; Rasmussen 1994). Other risks of general anaesthesia include: failed endotracheal intubation, failed ventilation, aspiration pneumonitis, dental trauma, postoperative nausea and vomiting, delayed breastfeeding, and sedation of the baby (Atlee 1999; Reisner 1999). Regional techniques such as epidural or spinal anaesthesia avoid these risks, allow the mother to be awake at the baby's birth, and may reduce the need for systemic opioid administration postoperatively. Epidural analgesia during labour can be extended to provide surgical anaesthesia should caesarean section be necessary (Lucas 1999). However, a spinal anaesthetic technique has the advantage of simplicity, rapid onset, low failure rate, minimal drug dose, and excellent muscle relaxation during surgery (Glosten 2000). This frequently makes it the anaesthetic technique of choice for both elective and emergency caesarean delivery when a functioning epidural catheter is not in place. Indeed, at least 40% of women having caesarean sections in the USA receive spinal anaesthesia (Hawkins 1997), as do most women undergoing elective caesarean operations in the UK (Husaini 1998; Shibli 2000).

Spinal anaesthesia to the level of T4 is necessary to provide an adequate block for caesarean birth (Glosten 2000; Ousley 2012; Russell 1995). As a consequence, an almost inevitable complete sympathetic block occurs, and decreased venous return to the heart – exacerbated by a degree of inferior vena caval compression – results in hypotension and decreased cardiac output (Rocke 1995). Hypotension during spinal anaesthesia for elective caesarean delivery occurs in as many as 70% to 80% of women receiving pharmacological prophylaxis (Mercier 2013).

Despite all regional techniques being associated with maternal hypotension, the slower onset and lower incidence of this complication during epidural anaesthesia may make the need for prophylactic medications such as ephedrine unnecessary (Glosten 2000; May 1995). In contrast, the frequent occurrence and rapid onset of hypotension during spinal anaesthesia has encouraged anaesthetists to try and prevent or minimise the associated maternal symptoms of vomiting, nausea, and impaired consciousness during the establishment of the block. The concomitant reduction in the utero-placental blood supply associated with maternal hypotension has deleterious effects such as fetal acidosis (Roberts 1995; Robson 1992), which may result in weak rooting and sucking reflexes of infants (Hollmen 1978); these can severely compromise the establishment of breastfeeding postdelivery (May 1995).

Preventing spinal hypotension appears more likely to decrease the frequency and severity of associated adverse maternal symptoms than treating established hypotension (Datta 1982; Husaini 1998; Kang 1982). Surprisingly few pre-eclamptic women having caesarean birth under spinal anaesthesia require intervention for hypotension (Clark 2005; Sharwood-Smith 1999), so routine prophylaxis is probably unnecessary in this particular patient group. Women in established labour who subsequently undergo spinal anaesthesia seem similarly unaffected by hypotension (Lapins 2001).

Description of the condition

Maternal hypotension is the most frequent complication of spinal anaesthesia, with an incidence approaching 100% (Glosten 2000; May 1995). Untreated severe hypotension can pose serious risks to both mother (unconsciousness, pulmonary aspiration, apnoea, or even cardiac arrest) and baby (impaired placental perfusion leading to hypoxia, fetal acidosis, and neurological injury). Although there is some variation, most workers define hypotension as a maternal systolic blood pressure below 70% to 80% of baseline recordings, an absolute value of less than 90 mmHg to 100 mmHg, or both (Glosten 2000).

Description of the intervention

Clinicians currently use a range of strategies including intravenous fluids, pharmacological treatments, and physical interventions to minimise or prevent hypotension. These strategies may include proper maternal position with the uterus displaced off the vena cava, infusion of fluids to increase effective blood volume, and the administration of ephedrine to vasoconstrict the peripheral circulation and increase heart rate (Glosten 2000). Other workers have administered the alpha agonists phenylephrine or metaraminol, which act primarily by vasoconstriction (Alahuhta 1992; Morgan 1994). Physical interventions such as leg wrappings are also used and may act by minimising venous pooling of blood in the legs (Van Bogaert 1998). All these methods aim to maintain blood pressure by increasing venous return to the heart, increasing the resistance of the peripheral circulation, or both. There is, however, no established ideal technique.

How the intervention might work

Health professionals can administer intravenous fluids, including crystalloids and colloids, to increase maternal blood volume, resulting in an increase in venous return, stroke volume, and blood pressure. Intravenous fluid administration prior to spinal anaesthesia for caesarean birth is accepted standard practice (Rout 1993b). The choice of fluid depends on individual and institutional habit, material cost (crystalloid is considerably cheaper), and the perceived relative benefits and risks. Uncommon but potentially serious adverse effects of colloids include anaphylactoid reactions (MIMS 1995), impaired coagulation (Sharma 1999), and the risk of infection such as hepatitis C from human albumin preparations. In addition, some authors have raised concerns regarding prior transmission of bovine spongiform encephalopathy from bovine-derived pharmaceuticals such as the gelatin Haemaccel (Wickham 1996).

Vasopressors, such as the alpha-agonist phenylephrine, cause peripheral vasoconstriction and an increase in systemic vascular resistance. This subsequently results in an increase in blood pressure. Combined alpha and beta-agonists, such as ephedrine, may also prevent hypotension by increasing both heart rate and systemic vascular resistance. Furthermore, anti-muscarinic agents, such as glycopyrrolate, may be useful to increase heart rate, resulting in a subsequent increase in blood pressure. Possible adverse effects of vasopressors include anaphylaxis, hypertension, and cardiac dysrhythmias (MIMS 1995). Furthermore, there is the potential for impaired utero-placental perfusion secondary to vasoconstriction (despite maintenance or restoration of maternal

blood pressure) with fetal or neonatal consequences as described above.

Physical interventions, such as leg wrapping and calf compression devices, may be helpful in improving venous return and therefore can improve blood pressure. However, these techniques may also have unintentional effects such as localised ischaemia, nerve injury, or unacceptable maternal discomfort.

Why it is important to do this review

Most women will experience hypotension after spinal anaesthesia for caesarean section if they do not receive a preventive intervention. There is no single widely accepted and evidence-based ideal intervention to prevent maternal hypotension associated with spinal anaesthesia.

OBJECTIVES

To assess the effects of prophylactic interventions for hypotension following spinal anaesthesia for caesarean section.

METHODS

Criteria for considering studies for this review

Types of studies

All published or unpublished randomised controlled trials that compare an intervention to prevent hypotension with placebo or alternative treatment in women having spinal anaesthesia for caesarean section. We did not include quasi-randomised, cluster or cross-over trials in this review update, in a departure from the protocol of the original version. We included abstracts if they reported sufficient information to enable an adequate assessment of methodology and risk of bias.

We excluded studies if hypotension was not an outcome measure or was not clearly defined prior to administering a rescue treatment.

Types of participants

Women having spinal anaesthesia for caesarean section.

Types of interventions

Intravenous fluids

- Colloids
- Crystalloids

Drugs

- Sympathomimetics: ephedrine, metaraminol, phenylephrine
- Other medications used to prevent hypotension, for example, ondansetron

Physical methods

- Leg bindings
- Compression stockings
- Other manoeuvres

We did not make comparisons between different anaesthetic techniques since this review question is concerned with preventive techniques in the context of standardised anaesthetic methods.

We excluded studies in which women received combined spinal-epidural anaesthesia or epidural anaesthesia.

Types of outcome measures

Primary outcomes

The incidence of maternal hypotension requiring pharmacological intervention (after intrathecal injection and prior to delivery), where hypotension was a certain decrease in systolic or mean blood pressure, as defined and measured by the authors of included studies (Table 1).

We excluded studies if hypotension was not an outcome measure or was not clearly defined prior to administering a rescue treatment.

Secondary outcomes

We considered any maternal or neonatal outcome that could reflect a consequence of the intervention.

Maternal

1. Hypertension requiring intervention
2. Cardiac dysrhythmia defined as any rhythm requiring intervention (e.g. bradycardia, tachycardia)
3. Nausea, vomiting
4. Anaphylaxis
5. Impaired consciousness, dizziness

Neonatal

1. Acidosis as defined by cord or neonatal bloods with a pH of less than 7.2
2. Apgar scores of less than 7 or 8 at five minutes
3. Admission to neonatal intensive care unit

The included studies rarely reported these secondary outcomes.

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

We searched Cochrane Pregnancy and Childbirth Trials Register by contacting their information specialist (9 August 2016).

The register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full 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 the link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the 'Specialized Register' section from the options on the left side of the screen.

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);

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.

Two people screen search results, and the full text or abstract (where full text was unavailable) of all relevant trial reports identified 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 which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

Searching other resources

We also retrieved additional relevant references referred to in the reviewed papers to see if they met the criteria for inclusion in this review.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Cyna 2006.

For this update, we used the following methods for assessing the reports identified during the updated search.

Selection of studies

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

We excluded studies for the following reasons.

- Hypotension was not an outcome measure or was not clearly defined prior to administering a rescue treatment.
- The study did not explicitly report incidence of hypotension.
- The report did not mention randomisation.
- Randomisation is clearly unsatisfactory.
- The spinal anaesthetic technique or dose of local anaesthetic is compared, or varies between participants, and is therefore not controlled.
- The studies investigated combined spinal-epidural anaesthetic technique.
- The studied intervention is implemented in response to a fall in blood pressure rather than for prevention (for the purposes of this specific update, review authors felt that the use of automated infusion devices responding to a perceived drop in blood pressure fell into this category, so we excluded these).

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, consulted a third person. We entered data into Review Manager 5 software (RevMan 5) and checked for accuracy (RevMan 2014).

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

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

Random sequence generation (checking for possible selection bias)

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

We assessed the method as being at:

- 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.

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 being at:

- 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.

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

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

We assessed the methods as being at:

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

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 being at low, high, or unclear risk of bias.

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether studies reported attrition and exclusions, 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 trial authors reported or could supply sufficient information, we re-included missing data in the analyses. We assessed methods as being at:

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

Selective reporting bias

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

We assessed the methods as being at:

- low risk of bias (where it is clear that authors reported all of the study's pre-specified outcomes and all expected outcomes of interest to the review);
- high risk of bias (where authors did not report all the study's pre-specified outcomes; did not pre-specify one or more reported primary outcomes; incompletely reported outcomes of interest, rendering them unusable; or failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias. This may have included concerns regarding specific study design or extreme baseline characteristic imbalance between study groups.

We assessed whether each study was free of other problems that could put it at risk of bias, assessing this domain as being at:

- low risk of other bias;
- high risk of other bias;
- unclear risk of other bias.

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias according to the criteria given in Higgins 2011. With reference to random sequence generation and other sources of bias, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses – see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented the results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

This update does not include any continuous data. In future updates, if appropriate, we will use the mean difference for continuous data if trials measure outcomes in the same way. We will use the standardised mean difference to combine trials that measure the same outcome but use different methods.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials were not eligible for inclusion in this review.

Cross-over trials

Cross-over trials were not were not eligible for inclusion in this review.

Trials with more than two treatment groups

We describe all intervention groups for multi-intervention studies in the Characteristics of included studies table. Depending on the comparisons investigated in the study, we used the methods for data analysis as detailed in section 16.5.4 of Higgins 2011. We combined groups to create a single pair-wise comparison, or we split the 'shared' or control group into two or more groups with smaller sample size and included two or more (reasonably independent) comparisons.

Dealing with missing data

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

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses, and we analysed all participants 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.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics and used a random-effects model throughout to account for heterogeneity resulting from the relatively small number of participants in each study (less than 200 participants).

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If a visual assessment suggested asymmetry, we discussed possible reasons for this. We only performed this analysis for the primary outcome.

Data synthesis

We carried out statistical analysis using RevMan 2014. We planned to use fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect, that is, where trials examined the same intervention and used sufficiently similar trial populations and methods. However, due to the small number of participants in trials contributing data, we used a random-effects model throughout this review. We treated the random-effects summary as the average range of possible treatment effects, and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

For the random-effects analyses, we presented the results as the average treatment effect with its 95% CI along with the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

In exploring heterogeneity when a comparison with three or more trials had an I^2 of more than 40%, we originally planned to investigate this using subgroup analyses and sensitivity analyses. Due to the small number of participants in each trial, we opted to use random-effects analysis.

We carried out the following subgroup analyses where possible.

1. Doses or volume of the intervention given.
2. Fluid preloading or coloading in addition to the intervention.

We used the outcome of maternal hypotension requiring intervention in subgroup analysis.

We assessed subgroup differences by interaction tests available within RevMan 2014. We reported the results of subgroup analyses, quoting the Chi^2 statistic and P value, plus the interaction test I^2 value. We did not perform subgroup analysis where we thought the different regimens or types of the interventions meant that subgroup analysis would not be appropriate or helpful (Analysis 7.1; Analysis 8.1; Analysis 12.1; Analysis 24.1; Analysis 37.1). Instead, we explored the different regimens in separate comparisons.

Sensitivity analysis

We performed sensitivity analyses by removing studies in which one or more factors indicated a higher risk of bias than in the rest of studies. We assessed only 2 trials as being at high risk of bias in two or more domains (Calvache 2011; Sutherland 2001), while another 15 were at high risk of bias in one domain (Bhagwanjee 1990; Bottiger 2010; Cardoso 2004a; Carvalho 2009; Cyna 2010; Dahlgren 2005; Dyer 2004; Eldaba 2015; Gulhas 2012; Magalhaes 2009; Mercier 2014; Muzlifah 2009; Pouliou 2006; Romdhani 2014; Ueyama 1999).

Summary of findings tables

For this update, we assessed the quality of the body of evidence using the GRADE approach, as outlined in the GRADE handbook and in relation to the following outcomes for the main comparisons. We chose six key comparisons for a specific focus, as they represent the most clinically relevant comparisons in this updated review.

Comparisons

1. Crystalloid versus control
2. Colloid versus crystalloid
3. Ephedrine versus phenylephrine
4. Ondansetron versus control
5. Lower limb compression versus control
6. Walking versus lying

Outcomes

1. Incidence of maternal hypotension requiring intervention
2. Incidence of maternal hypertension requiring intervention
3. Incidence of maternal bradycardia
4. Incidence of maternal nausea and/or vomiting
5. Neonatal acidosis as defined by cord or neonatal bloods with a pH of less than 7.2
6. Neonatal Apgar score of less than 8 at five minutes
7. Admission to neonatal intensive care unit

We also prepared a 'Summary of findings' table for the primary outcome (women with hypotension requiring intervention) for all of the six key comparisons for illustrative purposes.

We used the GRADEpro Guideline Development Tool to import data from RevMan 2014 in order to create 'Summary of findings' tables, creating a summary of the intervention effect and a measure of quality for each of the above outcomes. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. We downgraded the evidence from 'high quality' 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

For details of included and excluded studies, see Characteristics of included studies and Characteristics of excluded studies tables. Studies took place in Europe, North America, India, and the Middle East.

Results of the search

We assessed 380 studies in total. Our review includes 125 studies involving 9469 women.

In Cyna 2017 we excluded 228 studies; 13 of these were included in Cyna 2006, but we excluded them from the update due to a change in the inclusion criteria (see below for reasons). There are 25 studies awaiting further classification and 1 ongoing study. Since publication of Cyna 2017 one study (Mitra 2014) has been retracted

and this has now been reclassified from included to excluded, giving a total of 229 excluded studies.

Included studies

Interventions

We grouped the 125 included trials into three main categories of interventions.

Administration of fluids

- Crystalloid versus control (Idehen 2014; Imam 2012; King 1998; Morgan 2000; Ouerghi 2010)
- Different regimens of crystalloids (Alimian 2014; Dyer 2004; Farid 2016; Faydaci 2011; Jacob 2012; Jorgensen 2000; Khan 2013; Muzlifah 2009; Oh 2014; Rout 1992; Tercanli 2005; Wilson 1999)
- Colloids versus crystalloids (Alimian 2014; Arora 2015; Bottiger 2010; Bouchnak 2012; Cardoso 2004a; Dahlgren 2005; Dahlgren 2007; El-Mekawy 2012; Embu 2011; French 1999; Gunaydin 2009; Hasan 2012; Jabalameli 2011; Karinen 1995; Lin 1999; Madi-Jebara 2008; Mercier 2014; Ozkan 2004; Perumal 2004; Romdhani 2014; Selvan 2004; Siddik 2000; Singh 2009; Ueyama 1999; Unlugenc 2015; Upadya 2016; Yorozu 2002)
- Different regimens of colloids (Arora 2015; Carvalho 2009; Davies 2006; Nishikawa 2007; Selvan 2004; Siddik-Sayyid 2009; Ueyama 1999)
- Colloid versus control (Hasan 2012; Mathru 1980; Nishikawa 2007; Riley 1995; Tawfik 2014)
- Colloid plus crystalloid versus another colloid or crystalloid (Marciniak 2015; Mathru 1980)

Drugs

- Ephedrine versus control (Carvalho 1999a; Carvalho 1999b; Carvalho 2000; Damevski 2011; Gomaa 2003; Grubb 2004; Hall 1994; Imam 2012; King 1998; Loughrey 2002; Mathru 1980; Morgan 2000; Moslemi 2015; Ngan Kee 2000; Olsen 1994; Ozkan 2004; Ramin 1994; Singh 2016; Torres unpub; Tsen 2000; Turkoz 2002; Ueyama 1992; Webb 1998)
- Ephedrine versus crystalloids (Carvalho 2000; Chan 1997; Damevski 2011; El-Mekawy 2012; Imam 2012; Jabalameli 2011; King 1998; Kundra 2008; Morgan 2000)
- Ephedrine plus crystalloid versus colloid (Ozkan 2004)
- Ephedrine plus colloid versus crystalloid (Ozkan 2004)
- Ephedrine versus phenylephrine (Alahuhta 1992; Bhardwaj 2013; Gomaa 2003; Hall 1994; Magalhaes 2009; Moslemi 2015; Nazir 2012; Ueyama 2002)
- Ephedrine versus angiotensin (Ramin 1994)
- Different regimens of ephedrine (Carvalho 1999a; Carvalho 1999b; Carvalho 2000; Chohedri 2007; Hall 1994; King 1998; Loughrey 2002; Morgan 2000; Ngan Kee 2000; Ozkan 2004; Pouliou 2006)
- Ephedrine versus colloid (El-Mekawy 2012; Jabalameli 2011)
- Ephedrine versus metaraminol (Bhardwaj 2013)
- Phenylephrine versus control (Gomaa 2003; Kuhn 2016; Loughrey 2005; Moslemi 2015; Ngan Kee 2004a)
- Different regimens of phenylephrine (Doherty 2012)
- Phenylephrine versus mephentermine (Mohta 2010)
- Phenylephrine versus metaraminol (Bhardwaj 2013)
- Phenylephrine plus crystalloid different regimens (Ansari 2011)
- Phenyleprine versus leg compression (Kuhn 2016)
- Glycopyrrolate versus control (Ngan Kee 2013a; Ure 1999)
- Ondansetron versus control (Marciniak 2015; Nivatpumin 2016; Ortiz-Gomez 2014; Sahoo 2012; Terkawi 2015; Trabelsi 2015; Wang 2014a; Wang 2014b)
- Ondansetron versus ephedrine (Nivatpumin 2016)
- Granisetron versus control (Eldaba 2015)
- Ketamine versus saline (Gulhas 2012)
- Angiotension versus control (Ramin 1994)
- Dopamine versus control (Yokoyama 1997)

Physical methods

- Lower limb compression versus control (Adsumelli 2003; Bhagwanjee 1990; James 1973; Jorgensen 1996; Kohli 2013; Kuhn 2016; Rout 1993a; Singh 2014; Sood 1996; Sujata 2012; Sutherland 2001)
- Wedge versus supine (Calvache 2011)
- Head-up tilt versus horizontal (Loke 2002)
- Head-down tilt versus horizontal (Miyabe 1997)
- Crawford's wedge versus manual uterine displacement (Amaro 1998)
- Supine versus sitting (Kohler 2002)
- Walking versus lying (Cyna 2010)
- Lateral versus supine wedged position (Hartley 2001; Hwang 2012)
- Left lateral versus left lateral tilt (Rees 2002)
- Left lateral tilt versus left manual uterine displacement (Kundra 2007)
- Leg elevation versus control (Rout 1993a)
- Acupressure versus placebo (Stein 1997)
- Acupressure versus metoclopramide (Stein 1997)

Furthermore, we chose to focus on six key comparisons (crystalloid versus control, colloid versus crystalloid, ephedrine versus phenylephrine, ondansetron versus control, lower limb compression versus control, walking versus lying) in the Summary of findings 1, as we felt these represented the most important clinical comparisons.

Methods and techniques

Although definitions of hypotension in the included studies varied, most fell within the generally accepted range. Table 1 presents details (where trials did not specify systolic or mean arterial pressure, we assumed the definition to be systolic).

Participants

All but one of the included trials assessed women having (or probably having) elective caesarean sections. In Ueyama 1992, 40 women in labour were scheduled for emergency caesareans and 60 women not in labour were scheduled for elective caesareans.

Reviewed interventions were not necessarily applied prior to spinal injection. Clinicians administered pharmacological interventions prior or immediately after spinal injection, before onset of hypotension.

Excluded studies

Please see Characteristics of excluded studies.

Since the Cyna 2017 update was published, the study by Mitra 2014 has been retracted. We have now moved this study from included to excluded.

In Cyna 2017, we excluded 228 studies for the following reasons.

- Women received combined spinal epidural anaesthesia.
- Women received epidural anaesthesia.
- Trials did not report incidence of hypotension requiring intervention.
- Researchers did not investigate prevention of hypotension due to spinal anaesthesia (including studies investigating treatment of hypotension or prevention of oxytocin-induced hypotension)
- Authors reporting of data was inadequate for analysis (for example, the number of women in each study group).
- Anaesthetic regimen differed between study groups.
- Not a prospective randomised study.
- Quasi-randomised study.
- Unclear definition of hypotension.
- Study compared prevention of hypotension to treatment of hypotension.
- Retracted study.

We excluded 13 studies from the original 2006 review for the following reasons (Cyna 2006).

- Combined spinal-epidural (Mendonca 2003; Rucklidge 2002; Rucklidge 2005; Russell 2002; Vercauteren 2000; Yun 1998; Yentis 2000).
- Number of women allocated to each study group not reported (Miller 2000).
- Incidence of hypotension not reported (Van Bogaert 1998).
- Quasi-randomised (Rout 1993b).
- Intervention was to treat, not prevent, hypotension (Cooper 2007; Yadav 2012; Young 1996).

Risk of bias in included studies

Please see Figure 1 and Figure 2 for a summary of 'Risk of bias' assessments.

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

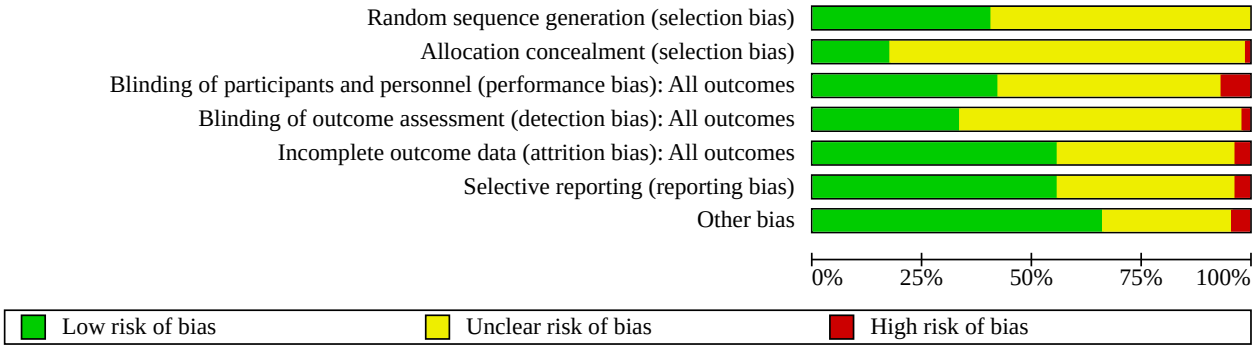


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

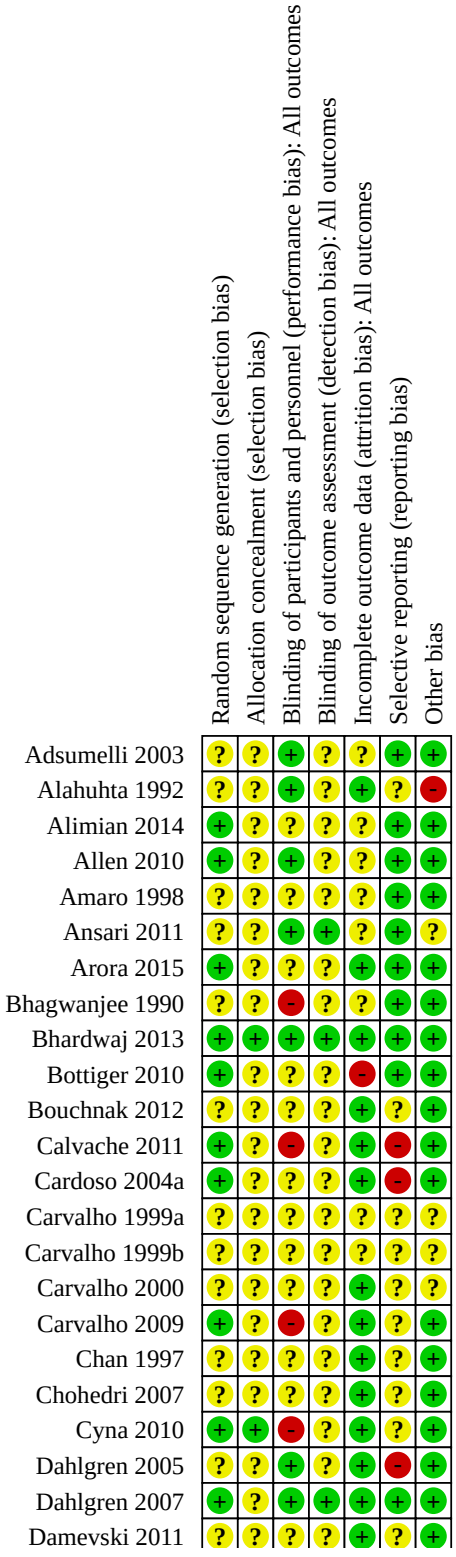


Figure 2. (Continued)

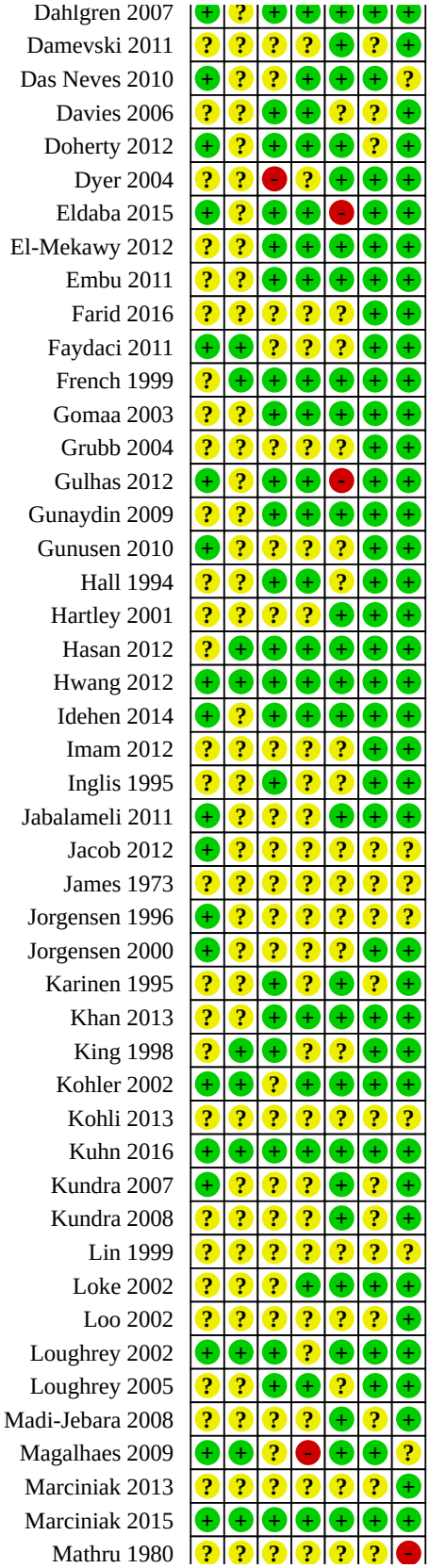


Figure 2. (Continued)

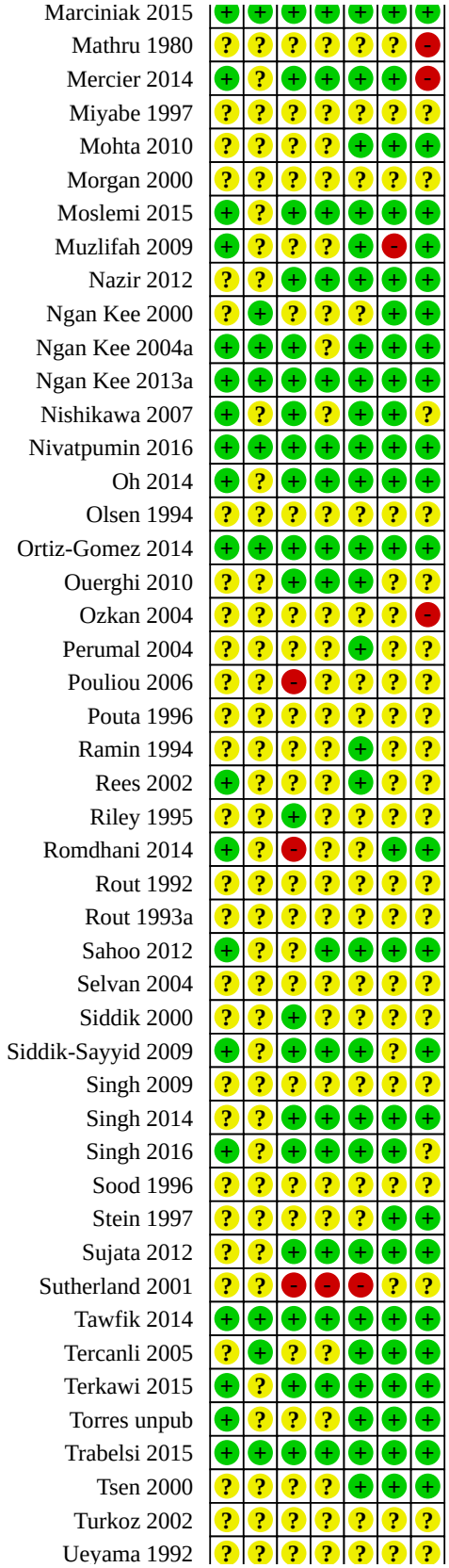
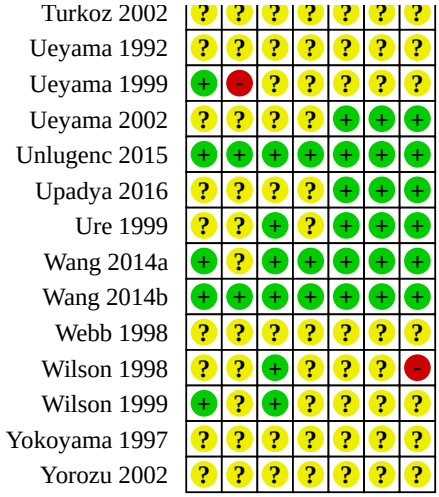


Figure 2. (Continued)



Allocation

Fifty-one studies reported adequate randomisation sequence generation, so we considered them to be at low risk of selection bias (Alimian 2014; Allen 2010; Arora 2015; Bhardwaj 2013; Bottiger 2010; Calvache 2011; Cardoso 2004a; Carvalho 2009; Cyna 2010; Dahlgren 2007; Das Neves 2010; Doherty 2012; Eldaba 2015; Faydaci 2011; Gulhas 2012; Gunusen 2010; Hwang 2012; Idehen 2014; Jabalameli 2011; Jacob 2012; Jorgensen 1996; Jorgensen 2000; Kohler 2002; Kuhn 2016; Kundra 2007; Loughrey 2002; Magalhaes 2009; Marciniak 2015; Mercier 2014; Moslemi 2015; Muzlifah 2009; Ngan Kee 2004a; Ngan Kee 2013a; Nishikawa 2007; Nivatpumin 2016; Oh 2014; Ortiz-Gomez 2014; Rees 2002; Romdhani 2014; Sahoo 2012; Siddik-Sayyid 2009; Singh 2016; Tawfik 2014; Terkawi 2015; Torres unpub; Trabelsi 2015; Ueyama 1999; Unlugenc 2015; Wang 2014a; Wang 2014b; Wilson 1999). The remaining 74 studies reported that the study was randomised; however, authors did not report the method of random sequence generation.

Only 22 studies contained a description of adequate allocation concealment (Bhardwaj 2013; Cyna 2010; Faydaci 2011; French 1999; Hasan 2012; Hwang 2012; King 1998; Kohler 2002; Kuhn 2016; Loughrey 2002; Magalhaes 2009; Marciniak 2015; Ngan Kee 2000; Ngan Kee 2004a; Ngan Kee 2013a; Nivatpumin 2016; Ortiz-Gomez 2014; Tawfik 2014; Tercanli 2005; Trabelsi 2015; Unlugenc 2015; Wang 2014b), mostly of opaque, sealed envelopes. One hundred and three studies did not report whether allocation was concealed or not, while one study did not conceal allocation at all (Ueyama 1999).

The Characteristics of included studies table includes details of the randomisation and allocation concealment processes.

Blinding

Participants and anaesthetists were blinded in 53 studies (Adsumelli 2003; Alahuhta 1992; Allen 2010; Ansari 2011; Bhardwaj 2013; Dahlgren 2005; Dahlgren 2007; Davies 2006; Doherty 2012; Eldaba 2015; El-Mekawy 2012; Embu 2011; French 1999; Gomaa 2003; Gulhas 2012; Gunaydin 2009; Hall 1994; Hasan 2012; Hwang 2012; Idehen 2014; Inglis 1995; Karinen 1995; Khan 2013; King 1998; Kuhn 2016; Loughrey 2002; Loughrey 2005; Marciniak 2015; Mercier 2014; Moslemi 2015; Nazir 2012; Ngan Kee 2004a; Ngan Kee 2013a; Nishikawa 2007; Nivatpumin 2016; Oh 2014; Ortiz-Gomez 2014; Ouerghi 2010; Riley 1995; Siddik 2000; Siddik-Sayyid 2009; Singh 2014; Singh 2016; Sujata 2012; Tawfik 2014; Terkawi 2015; Trabelsi 2015; Unlugenc 2015; Ure 1999; Wang 2014a; Wang 2014b; Wilson 1998; Wilson 1999). In the remaining studies, blinding was either not performed (8 studies) or not reported (64 studies). We assessed the eight studies in which it was clear that the participants and anaesthetists were not blinded as being at high risk of bias (Bhagwanjee 1990; Calvache 2011; Carvalho 2009; Cyna 2010; Dyer 2004; Pouliou 2006; Romdhani 2014; Sutherland 2001).

The outcome assessors were blinded in 42 studies (Ansari 2011; Bhardwaj 2013; Dahlgren 2007; Das Neves 2010; Davies 2006; Doherty 2012; Eldaba 2015; El-Mekawy 2012; Embu 2011; French 1999; Gomaa 2003; Gulhas 2012; Gunaydin 2009; Hall 1994; Hasan 2012; Hwang 2012; Idehen 2014; Khan 2013; Kohler 2002; Kuhn 2016; Loke 2002; Loughrey 2005; Marciniak 2015; Mercier 2014; Moslemi 2015; Nazir 2012; Ngan Kee 2013a; Nivatpumin 2016; Oh 2014; Ortiz-Gomez 2014; Ouerghi 2010; Sahoo 2012; Siddik-Sayyid 2009; Singh 2014; Singh 2016; Sujata 2012; Tawfik 2014; Terkawi 2015; Trabelsi 2015; Unlugenc 2015; Wang 2014a; Wang 2014b), and they were not blinded in 2 (Magalhaes 2009; Sutherland 2001). The remaining 81 studies did not report blinding of the outcome assessor.

Incomplete outcome data

There were no or only unlikely losses to follow-up in 70 studies. In 52 studies there was some evidence of incomplete data and small losses to follow-up, or insufficient information reported to assess this domain adequately (Adsumelli 2003; Alimian 2014; Allen 2010; Amaro 1998; Ansari 2011; Bhagwanjee 1990; Carvalho 1999a; Carvalho 1999b; Davies 2006; Farid 2016; Faydaci 2011; Grubb 2004; Gunusen 2010; Hall 1994; Imam 2012; Inglis 1995; Jacob 2012; James 1973; Jorgensen 1996; Jorgensen 2000; King 1998; Kohli 2013; Lin 1999; Loo 2002; Loughrey 2005; Marciniak 2013; Mathru 1980; Miyabe 1997; Morgan 2000; Ngan Kee 2000; Olsen 1994; Ozkan 2004; Pouliou 2006; Pouta 1996; Riley 1995; Romdhani 2014; Rout 1992; Rout 1993a; Selvan 2004; Siddik 2000; Singh 2009; Sood 1996; Stein 1997; Turkoz 2002; Ueyama 1992; Ueyama 1999; Webb

1998; Wilson 1998; Wilson 1999; Yokoyama 1997; Yorozu 2002). We assessed these studies as being at unclear risk of attrition bias. We considered the remaining four studies to be at high risk of bias due to losses to follow-up (Bottiger 2010 reported the exclusion of 3 women for unspecified reasons at an unclear point along the study pathway; Eldaba 2015 reported 5/200 exclusions due to failed blocks; Gulhas 2012 excluded 3/105 patients due to failed blocks; Sutherland 2001 reported 46/100 protocol violations).

The Characteristics of included studies table provides reasons for losses to follow-up.

Selective reporting

Selective reporting was not present in 70 studies (Adsumelli 2003; Alimian 2014; Allen 2010; Amaro 1998; Ansari 2011; Arora 2015; Bhagwanjee 1990; Bhardwaj 2013; Bottiger 2010; Dahlgren 2007; Das Neves 2010; Dyer 2004; Eldaba 2015; El-Mekawy 2012; Embu 2011; Farid 2016; Faydaci 2011; French 1999; Gomaa 2003; Grubb 2004; Gulhas 2012; Gunaydin 2009; Gunusen 2010; Hall 1994; Hartley 2001; Hasan 2012; Hwang 2012; Idehen 2014; Imam 2012; Inglis 1995; Jabalameli 2011; Jorgensen 2000; Khan 2013; King 1998; Kohler 2002; Kuhn 2016; Loke 2002; Loughrey 2002; Loughrey 2005; Magalhaes 2009; Marciniak 2015; Mercier 2014; Mohta 2010; Moslemi 2015; Nazir 2012; Ngan Kee 2000; Ngan Kee 2004a; Ngan Kee 2013a; Nishikawa 2007; Nivatpumin 2016; Oh 2014; Ortiz-Gomez 2014; Romdhani 2014; Sahoo 2012; Singh 2014; Singh 2016; Stein 1997; Sujata 2012; Tawfik 2014; Tercanli 2005; Terkawi 2015; Torres unpub; Trabelsi 2015; Tsen 2000; Ueyama 2002; Unlugenc 2015; Upadya 2016; Ure 1999; Wang 2014a; Wang 2014b). It was not clear in a further 51 studies whether selective reporting was present, with the remaining four studies demonstrating evidence of selective reporting (Calvache 2011; Cardoso 2004a; Dahlgren 2005; Muzlifah 2009).

Other potential sources of bias

We found no other potential sources of bias in 84 studies. It was unclear in a further 37 studies whether there was potential source of bias (Ansari 2011; Carvalho 1999a; Carvalho 1999b; Carvalho 2000; Das Neves 2010; Jacob 2012; James 1973; Jorgensen 1996; Kohli 2013; Lin 1999; Magalhaes 2009; Miyabe 1997; Morgan 2000; Nishikawa 2007; Olsen 1994; Ouerghi 2010;; Perumal 2004; Pouliou 2006; Pouta 1996; Ramin 1994; Rees 2002; Riley 1995; Rout 1992; Rout 1993a; Selvan 2004; Siddik 2000; Singh 2009; Singh 2016; Sood 1996; Sutherland 2001; Turkoz 2002; Ueyama 1992; Ueyama 1999; Webb 1998; Wilson 1999; Yokoyama 1997; Yorozu 2002). There was a potential source of bias with respect to funding source in one study: Mercier 2014 performed a study comparing colloid (HES) preload to crystalloid (Ringer's lactate) preload, which was fully funded by Fresenius Kabi, the company that produces HES. We assessed this study as being at high risk of other bias. Some evidence of asymmetry is apparent in two of the three funnel plots (Figure 3, Figure 4 and Figure 5), which suggests possible publication bias due to the number of small studies.

Figure 3. Funnel plot of comparison: 7 Colloid vs crystalloid, outcome: 7.1 Women with hypotension requiring intervention.

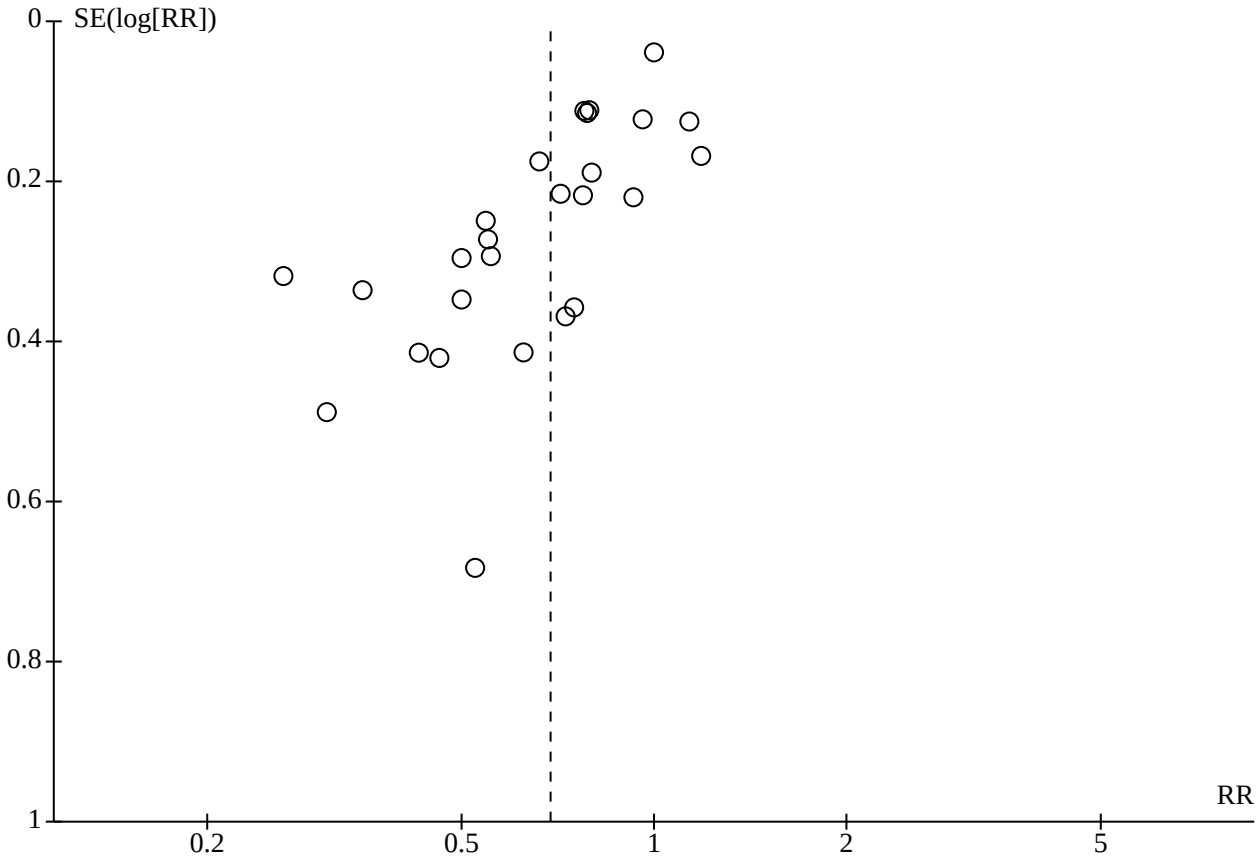


Figure 4. Funnel plot of comparison: 13 Ephedrine vs control, outcome: 13.1 Women with hypotension requiring intervention.

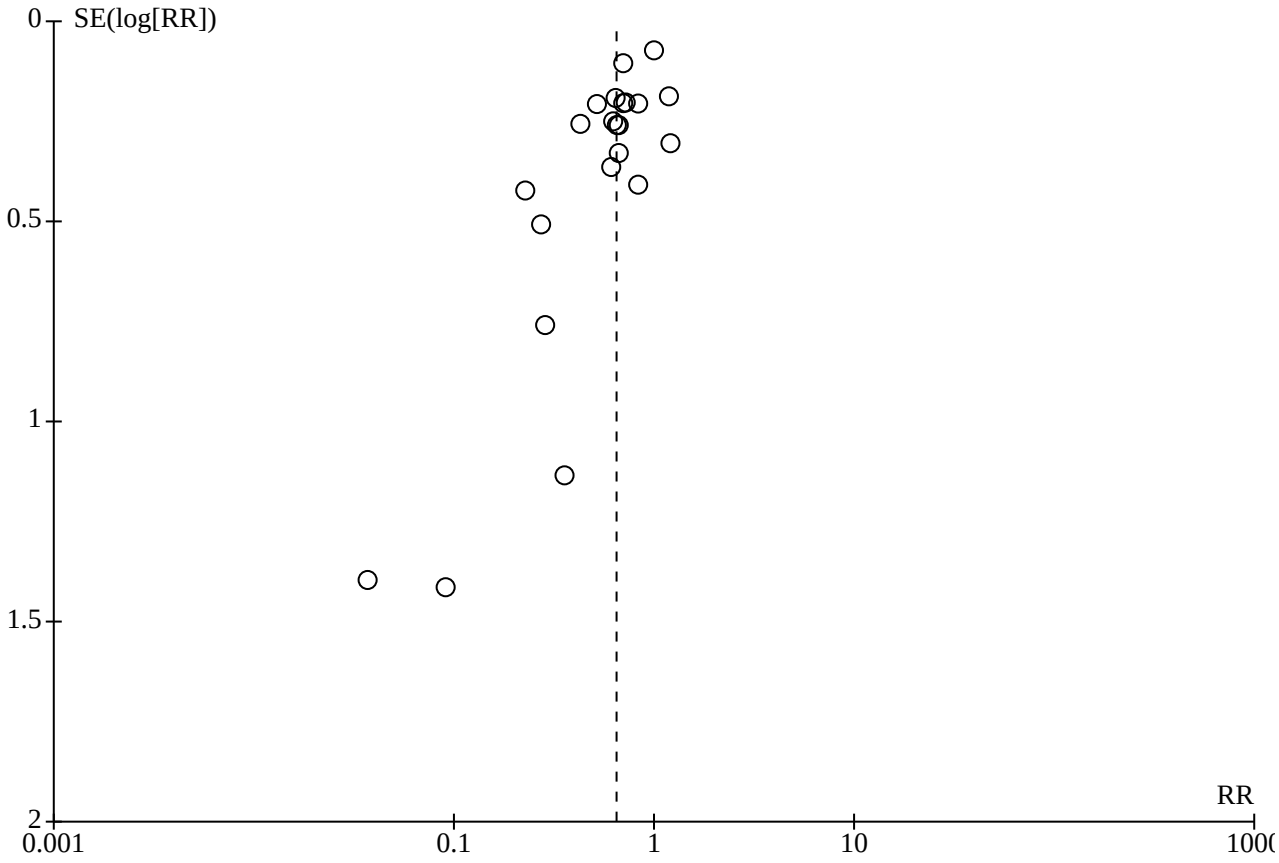
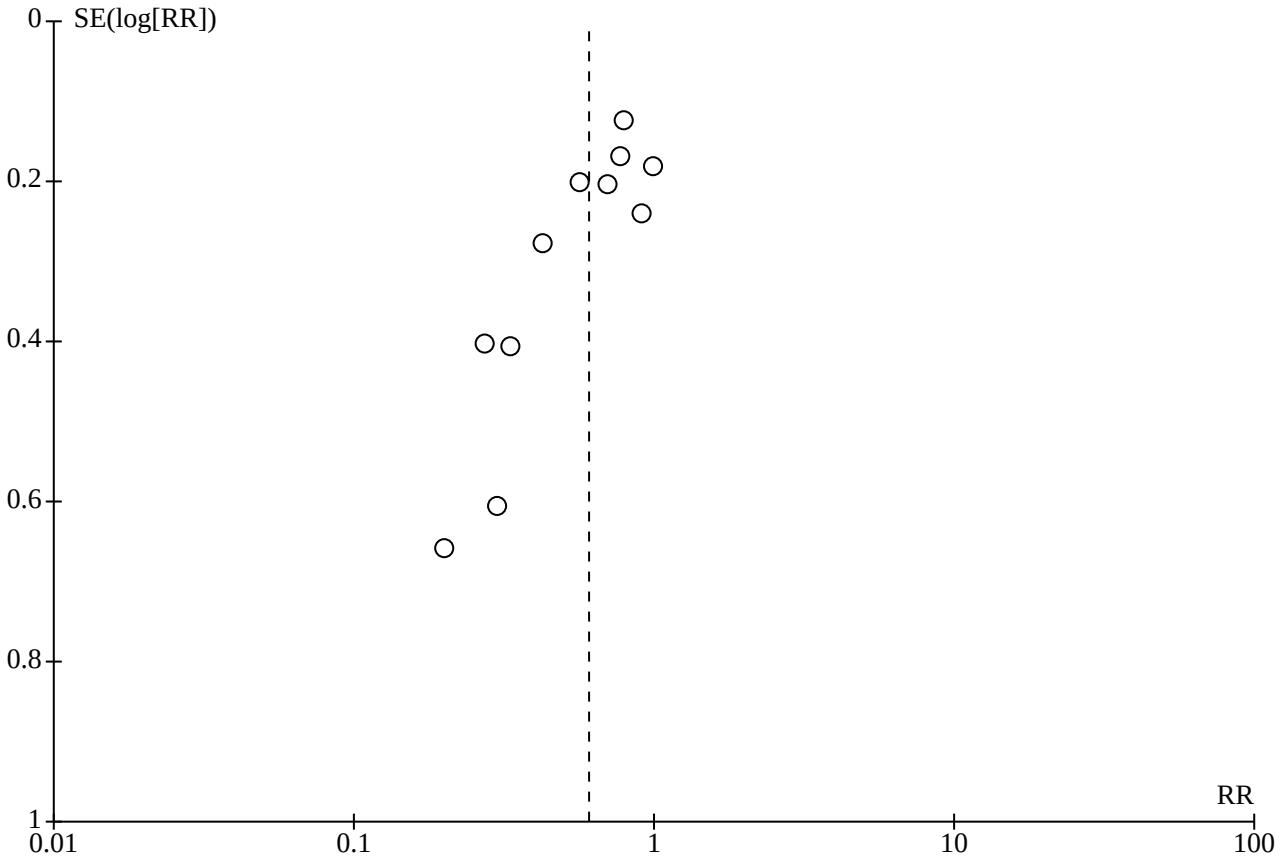


Figure 5. Funnel plot of comparison: 47 Lower limb compression vs control, outcome: 47.1 Women with hypotension requiring intervention.



There were 2 studies assessed as high risk as study participants received variable doses of local anaesthetic in their spinal block (Alahuhta 1992; Mathru 1980). Also, there were 2 studies assessed as high risk of bias as it was unclear whether the spinal anaesthetic technique and dose was standardised between the study groups (Ozkan 2004; Wilson 1998). It was unlikely that with randomisation this source of bias would have an important effect on the review findings.

Effects of interventions

See: **Summary of findings 1** Techniques for preventing hypotension during spinal anaesthesia for caesarean section: key interventions for the primary outcome (women with hypotension requiring intervention); **Summary of findings 2** Crystalloid versus control; **Summary of findings 3** Colloid versus crystalloid; **Summary of findings 4** Ephedrine versus phenylephrine; **Summary of findings 5** Ondansetron versus control; **Summary of findings 6** Lower limb compression versus control; **Summary of findings 7** Walking versus lying

We included 125 studies involving 9469 women and assessing 49 comparisons of different methods to prevent hypotension following spinal anaesthesia at caesarean.

As noted above, we grouped the comparisons into three main categories of interventions: fluids (data and analyses 1 to 11), drugs (data and analyses 12 to 36), and physical methods (data and analyses 37 to 49). Comparisons 1, 7, 16, 31, 37, and 43 constitute our key review comparisons; see Summary of findings 1 for a summary of the findings of each for our main review outcome: maternal hypotension requiring pharmacological intervention.

Fluids

This group of interventions comprises comparisons corresponding to data analyses 1 to 11. The section first presents comparisons with crystalloids, including crystalloid versus control (comparison 1; see Summary of findings 2), different regimens of crystalloids, and different types of crystalloids. Comparison 7 assesses colloid versus crystalloid directly (see Summary of findings 3), while the remaining comparisons focus on colloids alone (versus control: different regimens of colloids: and different types of colloids).

Crystalloids

Crystalloid versus control

See Summary of findings 2.

Primary outcome: maternal hypotension requiring pharmacological intervention

Crystalloids appeared to be more effective than control for preventing maternal hypotension requiring intervention (average

RR 0.84, 95% CI 0.72 to 0.98; 5 studies; 370 women; *low-quality evidence*; Analysis 1.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.19, 95% CI 0.01 to 3.91; 1 study; 69 women; *very low-quality evidence*; Analysis 1.2).

- Anaphylaxis

One study reported this outcome (Idehen 2014, 69 women). There were no events in either group (Analysis 1.3).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

One study reported this outcome (Idehen 2014, 60 babies; *low-quality evidence*). There were no events in either group (Analysis 1.4).

No trials reported other secondary outcomes for this comparison.

Different regimens of crystalloids

Crystalloid: rapid infusion versus slow infusion

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.86, 95% CI 0.45 to 1.64; 1 study, 20 women; Analysis 2.1).

Secondary outcomes

No trials reported secondary outcomes for this comparison.

Crystalloid: high versus low preload volume

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no conclusive evidence of a difference between the groups in rates of hypotension when comparing high volume preload (15 mL/kg to 20 mL/kg) to lower volume preload (10 mL/kg or less) (average RR 0.55, 95% CI 0.29 to 1.02; I^2 = 57%, 3 studies, 192 women; Analysis 3.1). There was considerable heterogeneity in the 20 mL subgroup (I^2 = 85%) but no evidence of subgroup differences (test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 = 0%).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.20, 95% CI 0.40 to 3.62, one study, 80 women; Analysis 3.2).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

One study reported this outcome (Faydaci 2011, 90 babies). There were no events in either group (Analysis 3.3).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing Muzlifah 2009 from Analysis 3.1 resulted in fewer women in the high volume preloading group experiencing hypotension than in the low volume group (average RR 0.43, 95% CI 0.23 to 0.78); data not shown.

Crystalloid: rapid coload versus preload

Primary outcome: maternal hypotension requiring pharmacological intervention

A rapid crystalloid coload was associated with a lower incidence of hypotension than a preload (average RR 0.70, 95% CI 0.59 to 0.83, 5 studies, 384 women; Analysis 4.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.67, 95% CI 0.42 to 6.60, 1 study, 100 women; Analysis 4.2).

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 1.43, 95% CI 0.59 to 3.45, 1 study, 100 women; Analysis 4.3).

- Nausea and/or vomiting

Rapid coload was associated with a higher risk of nausea than preload (average RR 1.98, 95% CI 1.26 to 3.12, 3 studies, 201 women; Analysis 4.4).

There was insufficient evidence to determine conclusively whether there was a difference between the groups in rates of vomiting (average RR 2.33, 95% CI 0.98 to 5.58, 2 studies, 160 women).

Neonatal

- Acidosis

Two studies reported this outcome (Dyer 2004; Oh 2014, 110 babies). There were no events in either group (Analysis 4.5).

- Apgar scores of less than 7 or 8 at five minutes

Three studies reported this outcome (Dyer 2004; Jacob 2012; Oh 2014, 210 babies). There were no events in either group (Analysis 4.6).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing Dyer 2004 from the analysis did not impact the results.

Crystalloid: warm versus cold saline

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.03, 95% CI 0.65 to 1.62, one study,113 women; Analysis 5.1).

Secondary outcomes

- Nausea and/or vomiting

There was insufficient evidence to determine whether warm or cold saline had an effect on nausea (RR 1.64, 95% CI 0.97 to 2.76, one study, 113 women) or vomiting (RR 2.95, 95% CI 0.12 to 70.87, one study, 113 women); see Analysis 5.2.

No trials reported other secondary outcomes for this comparison.

Different types of crystalloids

Dextrose plus saline versus saline alone

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the interventions (RR 0.88, 95% CI 0.68 to 1.14, 1 study, 120 women; Analysis 6.1.1).

Secondary outcomes

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.20, 95% CI 0.39 to 3.72, 1 study, 120 babies; Analysis 6.3).

- Apgar scores of less than 7 at five minutes

One study reported this outcome (Wilson 1999, 120 babies). There were no events in either group (Analysis 6.4).

No trials reported other secondary outcomes for this comparison.

Glucose versus saline

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the interventions (RR 1.05, 95% CI 0.74 to 1.48, 1 study, 70 women; Analysis 6.1.2).

Secondary outcomes

No studies reported secondary outcomes for this comparison.

Ringers lactate versus saline

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.17, 95% CI 0.65 to 2.09, 1 study, 60 women; Analysis 6.1.3).

Secondary outcomes

Neonatal

- Acidosis

One study reported this outcome (Alimian 2014, 60 babies). There were no events in either group (Analysis 6.2).

- Apgar scores of less than 8 at five minutes

One study reported this outcome (Alimian 2014, 60 babies). There were no events in either group (Analysis 6.5).

No trials reported other secondary outcomes for this comparison.

Colloids versus crystalloids

See Summary of findings 3.

Primary outcome: maternal hypotension requiring pharmacological intervention

The incidence of hypotension was lower with colloids compared to crystalloids (average RR 0.69, 95% CI 0.58 to 0.81; 27 studies, 2009 women; *very low-quality evidence*; Analysis 7.1). Substantial heterogeneity (I^2 = 82%, Tau^2 = 0.12) was likely due to differences in formulation and volume of fluid administered between studies. However, due to the variation in regimens between studies, it was not possible to conduct formal subgroup analyses. There was some evidence of asymmetry on funnel plot (Figure 3), which could be due to the large number of small studies contributing to this analysis.

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (average RR 0.64, 95% CI 0.09 to 4.46, 3 studies, 327 women; *very low-quality evidence*; Analysis 7.2).

- Cardiac dysrhythmia

There was no clear evidence of a difference in the groups in rates of tachycardia (RR 1.10, 95% CI 0.79, 1.53, 1 study, 60 women) or bradycardia (RR 0.98, 95% CI 0.54 to 1.78, 5 studies, 413 women; *very low-quality evidence*); see Analysis 7.3.

- Nausea and/or vomiting

There was no clear evidence of a difference in the groups for rates of nausea or vomiting (average RR 0.89, 95% CI 0.66 to 1.19, 14 studies, 1058 women, I^2 = 29%; *very low-quality evidence*), nausea alone (average RR 1.10, 95% CI 0.77 to 1.58, 5 studies, 390 women, I^2 = 10%), vomiting alone (average RR 1.35, 95% CI 0.55 to 3.27, 4 studies, 320 women, I^2 = 33%); see Analysis 7.4.

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (average RR 0.83, 95% CI 0.15 to 4.52, 6 studies, 678 babies, I^2 = 24%; *very low-quality evidence*; Analysis 7.5).

- Apgar scores of less than 7 or 8 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups in the rates of Apgar scores of less than 7 (average RR 0.16, 95% CI 0.01 to 2.90, 2 studies,127 babies) or of less than 8 (average RR 0.24, 95% CI 0.03 to 2.05, 10 studies, 730 babies; *very low-quality evidence*) at five minutes; see Analysis 7.6.

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing studies for at high risk of bias in one or more domain made little difference to the results of any analysis under this comparison (Bottiger 2010; Cardoso 2004a; Dahlgren 2005; Mercier 2014; Romdhani 2014; Ueyama 1999).

Colloids versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

There was a reduced incidence of hypotension in the colloid group (average RR 0.40, 95% CI 0.16 to 0.96, 5 studies, 426 women; Analysis 8.1). There was substantial heterogeneity (I^2 = 85%, Tau^2 = 0.71), likely due to differences in formulation and volume of fluid administered. In addition, Tawfik 2014 reported higher event rates than other studies.

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups (RR 7.70, 95% CI 0.46 to 127.78; 54 women; 1 study; Analysis 8.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (average RR 1.65, 95% CI 0.75 to 3.64, 2 studies, 245 women; Analysis 8.3).

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.24, 95% CI 0.34 to 4.48, 1 study, 205 babies; Analysis 8.4).

- Apgar scores of less than 7 or 8 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups in Apgar scores of less than 7 at five minutes (average RR 0.07, 95% CI 0.00 to 1.24, 4 studies, 205 babies; Analysis 8.5). Three of the four studies in this analysis reported no events in either arm. One study reported Apgar score of less than 8 at five minutes (Tawfik 2014, 205 women), and there were no events in either arm (Analysis 8.6).

No trials reported other secondary outcomes for this comparison.

Different regimens of colloids

Colloids: high versus low volume

Primary outcome: maternal hypotension requiring pharmacological intervention

In three studies, there was no difference in the incidence of hypotension when comparing high volume versus low volume colloids (average RR 0.75, 95% CI 0.27 to 2.08; 134 women; Analysis 9.1). Substantial heterogeneity (I^2 = 78, Tau^2 = 0.63) was present. None of the studies contributing to the analysis were good quality, and all were at unclear or high risk of selection bias, which may have impacted results (Davies 2006; Selvan 2004; Ueyama 1999).

Secondary outcomes

Neonatal

- Apgar of less than 9 at five minutes (non-prespecified outcome)

One study reported this outcome (Davies 2006, 70 babies). There were no events in either arm (Analysis 9.2).

No trials reported other secondary outcomes for this comparison.

Colloid: preload versus coload

Note: the comparison for crystalloid is coload versus preload.

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the groups (average RR 0.93, 95% CI 0.78 to 1.10, 4 studies, 320 women; Analysis 10.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (average RR 0.75, 95% CI 0.20 to 2.88, 2 studies, 82 women; Analysis 10.2. One study had no events). One study reported tachycardia (Carvalho 2009, 46 women); there were no events in either arm (Analysis 10.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 0.92, 95% CI 0.63 to 1.35, 1 study, 178 women), rates of nausea alone (RR 1.00, 95% CI 0.15 to 6.51, 1 study, 46 women). One study reported rates of vomiting alone (Carvalho 2009, 46 women); there were no events in either arm (Analysis 10.3).

- Anaphylaxis

One study reported this outcome (Siddik-Sayyid 2009, 178 women). There were no events in either group (Analysis 10.4).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

One study reported this outcome (Nishikawa 2007, 36 babies): there were no events in either arm (Analysis 10.5).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing Carvalho 2009 made very little difference to Analysis 10.1 and Analysis 10.2.

Different types of colloids

Two studies compared colloid + crystalloid versus another colloid or dextrose + crystalloid (Marciniak 2015; Mathru 1980)

Albumen and dextrose plus crystalloid versus dextrose plus crystalloid

Primary outcome: maternal hypotension requiring pharmacological intervention

One study compared colloid plus crystalloid versus another colloid or dextrose plus crystalloid (Mathru 1980).There was insufficient evidence to determine whether there was a difference between the groups (RR 0.13, 95% CI 0.01 to 2.30, 1 study, 45 women; Analysis 11.1.1).

Secondary outcomes

Neonatal

- Apgar scores of less than 7 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups for Apgar scores of less than 7 (RR 0.13, 95% CI 0.01 to 2.30, 1 study, 45 babies; Analysis 11.2).

No trials reported other secondary outcomes for this comparison.

Unbalanced versus balanced hydroxyethyl starch

Primary outcome: maternal hypotension requiring pharmacological intervention

One study compared unbalanced versus balanced hydroxyethyl starch (Marciniak 2015). There was no clear evidence of a difference between the groups (RR 1.04, 95% CI 0.78 to 1.39, 1 study, 51 women; Analysis 11.1.2).

Secondary outcomes

Neonatal

- Apgar scores of less than 8 at five minutes

Marciniak 2013 (51 women) reported this outcome. There were no events in either arm (Analysis 11.3).

No trials reported other secondary outcomes for this comparison.

Summary: fluids

In preventing hypotension following spinal anaesthesia at caesarean section, we found the following.

- Crystalloids may be more effective than control.
- Rapid crystalloid coload is more effective than crystalloid preload.
- Colloids are more effective than crystalloids.
- For colloids, there is no clear difference with high versus low volumes or with preloading versus coloading.

Drugs

This group of interventions comprises comparisons corresponding to data analyses 12 to 36. The section begins by reporting comparisons involving ephedrine, including ephedrine versus control, ephedrine versus other drugs; see Summary of findings 4 for comparison 'ephedrine versus phenylephrine'), different regimens of ephedrine, and different ephedrine regimens plus crystalloid or colloid. Other comparisons assess phenylephrine versus control, other drugs, different regimens of phenylephrine, and phenylephrine combined with crystalloid. Finally, we assess other drugs: glycopyrrolate, ondansetron; see Summary of findings 5 for 'ondansetron versus control'), granisetron, ketamine, angiotensin, and dopamine.

Ephedrine

Ephedrine versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

There was a lower incidence of hypotension in the ephedrine prophylaxis groups than in controls (average RR 0.65, 95% CI 0.53 to 0.80; 22 studies, 1401 women; Analysis 12.1). Substantial heterogeneity was present (I^2 = 75%, Tau^2 = 0.14), which was most likely due to differences in dosing of prophylactic ephedrine, rescue treatments for hypotension when it occurred, and administration routes for the ephedrine. Of note, most studies were unclear in reporting methods of sequence generation, allocation concealment, and blinding.

All studies examined intravenous (IV) ephedrine except for two studies where ephedrine was given intramuscularly (Gomaa 2003; Grubb 2004). Excluding these two studies from analyses reduced heterogeneity only slightly (I^2 = 69%, Tau^2 = 0.09). The asymmetrical funnel plot (Figure 4) may be due to small study effects or publication-type bias.

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was no conclusive evidence of a difference between the groups (average RR 1.61, 95% CI 1.00 to 2.61, 7 studies, 520 women; Analysis 12.2).

- Cardiac dysrhythmia

There was no clear evidence of a difference between the groups in rates of tachycardia (average RR 1.12, 95% CI 0.74 to 1.70, 2 studies, 93 women) and no conclusive evidence with respect to bradycardia (average RR 14.46, 95% CI 0.87, 241.09, 2 studies, 103 women, no events in one study). There were only seven events in the analysis for bradycardia, but they were all in the ephedrine group (Analysis 12.3).

- Nausea and/or vomiting

There was no conclusive evidence of a difference between the groups for rates of nausea or vomiting (average RR 0.71, 95% CI 0.22 to 2.34, 5 studies, 219 women, I^2 = 62%), or rates of vomiting alone (average RR 0.68, 95% CI 0.44 to 1.07, 6 studies, 516 women, I^2 = 47%). Rates of nausea alone were lower in the ephedrine group

(average RR 0.68, 95% CI 0.48 to 0.96, 8 studies, 620 women, I^2 = 25%; Analysis 12.4).

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.29, 95% CI 0.67 to 2.49, 9 studies, 576 babies; Analysis 12.5).

- Apgar scores of less than 7 or 8 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups in Apgar scores of less than 7 at five minutes (RR 1.14, 95% CI 0.34 to 3.81, 4 studies, 263 women). Ten studies (N = 579) reported Apgar score of less than 8 at five minutes and there were no events in either arm (Analysis 12.6).

No trials reported other secondary outcomes for this comparison.

Ephedrine versus other drug regimens

Ephedrine versus crystalloid

Primary outcome: maternal hypotension requiring pharmacological intervention

Fewer women in the ephedrine group developed hypotension compared with the crystalloid group (average RR 0.60, 95% CI 0.47 to 0.78, 9 studies, 613 women; Analysis 13.1). There was moderate heterogeneity between the studies (I^2 = 40%), which may be related to variation in methods and dose of ephedrine between the different studies.

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (average RR 1.10, 95% CI 0.37 to 3.28, 3 studies, 280 women, I^2 = 43%; Analysis 13.2).

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 0.33, 95% CI 0.01 to 7.99, 1 study, 100 women; Analysis 13.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups for rates of nausea or vomiting (average RR 1.00, 95% CI 0.48 to 2.08, 2 studies, 146 women) and no conclusive evidence of a difference for rates of vomiting alone (average RR 0.57, 95% CI 0.31 to 1.05, 3 studies, 220 women, I^2 = 33%). Rates of nausea alone were lower in the ephedrine group (average RR 0.54, 95% CI 0.31 to 0.93, 3 studies, 220 women); see Analysis 13.4.

- Impaired consciousness, dizziness

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.40, 95% CI 0.37 to 3.28, 1 study, 46 women; Analysis 13.5).

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (average RR 1.41, 95% CI 0.48 to 4.15, 2 studies, 218 babies). There were no events in one of the two studies (Analysis 13.6).

- Apgar scores of less than 7 or 8 at five minutes

One study (Carvalho 2000, 100 women) reported Apgar score of less than 7 at five minutes; no events occurred in either arm. Four studies (226 women) reported Apgar scores of less than 8 at five minutes; only one event occurred, which was in the ephedrine group (average RR 3.00, 95% CI 0.13 to 71.92; Analysis 13.7).

No trials reported other secondary outcomes for this comparison.

Ephedrine plus crystalloid versus colloid

Primary outcome: maternal hypotension requiring pharmacological intervention

One study investigating this comparison found no evidence of a difference in the incidence of hypotension (RR 0.65, 95% CI 0.38 to 1.12; Analysis 14.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

One study investigating this comparison found nausea (RR 0.42, 95% CI 0.22 to 0.81; 75 women) and vomiting (RR 0.17, 95% CI 0.04 to 0.77; 75 women) were less common in the ephedrine plus crystalloid group than in the colloid group (Analysis 14.2).

Ephedrine plus colloid versus crystalloid

Primary outcome: maternal hypotension requiring pharmacological intervention

Hypotension was less common in the ephedrine plus colloid group than in the crystalloid group (RR 0.39, 95% CI 0.21 to 0.74, 1 study, 75 women; Analysis 15.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

Nausea was less common in the ephedrine plus colloid group than in the crystalloid group (RR 0.27, 95% CI 0.11 to 0.65, 1 study, 75 women. There was insufficient evidence to determine whether there was a difference between the groups in rates of vomiting (RR 0.38, 95% CI 0.09 to 1.55, 1 study, 75 women); see Analysis 15.2.

No trials reported other secondary outcomes for this comparison.

Ephedrine versus phenylephrine

See Summary of findings 4.

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the groups (average RR 0.92, 95% CI 0.71 to 1.18, 8 studies, 401 women, I^2 = 37%; *very low-quality evidence*; Analysis 16.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (average RR 1.72, 95% CI 0.71 to 4.16, 2 studies, 118 women, *low-quality evidence*; Analysis 16.2).

- Cardiac dysrhythmia

Rates of bradycardia were lower in the ephedrine group (average RR 0.37, 95% CI 0.21 to 0.64, 5 studies, 304 women, *low-quality evidence*). There was insufficient evidence to determine whether there was a difference between the groups in rates of tachycardia (RR 2.22, 95% CI 0.44 to 11.18, 1 study, 57 women). See Analysis 16.3.

- Nausea and/or vomiting

There was no clear evidence of a difference between the groups (average RR 0.76, 95% CI 0.39 to 1.49, 4 studies, 204 women, I^2 = 37%, *very low-quality evidence*; Analysis 16.4).

Neonatal

- Acidosis

There was no clear evidence of a difference between the groups (average RR 0.89, 95% CI 0.07 to 12.00, 3 studies, 175 babies, *low-quality evidence*). Only two events occurred, both in the same study (Analysis 16.5).

- Apgar scores of less than 7 or 8 at five minutes

Six studies (321 babies, *low-quality evidence*) measured this outcome. There were no events in either group (Analysis 16.6).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing Magalhaes 2009 from Analysis 16.1, Analysis 16.3, Analysis 16.2, Analysis 16.6, and Analysis 16.4 made very little difference to the overall results.

Ephedrine versus angiotension

Primary outcome: maternal hypotension requiring pharmacological intervention

One study reported this outcome (Ramin 1994, 20 women). No events occurred in either arm (Analysis 17.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 3.00, 95% CI 0.14 to 65.90, 1 study, 20 women; Analysis 17.2).

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (RR 9.00, 95% CI 0.55 to 147.95, 1 study, 20 babies). Only four events occurred, all in the ephedrine arm (Analysis 17.3).

No trials reported other secondary outcomes for this comparison.

Ephedrine versus colloid

Primary outcome: maternal hypotension requiring pharmacological intervention

Rates of hypotension were lower in the ephedrine group (average RR 0.53, 95% CI 0.36 to 0.79, 2 studies, 160 women; Analysis 18.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 3.00, 95% CI 0.32 to 27.87, 1 study, 100 women; Analysis 18.2).

- Cardiac dysrhythmia

One study reported bradycardia (Jabalameli 2011, 100 women). There were no events in either arm (Analysis 18.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 5.00, 95% CI 0.25 to 101.58, 1 study, 100 women) or in rates of vomiting alone (RR 0.14, 95% CI 0.01 to 2.65, 1 study, 60 women). Rates of nausea alone were lower in the ephedrine group (RR 0.22, 95% CI 0.05, 0.94, 1 study, 60 women); see Analysis 18.4.

Neonatal

- Acidosis

One study reported this outcome (Jabalameli 2011, 100 babies). There were no events in either arm (Analysis 18.5).

- Apgar scores of less than 7 or 8 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups (RR 3.00, 95% CI 0.13 to 71.92, 1 study, 100 babies; Analysis 18.6).

No trials reported other secondary outcomes for this comparison.

Ephedrine versus metaraminol

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.56,95% CI 0.50 to 4.89, 1 study, 53 women; Analysis 19.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.62, 95% CI 0.26 to 1.47, 1 study, 53 women; Analysis 19.2).

- Cardiac dysrhythmia

One study reported bradycardia (Bhardwaj 2013, 53 women). There were no events in either arm (Analysis 19.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 7.26, 95% CI 0.39 to 134.01, 1 study, 53 women; Analysis 19.4).

Neonatal

- Acidosis

One study reported this outcome (Bhardwaj 2013, 53 babies). There were no events in either arm (Analysis 19.5).

- Apgar scores of less than 8 at five minutes

One study reported this outcome (Bhardwaj 2013, 53 babies). There were no events in either arm (Analysis 19.6).

No trials reported other secondary outcomes for this comparison.

Different ephedrine regimens

Ephedrine: lower dose versus higher dose

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the groups in dose comparisons of 5 mg versus 10 mg (RR 1.05, 95% CI 0.65 to 1.69, 2 studies, 100 women), 6 mg versus 12 mg (RR 1.83, 95% CI 0.83 to 4.04, 1 study, 46 women), 5 mg versus 15 mg (RR 2.00, 95% CI 0.94 to 4.27, 1 study, 40 women), 10 mg versus 15 mg (RR 1.83, 95% CI 0.84 to 3.99, 1 study, 40 women), 10 mg versus 20 mg (RR 1.06, 95% CI 0.80 to 1.39, 2 studies, 60 women), or 15 mg compared to 30 mg ephedrine (RR 2.11, 95% CI 1.06 to 4.21, 1 study, 100 women). However, rates of hypotension were higher with 10 mg compared to 30 mg (RR 2.43, 95% CI 1.30 to 4.54, 1 study, 40 women), and 20 mg compared to 30 mg (RR 2.29, 95% CI 1.21 to 4.32, 1 study, 40 women); see Analysis 20.1.

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups in comparisons of 5 mg versus 10 mg ephedrine (RR 1.20, 95% CI 0.44 to 3.30, 1 study, 40 women), 5 mg versus 15 mg (RR 0.50, 95% CI 0.23 to 1.07, 1 study, 40 women), 10 mg versus 15 mg (RR 0.42, 95% CI 0.18 to 0.96, 1 study, 40 women), 10 mg versus 20mg (RR 0.20, 95% CI 0.03 to 1.56, 1 study, 40 women), 10 mg versus 30 mg (RR 0.11, 95% CI 0.02 to 0.80, 1 study, 40 women), or 20 mg versus 30 mg ephedrine (RR 0.56, 95% CI 0.23 to 1.37, 1 study, 40 women); see Analysis 20.2.

- Nausea and/or vomiting

There was no clear evidence of a difference between the groups in rates of nausea and/or vomiting in comparisons of 6 mg versus 12 mg ephedrine (RR 0.81, 95% CI 0.38 to 1.74, 1 study, 46 women); see Analysis 20.3.1.

There was insufficient evidence to determine whether there was a difference between the dosing groups in rates of vomiting in comparisons of 5 mg versus 10 mg (RR 3.00, 95% CI 0.34 to 26.45, 1 study, 40 women), 5 mg versus 15 mg (RR 1.50, 95% CI 0.28 to 8.04, 1 study, 40 women), 10 mg versus 15 mg (RR 0.50, 95% CI 0.05 to 5.08, 1 study, 40 women), or 15 mg versus 30 mg ephedrine (RR 0.67, 95% CI 0.12 to 3.82, 1 study, 100 women); see Analysis 20.3.

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea, in comparisons of 5 mg versus 10 mg (RR 2.00, 95% CI 0.83 to 4.81, 1 study, 40 women), 5 mg versus 15 mg (RR 2.50, 95% CI 0.94 to 6.66, 1 study, 40 women), 10 mg versus 15 mg (RR 1.25, 95% CI 0.39 to 3.99, 1 study, 40 women, 10 mg versus 20 mg (RR 0.69, 95% CI 0.39 to 1.24, 1 study, 40 women), 10 mg versus 30 mg (RR 1.80, 95% CI 0.73 to 4.43, 1 study, 40 women), 15 mg versus 30 mg (RR 1.43, 95% CI 0.59 to 3.45, 1 study, 100 women), or 20 mg versus 30 mg ephedrine (RR 2.60, 95% CI 1.14 to 5.93, 1 study, 40 women); see Analysis 20.3.

Neonatal

- Acidosis (pH less than 7.2)

There was insufficient evidence to determine whether there was a difference between the groups in comparisons of 5 mg versus 10 mg ephedrine (RR 0.20, 95% CI 0.01 to 3.92, 1 study, 40 babies), 5 mg versus 15 mg (RR 0.33, 95% CI 0.01 to 7.72, 1 study, 40 babies), 6 mg versus 12 mg (RR 0.31, 95% CI 0.01 to 7.16, 1 study, 46 babies), 10 mg versus 15 mg (RR 2.00, 95% CI 0.20 to 20.33, 1 study, 40 babies), 10 mg versus 20 mg (RR 0.59, 95% CI 0.24 to 1.50, 1 study, 39 babies), 10 mg versus 30 mg (RR 1.13, 95% CI 0.36 to 3.55, 1 study, 38 babies), or 20 mg versus 30 mg (RR 1.89, 95% CI 0.69 to 5.21, 1 study, 37 babies); see Analysis 20.4.

- Apgar scores of less than 7 or 8 at five minutes

There was insufficient evidence to determine whether there was a difference between the groups, in comparisons of 6 mg versus 12 mg ephedrine (RR 0.31, 95% CI 0.01 to 7.16, 1 study, 46 babies).

No events occurred in comparisons of 5 mg versus 10 mg ephedrine (1 study, 40 babies), 5 mg versus 15 mg (1 study, 40 babies), 10 mg versus 15 mg (1 study, 40 babies), 10 mg versus 20 mg (1 study, 40 babies), 10 mg versus 30 mg (1 study, 40 babies), 20 mg versus 30 mg (1 study, 40 babies); see Analysis 20.5.

No trials reported other secondary outcomes for this comparison.

Ephedrine: slower rate versus faster rate

Primary outcome: maternal hypotension requiring pharmacological intervention

One study compared ephedrine given as a 10 mg in bolus followed by continuous infusion of 2 mg/min versus ephedrine 8 mg/min for 3 min, followed by 4 mg/min for 2 min, then 2 mg/min (Carvalho

2000). Rates of hypotension requiring intervention were higher in the bolus group (RR 3.50, 95% CI 1.26 to 9.72, 1 study, 80 women).

There was insufficient evidence to determine whether there was a difference between the groups, in comparisons of 0.5 mg/min versus 1 mg/min (RR 1.22, 95% CI 0.65 to 2.29, 1 study, 40 women), 0.5 mg/min versus 2 mg/min (RR 1.57, 95% CI 0.77 to 3.22, 1 study, 40 women), 0.5 mg/min versus 4 mg/min (1.22, 95% CI 0.65 to 2.29, 1 study, 40 women), 1 mg/min versus 2 mg/min (average RR 1.24, 95% CI 0.83 to 1.84, 3 studies, 107 women, I2=0%), 1 mg/min versus 3 to 4 mg/min (average RR 1.29, 95% CI 0.81 to 2.05, 2 studies, 99 women, I^2 = 0%), 2 mg/min versus 3 to 4 mg/min (average RR 1.21, 95% CI 0.60 to 2.43, 2 studies, 239 women, I^2 = 38%; Analysis 21.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

One study in 19 women comparing ephedrine 1 mg/min versus 2 mg/min reported bradycardia as an outcome (Hall 1994). There were no events in either arm (Analysis 21.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting, in a comparison of infusion at 1 mg/min versus 2 mg/min (RR 8.18, 95% CI 0.50 to 133.66, 1 study, 19 women; Analysis 21.4).

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea alone in comparisons of ephedrine bolus plus slow infusion versus faster infusion (as described above) (RR 1.83, 95% CI 0.75 to 4.48, 1 study, 80 women), or infusion of 0.5 mg/min versus 1 mg/min (RR 1.29, 95% CI 0.60 to 2.77, 1 study, 40 women), 0.5 mg/min versus 2 mg/min (RR 1.50, 95% CI 0.66 to 3.43, 1 study, 40 women), 0.5 mg/min versus 4 mg/min (RR 1.29, 95% CI 0.60 to 2.77, 1 study, 40 women), 1 mg/min versus 2 mg/min (RR 1.17, 95% CI 0.48, 2.86, 1 study, 40 women), 1 mg/min versus 4 mg/min (RR 1.00, 95% CI 0.43, 2.33, 1 study, 40 women), or 2 mg/min versus 4 mg/min (RR 0.86, 95% CI 0.35 to 2.10, 1 study, 40 women). See Analysis 21.4.

There was insufficient evidence to determine whether there was a difference between the groups in rates of vomiting alone, in comparisons of ephedrine bolus plus slow infusion versus faster infusion (as described above) (RR 1.67, 95% CI 0.43 to 6.51, 1 study, 80 women), or infusion of 0.5 mg/min versus 1 mg/min (RR 0.67, 95% CI 0.12, 3.57, 1 study, 40 women), 0.5 mg/min versus 2 mg/min (RR 2.00, 95% CI 0.20 to 20.33, 1 study, 40 women), 0.5 mg/min versus 4 mg/min (RR 2.00, 95% CI 0.20 to 20.33, 1 study, 40 women), 1 mg/min versus 2 mg/min (RR 3.00, 95% CI 0.34, 26.45, 1 study, 40 women), 1 mg/min versus 4 mg/min (RR 3.00, 95% CI 0.34 to 26.45, 1 study, 40 women) or 2 mg/min versus 4 mg/min (RR 1.00, 95% CI 0.07 to 14.90, 1 study, 40 women). See Analysis 21.4.

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups in comparisons of ephedrine bolus plus slow infusion versus faster infusion (as described above) (RR 1.66, 95% CI 0.53 to 5.23, 1 study, 78 babies), or infusion of 0.5 mg/min versus 1 mg/min (RR 0.33, 95% CI 0.04 to 2.94, 1 study, 40 babies), 0.5 mg/min versus 2 mg/min (3.00, 95% CI 0.13 to 69.52, 1 study, 40 babies), 0.5 mg/min versus 4 mg/min (RR 0.25, 95% CI 0.03, 2.05, 1 study, 40 babies), 1 mg/min versus 2 mg/min (RR 7.00, 95% CI 0.38 to 127.32, 1 study, 40 babies), 1 mg/min versus 4 mg/min (RR 0.75, 95% CI 0.19 to 2.93, 1 study, 40 babies), or 2 mg/min versus 4 mg/min (RR 0.11, 95% CI 0.01 to 1.94, 1 study, 40 babies); see Analysis 21.5.

- Apgar scores of less than 7 or 8 at five minutes

One study in 80 women reported this outcome (Carvalho 2000), comparing ephedrine bolus plus slow infusion versus faster infusion (as described above), and one study in 40 babies compared 0.5 mg/min versus 1 mg/min, 0.5 mg/min versus 2 mg/min, 0.5 mg/min versus 4 mg/min, 1 mg/min versus 2 mg/min, 1 mg/min versus 4 mg/min, and 2 mg/min versus 4 mg/min (Carvalho 1999b). There were no events in either arm of any of these studies (Analysis 21.6).

No trials reported other secondary outcomes for this comparison.

Ephedrine: oral versus intramuscular (IM) or intravenous (IV)

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no conclusive evidence of a difference between the groups when comparing oral versus IM administration of ephedrine (RR 3.00, 95% CI 0.95 to 9.48, 1 study, 40 women). Rates of maternal hypotension were higher in the oral group compared with the IV group (RR 19.00, 95% CI 1.18 to 305.88, 1 study, 40 women). See Analysis 22.1.

Secondary outcomes

Maternal

- Hypertension requiring intervention

There were no events in either arm when comparing oral ephedrine with IM or IV (1 study, 40 women; Analysis 22.2).

- Nausea and/or vomiting

There was no conclusive evidence of a difference between the groups in rates of nausea or vomiting when comparing oral versus IM (RR 1.33, 95% CI 0.34 to 5.21, 1 study, 40 women) or IV administration (RR 9.00, 95% CI 0.52 to 156.91, 1 study, 40 women); see Analysis 22.3.

No trials reported other secondary outcomes for this comparison.

Ephedrine: IM versus IV

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the groups (RR 0.75, 95% CI 0.43 to 1.30, 1 study, 60 women; Analysis 23.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There were no events in either arm when comparing IM ephedrine versus IV (1 study, 60 women; Analysis 23.2).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

There were no events in either arm when comparing IM ephedrine with IV (1 study, 60 babies; Analysis 23.3).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Sensitivity analysis was not possible for this comparison.

Phenylephrine versus control (placebo)

Primary outcome: maternal hypotension requiring pharmacological intervention

Five studies investigating this comparison found less hypotension with phenylephrine compared with control (average RR 0.45, 95% CI 0.26 to 0.80, 280 women, 5 studies, I^2 = 86%, Tau^2 = 0.34; Analysis 24.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of tachycardia (RR 0.87, 95% CI 0.13 to 5.73, 1 study, 56 women) or bradycardia (average RR 3.23, 95% CI 0.17 to 61.85, 3 studies, 180 women, I^2 = 73%, Tau^2 = 4.97); see Analysis 24.2.

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (average RR 0.70, 95% CI 0.16 to 0.80, 3 studies, 180 women, I^2 = 67%, Tau^2 = 0.34; Analysis 24.3).

Neonatal

- Acidosis

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.96, 95% CI 0.06 to 14.50, 1 study, 49 babies; Analysis 24.4).

- Apgar scores of less than 7 or 8 at five minutes

Three studies reported Apgar scores of less than 7 (Ngan Kee 2004a, 50 babies), or of less than 8 (Loughrey 2005; Moslemi 2015, 96 babies). There were no events in any study arm (Analysis 24.5; Analysis 24.6).

No trials reported other secondary outcomes for this comparison.

Phenylephrine versus other regimens or interventions

Phenylephrine versus mephentermine

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 2.00, 95% CI 0.19 to 20.90, 1 study, 60 women; Analysis 25.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 17.00, 95% CI 1.03 to 281.91, 1 study, 60 women; Analysis 25.2).

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 15.00, 95% CI 0.89 to 251.42, 1 study, 60 women; Analysis 25.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 0.20, 95% CI 0.01 to 4.00, 1 study, 60 women) or vomiting (RR 1.00, 95% CI 0.07 to15.26 1 study, 60 women); see Analysis 25.4.

No trials reported other secondary outcomes for this comparison.

Phenylephrine versus metaraminol

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.84, 95% CI 0.23 to 3.06, 1 study, 59 women; Analysis 26.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

Rates of hypertension were lower in the phenylephrine arm (RR 0.25, 95% CI 0.08 to 0.83, 1 study, 59 women; Analysis 26.2).

- Cardiac dysrhythmia

One study reported bradycardia (Bhardwaj 2013, 59 women). No events occurred in either arm (Analysis 26.3).

- Nausea and/or vomiting

One study reported this outcome (Bhardwaj 2013, 59 women). No events occurred in either arm (Analysis 26.4).

Neonatal

- Acidosis

One study reported this outcome (Bhardwaj 2013, 59 babies). No events occurred in either arm (Analysis 26.5).

- Apgar scores of less than 7 or 8 at five minutes

One study reported this outcome (Bhardwaj 2013, 59 babies). No events occurred in either arm (Analysis 26.6).

No trials reported other secondary outcomes for this comparison.

Phenylephrine versus leg compression

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.73, 95% CI 0.46 to 1.15, 1 study, 76 women; Analysis 27.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 0.50, 95% CI 0.05 to 5.28, 1 study, 76 women; Analysis 27.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.00, 95% CI 0.32 to 3.17 1 study, 76 women; Analysis 27.3).

No trials reported other secondary outcomes for this comparison.

Phenylephrine: different regimens

Phenylephrine infusion versus bolus

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.40, 95% CI 0.50 to 3.92, 1 study, 60 women; Analysis 28.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 1.22, 95% CI 0.59 to 2.51, 1 study, 60 women; Analysis 28.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 0.45, 95% CI 0.18 to 1.15, 1 study, 60 women; Analysis 28.3).

Neonatal

- Apgar scores of less than 8 at five minutes

One study reported this outcome (Doherty 2012, 60 babies). No events occurred in either arm (Analysis 28.4).

No trials reported other secondary outcomes for this comparison.

Phenylephrine: lower dose versus higher dose

Primary outcome: maternal hypotension requiring pharmacological intervention

When comparing 50 µg/mL phenylephrine versus 100 µg/mL phenylephrine used as an infusion starting at 60mL/h, rates of hypotension were higher in the lower dose group (RR 8.17, 95% CI 1.04 to 64.30, 1 study, 117 women; Analysis 29.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

When comparing crystalloid plus 50 µg/mL versus 100 µg/mL phenylephrine, there was no conclusive evidence of a difference between the groups (RR 0.23, 95% CI 0.05 to 1.02, 1 study, 117 women; Analysis 29.2).

- Cardiac dysrhythmia

When comparing crystalloid plus 50 µg/mL versus 100 µg/mL phenylephrine, fewer episodes of bradycardia occurred in the lower dose group (RR 0.11, 95% CI 0.01 to 0.80, 1 study, 117 women; Analysis 29.3).

- Nausea and/or vomiting

When comparing crystalloid plus 50 µg/mL versus 100 µg/mL phenylephrine, there was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 3.50, 95% CI 0.37 to 32.67, 1 study, 117 women; Analysis 29.4).

Neonatal

- Acidosis

One study reported this outcome (Ansari 2011, 117 babies). No events occurred in either arm (Analysis 29.5).

- Apgar scores of less than 7 or 8 at five minutes

One study reported this outcome (Ansari 2011, 117 babies). No events occurred in either arm (Analysis 29.6).

No trials reported other secondary outcomes for this comparison.

Glycopyrrolate versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (average RR 0.63, 95% CI 0.21 to 1.91, 2 studies, 142 women; Analysis 30.1).

Secondary outcomes

Maternal

- Hypertension requiring intervention

Rates of hypertension were higher in the glycopyrrolate group (RR 2.67, 95% CI 1.31 to 5.43, 1 study, 93 women; Analysis 30.2).

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 0.21, 95% CI 0.01 to 4.32, 1 study, 93 women; Analysis 30.3).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 2.49, 95% CI 0.69 to 9.04, 1 study, 93 women), or rates of nausea

alone (0.61, 95% CI 0.36 to 1.06, 1 study, 49 women) or vomiting alone (RR 0.52, 95% CI 0.10 to 2.59, 1 study, 49 women; Analysis 30.4).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

Two studies reported this outcome (Ngan Kee 2013a, Ure 1999, 142 babies). No events occurred in either study (Analysis 30.5).

No trials reported other secondary outcomes for this comparison.

Ondansetron versus control

See Summary of findings 5.

Primary outcome: maternal hypotension requiring pharmacological intervention

There was a lower incidence of hypotension in the ondansetron group (average RR 0.67, 95% CI 0.54 to 0.83, 8 studies, 740 women, I^2 = 35%, Tau^2 = 0.05, *low-quality evidence*).

The studies compared doses of 2 mg, 4 mg, 6 mg, and 8 mg ondansetron versus control. The test for subgroup differences indicated a significant difference between the subgroups (Chi^2 = 11.97, df = 3 (P = 0.008), I^2 = 74.9%). The treatment effect was strongest in the 4 mg subgroup, and when we excluded this subgroup from the analysis there was no longer any indication of a difference between the subgroups (Chi^2 = 2.07, df = 2 (P = 0.36), I^2 = 3.3%). The possible explanation for the effectiveness of this lower dose compared with higher doses is unclear (Analysis 31.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was a lower rate of bradycardia in the ondansetron group (average RR 0.49, 95% CI 0.28 to 0.87, 8 studies, 740 women, *low-quality evidence*; Analysis 31.2).

- Nausea and/or vomiting

There was a lower rate of nausea or vomiting in the ondansetron group (average RR 0.35, 95% CI 0.24 to 0.51, 7 studies, 653 women, *low-quality evidence*; Analysis 31.3).

- Anaphylaxis

One study measured this outcome (Wang 2014a, 150 women). There were no events in either arm (Analysis 31.4).

Neonatal

- Acidosis

Two studies measured this outcome. There was insufficient evidence to determine whether there was any difference between the groups (average RR 0.48, 95% CI 0.05 to 5.09, 2 studies, 134 babies, *low-quality evidence)*. There were no events in one of the studies (Analysis 31.6).

- Apgar scores of less than 8 at five minutes

Three studies measured this outcome (Wang 2014a, Wang 2014b, Marciniak 2015, 284 babies, *low-quality evidence*). There were no events in any of the studies (Analysis 31.5).

No trials reported other secondary outcomes for this comparison.

Ondansetron versus ephedrine

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.07, 95% CI 0.76 to 1.49, 1 study, 112 women; Analysis 32.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was no clear evidence of a difference between the groups in the rate of bradycardia (RR 3.00, 95% CI 0.12 to 72.10, 1 study, 112 women; Analysis 32.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in the rate of nausea or vomiting (RR 0.38, 95% CI 0.10 to 1.34, 1 study, 112 women; Analysis 32.3).

No trials reported other secondary outcomes for this comparison.

Granisetron versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

One study, Eldaba 2015, investigated this comparison and found rates of hypotension were lower with granisetron than with saline control (RR 0.05, 95% CI 0.02 to 0.14, 1 study, 200 women; Analysis 33.1).

Secondary outcomes

No studies reported secondary outcomes for this comparison.

Sensitivity analysis

Sensitivity analysis was not possible under this comparison.

Ketamine versus saline

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no conclusive evidence of a difference between the groups (RR 0.79, 95% CI 0.62 to 1.01, 1 study, 105 women). The study compared two different doses of IV ketamine (0.25 mg/kg and 0.5 mg/kg) versus saline.There was no evidence of a difference between the effects of the two doses (test for subgroup differences: Chi^2 = 0.25, df = 1 (P = 0.62), I^2 = 0%; Analysis 34.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (RR 0.79, 95% CI 0.50 to 1.25, 1 study, 105 women; Analysis 34.2).

Neonatal

- Apgar scores of less than 8 at five minutes

One study reported this outcome (Gulhas 2012, 105 women). No events occurred in either arm (Analysis 34.3).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Sensitivity analysis was not possible under this comparison.

Angiotensin versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.09, 95% CI 0.01 to 1.45, 1 study, 20 women; Analysis 35.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.20, 95% CI 0.01 to 3.70, 1 study, 20 women; Analysis 35.2).

Neonatal

- Acidosis

One study reported this comparison (Ramin 1994, 20 babies). There were no events in either arm (Analysis 35.3).

No trials reported other secondary outcomes for this comparison.

Dopamine versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

One small study, Yokoyama 1997, found that dopamine was more effective than control in preventing hypotension (RR 0.05, 95% CI 0.00 to 0.75, 1 study, 30 women; Analysis 36.1).

Secondary outcomes

Neonatal

- Apgar scores of less than 8 at five minutes

One study reported this outcome (Yokoyama 1997, 30 babies). There were no events in either arm (Analysis 36.2).

No trials reported other secondary outcomes for this comparison.

Summary: drugs

In preventing hypotension following spinal anaesthesia at caesarean section, we found the following.

- Ephedrine is more effective than control, crystalloid, or colloid.
- There were no differences in hypotension between ephedrine and phenylephrine, ephedrine and metaraminol, or ephedrine and angiotension. Higher doses or higher rates of ephedrine infusions result in no differences in hypotension. IV ephedrine is associated with less hypotension than oral ephedrine. There is no difference when comparing IM to IV ephedrine.
- Phenylephrine is more effective than control in preventing hypotension. We found no difference in hypotension between phenylephrine and metaraminol.
- We found no clear differences in the incidence of hypotension between glycopyrrolate and control.
- We found no clear differences between ondansetron and control.
- We found no clear differences in hypotension between angiotensin and control, or between ketamine and control.
- Dopamine appears effective for preventing hypotension.

Physical methods

This group of interventions comprises comparisons corresponding to data analyses 37 to 49. Comparison 37 assesses lower limb compression versus control (Summary of findings 6), while other comparisons assess different positioning techniques (see Summary of findings 7 on comparison, 'walking versus lying'), and acupressure.

Lower limb compression versus control

See Summary of findings 6.

Primary outcome: maternal hypotension requiring pharmacological intervention

Lower limb compression was more effective than control for preventing hypotension (average RR 0.61, 95% CI 0.47 to 0.78, 11 studies, 705 women, *very low-quality evidence*; Analysis 37.1). There was substantial heterogeneity (I^2 = 65, Tau^2 = 0.10), which may be due to the different types of compression used (bandages, boots, or stockings). We did not perform a subgroup analysis here as we did not feel it would be meaningful. It also may have been due to differences in formulation and volume of IV fluids given. The asymmetrical funnel plot (Figure 5) may be due to small study effects or publication-type bias.

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups in rates of bradycardia (RR 0.63, 95% CI 0.11 to 3.56, 1 study, 74 women, *very low-quality evidence*; Analysis 37.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea or vomiting (average RR 0.42, 95% CI 0.14 to 1.27, 4 studies, 276 women, I^2 = 32%, *very-low quality evidence*) or rates of nausea alone (RR 1.44, 95% CI 0.25 to 8.20, 1 study, 92 women). One study in 92 women measured rates of vomiting; there were no events in either arm (Sujata 2012; Analysis 37.3).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

Three studies measured this outcome (Adsumelli 2003; Jorgensen 1996; Sood 1996, 130 babies, *very low-quality evidence*). There were no events in any of the studies (Analysis 37.4).

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Removing Bhagwanjee 1990 and Sutherland 2001 made little difference to the overall results in Analysis 37.1.

Comparisons of positioning

Wedge versus supine

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups in the incidence of hypotension (RR 0.85, 95% CI 0.53 to 1.37, 1 study, 80 women; Analysis 38.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 0.27, 95% CI 0.12 to 0.60, 1 study, 80 women) or vomiting (RR 0.11, 95% CI 0.01 to 2.00, 1 study, 80 women); see Analysis 38.2.

No trials reported other secondary outcomes for this comparison.

Sensitivity analysis

Sensitivity analysis was not possible under this comparison.

Head-up tilt versus horizontal

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.71, 95% CI 0.47 to 1.06, 1 study, 40 women; Analysis 39.1).

Secondary outcomes

Neonatal

- Apgar scores of less than 8 at five minutes

One study measured this outcome (Loke 2002, 40 babies). There were no events in either arm (Analysis 39.2).

No trials reported other secondary outcomes for this comparison.

Head-down tilt versus horizontal

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.07, 95% CI 0.81 to 1.42, 1 study, 40 women; Analysis 40.1).

No studies reported secondary outcomes for this comparison.

Crawford's wedge versus manual uterine displacement

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.92, 95% CI 0.57 to 1.49, 1 study, 40 women; Analysis 41.1).

Secondary outcomes

Neonatal

- Apgar scores of less than 8 at five minutes

One study measured this outcome (Amaro 1998, 40 babies). There were no events in either arm (Analysis 41.2).

No trials reported other secondary outcomes for this comparison.

Supine versus sitting

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.81, 95% CI 0.58 to 1.12, 1 study, 98 women; Analysis 42.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 0.65, 95% CI 0.40 to 1.07, 1 study, 98 women) or vomiting (RR 0.38, 95% CI 0.02 to 9.01, 1 study, 98 women; Analysis 42.2).

Neonatal

- Acidosis

One study measured this outcome (Kohler 2002, 98 babies). There were no events in either arm (Analysis 42.3).

- Apgar scores of less than 7 or 8 at five minutes

One study measured this outcome (Kohler 2002, 98 women). There were no events in either arm (Analysis 42.4).

No trials reported other secondary outcomes for this comparison.

Walking versus lying

See Summary of findings 7.

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.71, 95% CI 0.41 to 1.09, 1 study, 37 women, *very low-quality evidence*; Analysis 43.1).

No studies reported secondary outcomes for this comparison.

Sensitivity analysis

Sensitivity analysis was not possible under this comparison.

Lateral versus supine wedged position

Primary outcome: maternal hypotension requiring pharmacological intervention

There was no clear evidence of a difference between the groups (average RR 0.91, 95% CI 0.75 to 1.09, 2 studies, 126 women; Analysis 44.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 0.81, 95% CI 0.45 to 1.48, 1 study, 86 women; Analysis 44.4).

- Cardiac dysrhythmia

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.50, 95% CI 0.05 to 5.08, 1 study, 40 women; Analysis 44.2.

Neonatal

- Admission to neonatal intensive care unit

One study measured this outcome (Hartley 2001, 40 babies). There were no events in either arm (Analysis 44.3).

No trials reported other secondary outcomes for this comparison.

Left lateral versus left lateral tilt

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 1.20, 95% CI 0.80 to 1.79, 1 study, 58 women; Analysis 45.1).

Secondary outcomes

Maternal

- Cardiac dysrhythmia

There was no conclusive evidence of a difference between the groups in rates of bradycardia (RR 0.10, 95% CI 0.01 to 1.68, 1 study, 58 women; Analysis 45.2).

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 0.45, 95% CI 0.18 to 1.11, 1 study, 58 women) or vomiting (RR 0.15, 95% CI 0.01 to 2.83, 1 study, 58 women; Analysis 45.3).

No trials reported other secondary outcomes for this comparison.

Left lateral tilt versus left manual uterine displacement

Primary outcome: maternal hypotension requiring pharmacological intervention

Left uterine displacement was associated with a reduced rate of hypotension compared to left lateral tilt (RR 0.63, 95% CI 0.49 to 0.80, 1 study, 90 women; Analysis 46.1).

No studies reported other outcomes for this comparison.

Leg elevation versus control

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.73, 95% CI 0.42 to 1.26, 1 study, 63 women; Analysis 47.1).

No other outcomes were reported for this comparison

Comparisons of acupressure

Acupressure versus placebo

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.84, 95% CI 0.58 to 1.22, 1 study, 50 women; Analysis 48.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

Rates of nausea were lower in the acupressure group than in the placebo group (RR 0.32, 95% CI 0.15 to 0.66, 1 study, 50 women). There was no clear evidence of a difference between the groups in rates of vomiting (RR 0.50, 95% CI 0.14 to 1.78, 1 study, 50 women). See Analysis 48.2.

- Apgar scores of less than 7 at five minutes

One study measured this outcome (Stein 1997, 50 babies). There were no events in either arm (Analysis 48.3).

No trials reported other secondary outcomes for this comparison.

Acupressure versus metoclopramide

Primary outcome: maternal hypotension requiring pharmacological intervention

There was insufficient evidence to determine whether there was a difference between the groups (RR 0.94, 95% CI 0.63 to 1.40, 1 study, 50 women; Analysis 49.1).

Secondary outcomes

Maternal

- Nausea and/or vomiting

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea (RR 1.50, 95% CI 0.48 to 4.68, 1 study, 50 women) or vomiting (RR 3.00, 95% CI 0.33 to 26.92, 1 study, 50 women; Analysis 49.2).

Neonatal

- Apgar scores of less than 7 or 8 at five minutes

One study measured Apgar scores of less than 7 at five minutes (Stein 1997, 50 babies). There were no events in either arm (Analysis 49.3).

No trials reported other secondary outcomes for this comparison.

Summary: physical methods

In preventing hypotension following spinal anaesthesia at caesarean section, we found the following.

- Lower leg compression is more effective than control (i.e. no leg compression) for preventing hypotension, although different methods of compression appear to vary in their effectiveness.
- Manual left uterine displacement while supine is more effective than left lateral tilt of the bed for preventing hypotension.
- In other comparisons between different physical methods such as position, wedging or leg elevation, we found none to be effective, but these trials were often small and may benefit from further research. Similarly, walking into the operating theatre as opposed to lying on the barouche is a non-invasive, safe, and simple intervention and may also be worth further investigating in a larger study.
- There was insufficient evidence to show whether acupressure is more effective than placebo or metoclopramide.

DISCUSSION

This review is the most comprehensive to date examining the effects of interventions used to prevent hypotension following spinal anaesthesia for caesarean section.

Summary of main results

Although some interventions assessed in this review (such as colloids, ephedrine, or lower leg compression) can reduce the incidence of hypotension, we found none that eliminate the need to treat maternal hypotension during spinal anaesthesia for caesarean section. It is likely that one or more interventions used together, as commonly occurs in clinical practice, is most effective.

Our key findings include the following.

Fluids

- Crystalloids alone may be inadequate for preventing hypotension.
- Crystalloids may be most effective when given in higher volume as a rapid coload.
- Colloids may be more effective than crystalloids.

Drugs

- Vasopressors, such as ephedrine, phenylephrine, and metaraminol appear to be effective and may be more effective than fluids alone or control.
- Ondansetron may be more effective than control for preventing hypotension.
- There is no clear evidence to show that glycopyrrolate, ketamine, or angiotensin are effective for preventing hypotension.

Physical methods

- Lower leg compression is more effective than control for preventing hypotension.
- Manual uterine displacement while supine may be more effective than left lateral tilt.
- We did not find other physical methods such as position, wedging, or leg elevation to be effective, but these trials were often small and may benefit from further research.

Mortality and serious morbidity in this population are rare (Hibbard 1996). The reviewed trials report no serious adverse events such as anaphylaxis, cerebral haemorrhage, or maternal death. We did not see any differences in the incidence of fetal acidosis when comparing ephedrine with phenylephrine for preventing hypotension during spinal anaesthesia, although Ngan Kee 2006 has suggested an increased risk when using ephedrine to treat, rather than prevent, hypotension.

Overall completeness and applicability of evidence

This review is very likely to represent the key research findings to date and to be applicable to clinical practice. We suggest some caution about the magnitude of the findings of some intervention comparisons given that many of these comparisons are only supported by either a single study or several small studies of unclear quality. Despite our finding that colloids were more effective than crystalloids for reducing maternal hypotension after spinal anaesthesia, the included trials were too small to show the well-recognised and serious potential risks that colloid administration represents.

The findings of this review will be less relevant for women with pre-eclampsia, who appear less likely to require prophylactic measures or emergency procedures than normotensive women (Clark 2005). Most studies in this review excluded women with pre-existing hypertension.

One of the main limitations of a review of this type is outcome definition. There were multiple different definitions of hypotension between studies (Table 1). In this review, we used the definition of hypotension provided by study authors to pool these data in our meta-analyses.

All studies investigated women having elective caesarean births except for one study that included women undergoing emergency caesarean sections.

As can be seen from the Results section and from the meta-analyses, we found a large number of small studies with little to no information for enabling an adequate 'Risk of bias' assessment. Many studies did not report details about their method of randomisation, allocation concealment, and blinding, which limits our ability to draw clear conclusions. Furthermore, several pooled results showed high levels of heterogeneity between studies, which is most likely due to differences in study design interventions, anaesthetic techniques and variations in definition of hypotension.

We note that there are several studies awaiting assessment and acknowledge that there will be a lag time in assessing and incorporating these studies in future reviews. However, it appears unlikely that these studies will impact our key findings.

Quality of the evidence

The GRADE assessments for the key outcomes (incidence of maternal hypotension/hypertension requiring intervention; incidence of maternal bradycardia; incidence of maternal nausea and/or vomiting; neonatal acidosis as defined by cord or neonatal bloods with a pH of less than 7.2; neonatal Apgar score of

less than 8 at five minutes; admission to neonatal intensive care unit) showed either low or very low quality. We chose six key comparisons for GRADE quality assessments because they represent the most clinically relevant comparisons in the updated review (see Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7). Many studies were small, and their lack of detail in reporting led us to assess them as being at unclear risk of bias in method of randomisation, allocation concealment, and blinding. Seventeen studies had one or more factors designated as causing high risk of bias, but sensitivity analyses removing 12 studies where possible did not change the findings (Bhagwanjee 1990; Bottiger 2010; Cardoso 2004a; Carvalho 2009; Dahlgren 2005; Dyer 2004; Magalhaes 2009; Mercier 2014; Muzlifah 2009; Romdhani 2014; Sutherland 2001; Ueyama 1999). The remaining five studies were single studies for which sensitivity analyses were not possible (Calvache 2011; Cyna 2010; Eldaba 2015; Gulhas 2012; Pouliou 2006). As well as for study design, we downgraded evidence for indirectness (because most studies included only women having elective caesarean sections), inconsistency, and imprecision.

We noted significant heterogeneity for some comparisons, namely crystalloid versus colloid, colloid of different volumes, ephedrine versus control, ephedrine versus crystalloid, ephedrine versus phenylephrine. Sensitivity analysis showed minimal changes in overall findings.

Potential biases in the review process

There are several potential sources of bias in this review process.

Firstly, there were several differences between previous published versions and this version, including:

- specific exclusion of quasi-randomised, cluster, and cross-over trials; and
- specific exclusion of studies investigating prevention of hypotension with combined spinal-epidural techniques.

Given the large number of randomised controlled trials investigating the core review objective (assessing the effects of prophylactic interventions for hypotension following spinal anaesthesia for caesarean section), the authors agreed that incorporating these trials into this review would contribute to a lower quality and less robust review.

Secondly, one of the review authors (AMC) was the lead author on an included study (Cyna 2010). We minimised this potential source of bias by ensuring that review authors independent of this study (RSL and CC) performed the data extraction.

Thirdly, there were 2 studies assessed as high risk as study participants received variable doses of local anaesthetic in their spinal block (Alahuhta 1992; Mathru 1980). Also, there were 2 studies assessed as high risk of bias as it was unclear whether the spinal anaesthetic technique and dose was standardised between the study groups (Ozkan 2004; Wilson 1998). It was unlikely that with randomisation this source of bias would have an important effect on the review findings.

Finally, for the purposes of this review, we specifically excluded the use of infusion pumps programmed with algorithms to address hypotension. It was difficult to determine whether this approach constituted prevention or treatment of hypotension, but discussion among review authors produced a consensus that it was the latter. Future reviews may consider whether it may be appropriate to include the results of these other computer-controlled techniques.

Agreements and disagreements with other studies or reviews

Our results are consistent with one meta-analysis that found that prophylactic ondansetron reduces the incidence of spinal induced hypotension (Gao 2015). This meta-analysis also suggested that given the large heterogeneity and small sample sizes, there should be further large and high-quality randomised trials investigating the efficacy of ondansetron for preventing hypotension in this setting.

Our results are also consistent with a systematic review that found limited evidence to support or clearly disprove the value of maternal positioning, including the use of table tilting and wedges (Cluver 2013). They also found that manual displacement of the uterus may be better than a left lateral tilt, but larger studies need to confirm this – a conclusion consistent with our results.

Finally, a recent review determined the effects of colloids and crystalloids in the incidence of hypotension induced by spinal anaesthesia in elective caesarean section and also showed that colloid administration reduced the incidence of hypotension associated with spinal anaesthesia in elective caesarean section compared with crystalloid use (Rippoles 2015). However, these authors make no mention of the serious potential risks that colloid administration may represent or the additional costs involved. Indeed, a recent Cochrane Review found no evidence that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids in patients with trauma, burns, or following surgery. The review authors suggest that as colloids were no more effective for preventing mortality than crystalloid and were considerably more expensive, it is hard to see any justification for their continued use in clinical practice (Perel 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review will be mostly applicable to obstetric anaesthesia where women are having planned caesarean section under spinal anaesthesia. No single or combined prophylactic intervention avoids the need to treat some women for hypotension following spinal anaesthesia for caesarean section. Colloid or crystalloid preloading or coloading, the administration of parenteral ephedrine, phenylephrine, metaraminol, and ondansetron, and lower limb compression (by bandages, stockings or inflatable boots) reduce but do not eliminate the incidence of spinal hypotension requiring intervention in this setting. Despite colloids being more effective than crystalloids for reducing the incidence of maternal hypotension, the well-recognised serious potential risks and additional costs that colloid administration may represent also need consideration. It is not possible to draw conclusions with respect to the optimum volume of intravenous fluid, route or timing of administration of vasopressors, or method of lower limb compression. Ephedrine may produce a dose-related increase in blood pressure and heart rate. We cannot draw any other conclusions regarding adverse effects of the studied interventions, probably due to their low incidence, the small

number of women studied, and the incompleteness of data for these outcomes. It is likely that combinations of interventions will be more effective than individual ones.

Implications for research

Suggested clinical trials

- Timing of sympathomimetic administration (for example: ephedrine, phenylephrine)
- Optimum fluid-preloading or coloading volume (dose-finding)
- Comparison of the relative efficacy and adverse effects of different methods of lower limb compression, for example, inflatable boots or thromboembolic deterrent stockings
- Further study of haemodynamic stability in labouring versus non-labouring women receiving spinal anaesthesia for caesarean section (one small study to date, Lapins 2001)
- Optimal dose of ondansetron
- Other drugs such as norepinephrine
- Walking versus lying on a bed when entering the operating theatre prior to spinal anaesthesia
- Computer-controlled closed loop infusion algorithms

Future studies in this area could: include clearer reporting of methodological aspects, such as allocation, to confirm internal validity; have larger sample sizes (i.e. at least 100 participants); and include an assessment of maternal acceptability of the various prophylactic interventions under investigation. Future research could avoid interventions that fail to use standard, externally valid comparisons. Most importantly, future studies need to report the incidence of hypotension requiring an intervention. For comparisons where there are many existing studies, any further studies need to be higher quality and involve larger sample sizes.

It would also be important to obtain further information on the potential serious but rare side effects of colloid administration in this setting, from large-scale epidemiological studies or registries.

Suggested systematic reviews

Our initial search identified several trials comparing different anaesthetic techniques or drugs, which may have an impact on haemodynamics, for example the possible local anaesthetic-sparing effect of spinal opioids such as morphine, fentanyl, or the shorter-acting sufentanil. It may also be that the incidence of hypotension can be predictably affected by the technique itself rather than (or in addition to) the prophylactic measures we have examined.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adsumelli 2003

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: healthy term parturients, elective CS under spinal anaesthesia, ASA I-II. *Exclusion criteria*: women with chronic hypertension, multiple pregnancy, pregnancy-induced hypertension, diabetes mellitus, body weight > 110 kg and contraindications to a spinal anaesthetic *Setting*: USA
Interventions	**Compression device versus no compression device** Group 1 (n = 25): sequential compression device; with thigh-high sleeves and a preset pressure of 50 mmHg Group 2 (n = 25): no sleeves on lower limbs Preloading with 20 mL/kg Ringer's lactate Standardised anaesthetic technique and dose for all women
Outcomes	*Maternal*: hypotension *Neonatal*: Apgar score < 8 at 5 min
Notes	Hypotension: defined as decrease MAP measurement by > 20% of baseline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method unknown
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes." No further detail given

Adsumelli 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Hypotension treated by an anaesthetist who was blinded to the assigned group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Alahuhta 1992

Study characteristics	
Methods	RCT
Participants	19 women *Inclusion criteria*: healthy women undergoing elective caesarean under spinal anaesthesia (38-42 weeks' gestation) for fetal breech presentation or cephalopelvic disproportion in otherwise uncomplicated singleton pregnancies *Exclusion criteria*: not reported *Setting*: Finland
Interventions	**Ephedrine versus phenylephrine** Group 1 (n = 9): ephedrine (mean 27.9 mg, range 16.7 to 32.5) Group 2 (n = 8): phenylephrine (mean 488 µg, range 334 to 767) Standardised anaesthetic technique for all women but variable heavy 0.5% bupivicaine dose (range 2.3-2.6 mL)
Outcomes	*Maternal*: hypotension (defined as a fall in SAP of more than 10 mmHg from baseline); heart rate *Neonatal*: arterial umbilical blood < pH 7.2; Apgar < 8 at 5 min; fetal heart rate; birthweight
Notes	Hypotension requiring intervention: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Alahuhta 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double blind" – third-party preparation and coding of solutions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/19 – 1 from each group; 1 technical failure, 1 maternal bradycardia requiring atropine treatment
Selective reporting (reporting bias)	Unclear risk	Not all expected outcomes were reported
Other bias	High risk	Similar baseline characteristics Variable dose of local anaesthetic used for spinal anaesthesia

Alimian 2014

Study characteristics	
Methods	RCT
Participants	90 women undergoing elective caesarean section *Inclusion criteria*: normal single pregnancy, gestational age > 37 weeks, no history of hypertension *Exclusion criteria*: contraindications for spinal anaesthesia, third trimester bleeding, BMI > 30 kg/m^2, previous allergy to hydroxyethyl starch (HES) preparations, known cardiomyopathy, height < 155 cm, sympathetic block higher than T4 *Setting*: France and USA
Interventions	**Ringer's lactate preload vs sodium chloride preload vs HES preload** Group 1: Ringer's lactate group, 1000 mL Group 2: sodium chloride 0.9% group, 1000 mL Group 3: HES group, 7.5 mL/kg
Outcomes	*Maternal*: BP, heart rate *Neonatal*: umbilical cord pH, Apgar score
Notes	Hypotension was defined as a drop in systolic blood pressure of > 20% from baseline or systolic blood pressure < 100 mmHg.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation technique

Alimian 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" – no further detail provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" – no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	None evident

Allen 2010

Study characteristics	
Methods	RCT
Participants	109 women *Inclusion criteria*: ASA physical status I and II pregnant women scheduled for elective caesarean delivery under spinal anaesthesia; singleton gestation at a gestational age of > 36 weeks *Exclusion criteria*: women who were in labour, BMI > 45 kg/m^2, type 1 diabetes mellitus, hypertensive disease, cardiac disease, a fetus with severe congenital anomalies, history of monoamine oxidase inhibitor use, or those who were included in any other anaesthesia drug studies *Setting*: USA
Interventions	**Phenylephrine dosage variations versus placebo** Group 1: phenylephrine infusion 25 µg/min Group 2: phenylephrine infusion 50 µg/min Group 3: phenylephrine infusion 75 µg/min Group 4: phenylephrine infusion 100 µg/min Group 5: placebo (normal saline 50 mL) infusion All infusions were commenced immediately after spinal injection, at 60 mL/h in combination with a standardised fluid coload. The study drug was infused until 10 min after delivery, after which the study ended and further management was at the discretion of the anaesthesiologist. All women received a standardised aspiration prophylaxis, a standardised spinal anaesthetic technique and dose, and a standardised oxytocin bolus and subsequent infusion after delivery.

Allen 2010 *(Continued)*

	Hypotension (requiring intervention) was treated by administering a 100 µg bolus of phenylephrine. Hypertension treatment: treated by stopping the infusion. Infusions were only restarted when the SBP decreased to below the upper limit of the target range above baseline). NOTE: if the study drug infusion had to be stopped on 3 occasions, then it was stopped permanently, and BP was maintained with phenylephrine boluses for the remainder of the study. Bradycardia treatment: administration of glycopyrrolate 0.4 mg
Outcomes	*Maternal*: hypotension, pre and postdelivery birth; hypotension requiring intervention; nausea and vomiting; cardiac dysrhythmia; pre and postbirth reactive hypertension; bradycardia *Neonatal*: acidosis (cord or neonatal bloods with pH < 7.2); neonatal Apgar score < 8 at 5 min
Notes	Hypotension defined as SBP < 20% below baseline Hypotension requiring intervention defined as SBP decrease > 20% baseline or < 90 mmHg Hypertension defined as SBP > 20% above baseline Bradycardia defined as < 50 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of 20
Allocation concealment (selection bias)	Unclear risk	Each study syringe was identified by a study number. The infusions were prepared in identical 50 mL syringes by a physician not involved in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind". To maintain blinding, the infusions were prepared in identical 50 mL syringes containing normal saline for the placebo, or the appropriate concentrations of phenylephrine (25 µg, 50 µg, 75 µg, or 100 µg) for the drug interventions. A physician not involved in the study coded and prepared the syringes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated who was responsible for recording of outcomes, and whether they were blinded to the allocated intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/109 patients excluded (not specified which groups they were from), due to inadequate or failed spinal anaesthesia. Insufficient samples were obtained for umbilical cord blood gases for some babies because of insufficient samples, clotted samples or sampling errors: 1 (placebo group); 2 (phenylephrine 25 µg group); 2 (phenylephrine 50 µg group) and 5 (phenylephrine 100 µg group).
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	No apparent sources of other bias Study funded by Duke University Medical Center Department of Anesthesiology, Division of Women's Anesthesia

Amaro 1998

Study characteristics	
Methods	Randomisation: method not described
Participants	40 women *Inclusion criteria*: ASA I, term, singleton, cephalic, elective CS *Exclusion criteria*: not specified *Setting*: Brazil
Interventions	**Crawford's wedge versus uterine displacement** Group 1 (n = 20): wedged lateral position using modified Crawford's wedge (15 degrees left lateral tilt) Group 2 (n = 20): manual uterine displacement by surgical assistant All women received a standardised preload and standardised spinal anaesthetic technique and dose
Outcomes	*Maternal*: hypotension, magnitude of BP reduction and time of occurrence, block height, ephedrine consumption, induction – and hysterotomy – birth times. *Neonatal*: umbilical artery pH (expressed as mean and SD), Apgar scores at 1 min and 5 min
Notes	Hypotension defined as decrease in SBP > 20% baseline or < 100 mmHg absolute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation methods not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Ansari 2011

Study characteristics	
Methods	RCT
Participants	128 women *Inclusion criteria*: women with a normal singleton pregnancy at 37 weeks' gestation or more scheduled for elective CS *Exclusion criteria*: ASA grade III or more; height < 150 cm or > 180 cm; body mass < 60 kg or > 100 kg; pre-eclampsia; known fetal abnormality; or any other contraindication to spinal anaesthesia *Setting*: United Arab Emirates
Interventions	**Phenylephrine 50 µg versus 100 µg infusion** Group 1: phenylephrine 50 µg/mL infusion Group 2: phenylephrine 100 µg/mL infusion Phenylephrine infusion was commenced immediately after spinal anaesthesia in conjunction with standardised IV coload with warm Hartmann's solution. Initial phenylephrine rate of 60 mL/h for the first 3 min and stopped if SBP was > 120% of the baseline. After the first 3 min, the infusion was continued at the same rate if SBP was between 80% and 100% of baseline, until the time of giving birth; infusion was discontinued if the SBP was more than 100% of baseline value. All women received standardised aspiration prophylaxis and standardised spinal anaesthetic technique and dose. Hypotension requiring intervention: rescue dose of phenylephrine 50 µg if BP decreased to < 80% baseline for 2 consecutive readings, despite phenylephrine infusion. Bradycardia requiring intervention: if bradycardia without hypotension, phenylephrine infusion was discontinued for 1 min; if bradycardia developed with hypotension, IV glycopyrronium 200 µg was administered.
Outcomes	*Maternal*: BP; hypotension; hypertension; bradycardia; total dose of phenylephrine; nausea and vomiting *Neonatal*: Apgar scores at 1 min and 5 min; umbilical arterial pH and gases
Notes	Hypotension defined as SBP < 80% baseline Hypertension defined as SBP > 120% baseline Bradycardia defined as heart rate < 50 bpm

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" – no further details reported
Allocation concealment (selection bias)	Unclear risk	"Closed similar" envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	An anaesthetist who was not involved in case management prepared a 20 mL syringe for phenylephrine infusion with the designated concentration; both women and the anaesthetist in charge of the case were blinded to the concentration of phenylephrine in the syringe

Ansari 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but likely in view of the above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/128 lost to follow-up (not reported by assigned group): • inadequate block and repeat subarachnoid injection required (n = 2) • trial design not strictly followed (n = 4) • umbilical blood gas results had technical problems (n = 5)
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported.
Other bias	Unclear risk	Some suggestion of imbalance in randomisation and/or differential losses to follow-up (54 and 63 women analysed in each group)

Arora 2015

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA grade I/II, full term (36-40 weeks' gestation), uncomplicated singleton pregnancy, elective LSCS under spinal anaesthesia *Exclusion criteria*: fetal distress, antepartum haemorrhage, pregnancy-induced hypertension, diabetes mellitus, multiple gestation, significant cardiorespiratory disorder or intrapartum cardiomyopathy *Setting*: India
Interventions	**Colloid preload versus colloid coload versus crystalloid preload** Group 1: 10 mL/kg colloid preload (6% HES administered 20 min prior to SAB) Group 2: 10 mL/kg colloid co-load (6% HES administered by rapid infusion in 10 min immediately after SAB) Group 3: 10 mL/kg crystalloid preload (Ringer's lactate administered 20 min prior to SAB) All women received the same aspiration prophylaxis, anaesthetic technique and dose, IV cannula. 10 min after induction of spinal anaesthesia, normal saline was given in all 3 groups at rate of 200 mL/h. Hypotension was treated by increasing rate of fluid infusion and IV ephedrine 5 mg until the BP had improved to within 20% of baseline.
Outcomes	*Maternal*: incidence of hypotension, dose of ephedrine
Notes	Hypotension was defined as SBP < 80% baseline
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation

Arora 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Bhagwanjee 1990

Study characteristics	
Methods	RCT
Participants	24 women *Inclusion criteria*: healthy, term parturients undergoing elective CS. *Exclusion criteria*: placental dysfunction, intrauterine growth retardation, abnormal fetal presentation, weight more than 90 kg *Setting*: South Africa
Interventions	**Lower limb compression versus control** Group 1: legs wrapped with 10 cm Esmarch bandages from ankle to mid-thigh immediately following spinal with preservation of pedal pulses Group 2: control All women received standardised IV preload with plasmalyte followed by a standardised spinal anaesthetic technique and dose
Outcomes	*Maternal*: hypotension; spinal to birth time; uterine incision to birth time *Neonatal*: Apgar scores (minus colour) at 2 min and 5 min; umbilical arterial and venous blood gas oxygen tension and saturation
Notes	Hypotension defined as SBP < 100 mmHg or less than 80% baseline
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Bhagwanjee 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not reported – unlikely due to nature of intervention (leg wrapping)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not reported
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	Similar baseline characteristics. None apparent

Bhardwaj 2013

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA grade I, elective CS under spinal anaesthesia, singleton pregnancy, no fetal abnormalities, no pre-eclampsia, no cerebrovascular diseases *Setting*: India
Interventions	**Phenylephrine infusion versus ephedrine infusion versus metaraminol infusion** Group 1: phenylephrine 30 µg/mL (15 µg/min) Group 2: ephedrine 5 mg/mL (2.5 mg/min) Group 3: metaraminol 0.5 mg/mL (0.25 mg/min) Immediately following SAB, patients received 1 mL bolus of study drug and then a infusion at 15 mL/h All women received standardised: aspiration prophylaxis, monitoring, IV cannulation, isotonic saline coload, spinal anaesthetic technique and dose If SBP increased 1.25 times above baseline, infusion was ceased. If SBP dropped 10% below the baseline, 1 mL bolus of study drug given. If maternal heart rate < 60 bpm and SBP < 80% of baseline, or if maternal heart rate < 50 and SBP < 100% of baseline, or if maternal heart rate < 45 regardless of BP, glycopyrrolate 0.2 mg IV given
Outcomes	*Maternal*: incidence of maternal hypotension, incidence of maternal hypertension, heart rate, nausea/vomiting, total dose of vasopressor

Bhardwaj 2013 *(Continued)*

	Neonatal: Apgar scores at 1 min and 5 min, umbilical cord gases
Notes	Hypotension: SBP < 80% of baseline Hypertension: SBP > 120% of baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomised sequence
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Study drugs prepared by another anaesthetist not involved in other aspects of the participants' care, into a unlabelled 20 mL syringe
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Below exclusions reported: Group 2 – 1 failed SAB Group 3 – 1 failed SAB Group 1 – 2 pump failures
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Bottiger 2010

Study characteristics

Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I/II, elective caesarean delivery *Exclusion criteria*: none stated *Setting*: USA
Interventions	**Crystalloid preload versus colloid preload** Group 1: crystalloid preload (1500 mL Ringer's lactate) Group 2: colloid preload (0.5L 6% HES)

Bottiger 2010 *(Continued)*

	Women in both groups received 100 µg/min phenylephrine infusion following spinal anaesthesia which continued until uterine incision. The phenylephrine infusion was adjusted according to heart rate and SBP which was maintained at 20% of the baseline. No further information regarding spinal anaesthetic technique/dose etc was provided.
Outcomes	*Maternal*: vasopressor dose, incidence of hypotension, incidence of nausea and vomiting, incidence of bradycardia *Neonatal*: Apgar score
Notes	Hypotension was defined as a 20% fall in SBP from baseline. Hypertension was defined as an increase of 20% from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method not explicitly stated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	3 women excluded for unspecified reasons and at an unclear point along the study pathway Additionally, study states "60 patients were included as part of a 90 patient study"
Selective reporting (reporting bias)	Low risk	None evident
Other bias	Low risk	None evident

Bouchnak 2012

Study characteristics

Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I scheduled for elective CS, singleton term pregnancy *Exclusion criteria*: chronic or gestational hypertension, cardiac disease, diabetes, known fetal abnormalities, contraindication to spinal anaesthesia

Bouchnak 2012 *(Continued)*

	Setting: Tunisia
Interventions	**Colloid preload versus crystalloid preload** Group 1: HES 130/0.4 500 mL preload 15 min prior to spinal anaesthesia. Group 2: saline – normal saline solution preload 1000 mL within 15 min prior to spinal anaesthesia All women received standardised anaesthetic technique and dose. Hypotension requiring intervention: 6 mg bolus ephedrine when SBP was < 80% of baseline.
Outcomes	*Maternal*: hypotension; SBP; adverse effects; need for ephedrine; heart rate; tachycardia (> 100 bpm); nausea; vomiting; pruritus *Neonatal*: umbilical blood gases; Apgar scores ar 1 min and 5 min; birthweight
Notes	Hypotension defined as SBP < 80% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported only as "randomized"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Some outcomes not fully (numerically) reported
Other bias	Low risk	Similar baseline characteristics

Calvache 2011

Study characteristics

Methods	RCT
Participants	80 women *Inclusion criteria*: ASA I/II women aged 18-45 years with an uncomplicated singleton pregnancy at term who were scheduled for caesarean under spinal anaesthesia

Calvache 2011 *(Continued)*

	Exclusion criteria: pregnancy-induced hypertension, cardiac disease, diabetes, fetal complications and women in labour: post hoc exclusions (surgery lasting > 2 h; requirement for perioperative sedation; conversion to general anaesthesia, surgical complications such as intraoperative haemorrhage, protocol violations) *Setting*: Colombia
Interventions	**Wedge versus supine position** Group 1: wedge after intrathecal injection women were placed from the left lateral position to the supine position, with a right-lumbar pelvic wedge (wooden, 35 cm long, 20 cm wide and with 20 degrees inclination), placed at the right posterior-superior iliac crest and lumbar region Group 2: supine: after intrathecal injection, women were placed from the left lateral position to the supine position All women received no premedication, standardised oxygen therapy, standardised spinal anaesthetic technique and dose, and standardised crystalloid co-load Hypotension was treated with IV boluses of ethylephrine 1 mg until hypotension was corrected. Bradycardia was treated with 0.5 mg atropine.
Outcomes	*Maternal*: hypotension BP; vasopressor requirements (median ethylephrine consumption); nausea; vomiting; bradycardia
Notes	Hypotension was defined as a 25% reduction in SBP from baseline. Bradycardia was defined as heart rate < 40 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	"Randomly allocated" ... "by independent anesthetist"; no further details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	A single unblinded anaesthetist performed spinal anaesthesia, positioning of women, anaesthetic management and data collection
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data analysis was blinded, but not mentioned if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	High risk	No neonatal outcomes reported
Other bias	Low risk	Similar baseline characteristics

Cardoso 2004a

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: term singleton pregnancies, ASA I, undergoing caesarean under spinal anaesthesia *Exclusion criteria*: chronic hypertension, gestation-induced hypertension, cardiovascular or vascular brain disease, known fetal abnormalities and women with total or partial spinal anaesthesia failure *Setting*:Brazil
Interventions	**Colloid versus crystalloid preload:** Group 1: received preload of modified fluid gelatin, 10 mL/kg Group 2: received preload of Ringer's lactate, 10 mL/kg All women received a standardised spinal anaesthetic technique and dose and standardised uterine displacement.
Outcomes	*Maternal*: hypotension; nausea; vomiting; vasopressor consumption *Neonatal*: cord blood (presented as mean and SD); Apgar < 7 at 5 min
Notes	Hypotension was defined as decreases of more than 10% or more than 20% of baseline SBP.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomly allocated": method not described
Allocation concealment (selection bias)	Unclear risk	"Drawing of closed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" – no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	High risk	Minimal results reporting: outcomes reported as means and SD only
Other bias	Low risk	Similar baseline characteristics

Carvalho 1999a

Study characteristics	
Methods	RCT
Participants	N = 80 *Inclusion criteria*: healthy women undergoing spinal anaesthesia for elective caesarean *Exclusion criteria*: not specified *Setting*: Brazil
Interventions	**Ephedrine (different doses) versus control** Group 1: 5 mg ephedrine administered immediately after spinal anaesthesia Group 2: 10 mg ephedrine administered immediately after spinal anaesthesia Group 3: 15 mg ephedrine administered immediately after spinal anaesthesia Group 4: control – no ephedrine Standardised spinal anaesthetic technique and dose
Outcomes	*Maternal*: hypotension; nausea; vomiting; hypertension requiring intervention *Neonatal*: cord/neonatal blood < 7.2; Apgar < 8 at 5 min
Notes	Hypotension defined as fall in SAP below 20% baseline Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, but method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Carvalho 1999b

Study characteristics	
Methods	Randomised trial
Participants	100 women *Inclusion criteria*: healthy women undergoing spinal anaesthesia for elective caesarean *Exclusion criteria*: not specified *Setting*: Brazil
Interventions	**Ephedrine infusion (different rates) versus control** Group 1: ephedrine infusion 0.5 mg/min administered immediately after spinal anaesthesia Group 2: ephedrine infusion 1 mg/min administered immediately after spinal anaesthesia Group 3: ephedrine infusion 2 mg/min administered immediately after spinal anaesthesia Group 4: ephedrine infusion 4 mg/min administered immediately after spinal anaesthesia Group 5: no ephedrine All women received a standardised anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; vomiting; hypertension requiring intervention. *Neonatal*: cord/neonatal blood < 7.2; Apgar < 8 at 5 min
Notes	Hypotension defined as fall in SAP below 20% baseline Abstract only

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Carvalho 1999b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Carvalho 2000

Study characteristics	
Methods	RCT
Participants	120 women *Inclusion/exclusion criteria*: not available as whole paper was not translated *Setting:* Brazil
Interventions	**Ephedrine bolus + infusion versus ephedrine infusion alone versus rescue bolus of ephedrine only** Group 1: ephedrine 10 mg in bolus followed by continuous infusion of 2 mg/min until birth Group 2: ephedrine 8 mg/min for 3 min, followed by 4 mg/min for 2 min, then 2 mg/min until birth Group 3: control: Ringer's lactate preload and rescue bolus of ephedrine in case of hypotension All women received a standardised preload of Ringer's lactate and standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; nausea; vomiting; hypertension requiring intervention *Neonatal*: umbilical artery pH; Apgar < 8 at 5 min
Notes	Hypotension defined as SBP < 80% of baseline Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	Losses to follow-up: 2/120 for cord blood pH measurement (in the ephedrine infusion group)

Carvalho 2000 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Carvalho 2009

Study characteristics	
Methods	RCT
Participants	46 women *Inclusion criteria*: women scheduled for caesarean under spinal anaesthesia; age 18-54 years; weight ≤ 100 kg; height ≥ 150 cm; ASA physical status I or II; uncomplicated term pregnancy *Exclusion criteria*: pregnancy-induced hypertension; cardiac disease; diabetes or fetal complications; women in labour *Setting*: USA
Interventions	**Colloid preloading versus colloid coloading** Group 1: colloid preload: 500 mL 6% hetastarch IV slowly over 20 min before spinal anaesthesia Group 2: colloid coload: 500 mL 6% hetastarch IV as quickly as possible, with the aid of a pressure bag, immediately after spinal anaesthesia All women received standardised aspiration prophylaxis and standardised spinal anaesthetic technique and dose. Hypotension requiring intervention was managed with vasopressor mix of 5 mg/mL ephedrine plus 25 µg/mL phenylephrine given according to a strict predefined algorithm (systolic pressure ≥ 90% of baseline: no vasopressor; 80%-89% systolic pressure: 1 mL equivalent to ephedrine 5 mg + phenylephrine 25 µg; 79%-79% systolic pressure: 2 mL equivalent to ephedrine 10 mg + phenylephrine 50 µg; systolic pressure < 70%: 3 mL equivalent to ephedrine 15 mg + phenylephrine 75 µg)
Outcomes	*Maternal*: hypotension; bradycardia; tachycardia; nausea, vomiting; total vasopressor dose *Neonatal*: umbilical and venous arterial pH; Apgar scores; neonatal weight
Notes	Hypotension defined as SBP < 90% baseline Bradycardia defined as heart rate < 40 bpm Tachycardia defined as heart rate > 140 bpm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers generated using MS Excel
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque envelopes

Carvalho 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind the interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes were reported, although some were reported in a form that could not used in this review
Other bias	Low risk	Similar baseline characteristics

Chan 1997

Study characteristics	
Methods	RCT
Participants	46 women *Inclusion criteria*: healthy parturients with normal pregnancies undergoing elective CS at term *Exclusion criteria*: not specified *Setting*: China
Interventions	**Prophylactic ephedrine versus crystalloid preload** Group 1: ephedrine 0.25 mg/kg in 5 mL normal saline over 3 min immediately after spinal injection Group 2: Hartmann's solution 20 mL/kg 10-15 min prior to spinal injection Standardised spinal anaesthetic technique and dose
Outcomes	*Maternal*: hypotension); level of sensory block; Doppler ultrasound uterine blood flow measurements before and 5 min after spinal injection; nausea and vomiting; shivering; cardiac dysrhythmia; uterine incision-birth time *Neonatal*: arterial and venous cord blood gases; Apgar scores at 1 min and 5 min
Notes	Hypotension defined as a decrease in systolic pressure of > 20% of baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned": method not described
Allocation concealment (selection bias)	Unclear risk	Method not described

Chan 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Neonatal assessment only (a preoperative Doppler ultrasound of uterine blood flow conducted by obstetrician who was blinded to the "treatment received") – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes reported
Other bias	Low risk	Similar baseline characteristics

Chohedri 2007

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I-II ambulatory pregnant women for whom elective caesarean with spinal anaesthesia was planned (no instances of fetal distress) *Setting*: Iran
Interventions	**Ephedrine: comparison of different routes of administration** Group 1: oral ephedrine, 25 mg administered before spinal Group 2: IM injection of ephedrine, 25 mg, 30 min before spinal Group 3: IV bolus of ephedrine, 25 mg in 2 mL injected over a 1-min period, immediately after spinal induction All women received a standardised 20 mL/kg preload of Ringer's lactate solution and a standardised spinal anaesthetic technique. The anaesthetic dose was increased from 60 mg lidocaine to 70 mg lidocaine if the woman's height was > 160 cm. Hypotension requiring intervention was managed with 10 mg ephedrine IV bolus increments every min until SBP returned to normal (> 100 mmHg and > 70% baseline).
Outcomes	*Maternal*: hypotension; hypertension (increase of 30% from baseline); heart rate (tachycardia increase of 30% from baseline), nausea *Neonatal*: Apgar scores
Notes	Hypertension was defined as an increase in BP by 30% from baseline. Tachycardia was defined as an increase in heart rate of 30% from baseline.
Risk of bias	

Chohedri 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	"[R]andomly divided into three equal groups of 20"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" – no further detail provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" – no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Unclear risk	Not all expected outcomes were reported, e.g. only 1 neonatal outcome reported in a way that could not be used in this review
Other bias	Low risk	No apparent source of other bias

Cyna 2010

Study characteristics	
Methods	RCT
Participants	45 women *Inclusion criteria*: women aged > 18 years, > 34 weeks' gestation, singleton pregnancy presenting for elective CS under spinal anaesthesia *Exclusion criteria*: women unable to stand or walk for 15 min, with pre-existing hypertension or pre-eclampsia, multiple pregnancy or grade 3-4 placenta praevia *Setting*: Australia
Interventions	**Walking versus lying down** Group 1: walking: women were asked to walk to the operating theatre for at least 15 min prior to positioning for spinal anaesthesia Group 2: lying: women were taken to theatre on a barouche or trolley; lying with a wedge Spinal anaesthesia technique, IV fluids given, vasopressors given were not reported
Outcomes	*Maternal*: incidence of hypotension
Notes	Hypotension defined as fall in SBP 20% from baseline or < 100 mmHg systolic Ephedrine and metaraminol were used to treat hypotension

Cyna 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	"Consecutively numbered sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and anaesthetists not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant's data were lost, leaving 44 women suitable for analysis. Lying group: 3 participants in the lying group has a failed spinal and converted to general anaesthesia; 2 participants withdrew without explanation Walking group: 2 patients had protocol violation (not given 6 mg prophylactic ephedrine) Intention-to-treat analyses performed 17 women in lying group and 20 women in walking group were analysed.
Selective reporting (reporting bias)	Unclear risk	Exact values of outcomes not reported in abstract
Other bias	Low risk	Similar baseline characteristics

Dahlgren 2005

Study characteristics

Methods	RCT
Participants	110 women *Inclusion criteria*: healthy women with normal term singleton pregnancies presenting for elective CS *Setting*: Sweden
Interventions	**Crystalloid versus colloid preload** Group 1: acetated Ringer's solution, 1000 mL, preceded by 20 mL 15% saline 0.9% IV Group 2: dextran 60 3%, 1000 mL, preceded by 20 mL dextran 1 IV All women received a standardised spinal anaesthetic technique and dose. Hypotension was managed by a standardised regimen of ephedrine dosing.

Dahlgren 2005 *(Continued)*

Outcomes	*Maternal*: hypotension; clinically significant hypotension; severe hypotension ephedrine consumption; blood loss *Neonatal*: umbilical artery < pH 7.2; pCO_2; base deficit
Notes	Hypotension defined as SAP dropping below 100 mmHg; clinically significant hypotension as drop in SAP > 20% below baseline and severe hypotension defined as SAP < 80 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinded" – solution prepared and administered by an anaesthetic nurse not otherwise involved in the care of the woman (including the initial injection)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses: 1/110 – 1 woman from crystalloid group excluded due to protocol violation; 1 woman allocated to crystalloid subsequently found to have received colloid.
Selective reporting (reporting bias)	High risk	Not all outcomes listed in the paper were reported
Other bias	Low risk	Some baseline differences, e.g. 32% nulliparous in the crystalloid group compared with 21% in the colloid group

Dahlgren 2007

Study characteristics

Methods	RCT
Participants	55 women presenting for elective CS *Inclusion criteria*: healthy women with term singleton normal pregnancies *Setting*: Sweden
Interventions	**Colloid versus crystalloid preload** Group 1: colloid group: 20 mL of 15% dextran 1, followed by 1000 mL IV infusion of 3% dextran 60. This solution was administered during 20 min immediately preceding intrathecal injection. Group 2: crystalloid group: 20 mL IV injection of 0.9% saline, followed by 1000 mL IV infusion of acetated Ringer's solution. This solution was administered during 20 min immediately preceding intrathecal injection.

Dahlgren 2007 *(Continued)*

	All women received standardised fasting protocol, no premedication and a standardised spinal anaesthetic technique and dose. Hypotension requiring intervention was managed with ephedrine 5 mg if SBP dropped below 100 mmHg, and repeated as required.
Outcomes	*Maternal*: hypotension – overall, clinically significant or severe Criteria for rescue: if the woman developed discomfort associated with a decrease in SBP of at least 20% from baseline, even if it was above 100 mmHg
Notes	'Overall' hypotension defined as a fall in systolic pressure below 100 mmHg 'Clinically significant' hypotension defined as hypotension associated with maternal discomfort (nausea, retching/vomiting, dizziness or chest symptoms) 'Severe' hypotension defined as a reduction of the SAP below 80 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly allocated" – method not specified
Allocation concealment (selection bias)	Unclear risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blind'. The woman, the anaesthesiologist and all other personnel in the operating room were unaware of the study group. The study solutions were prepared and administered by an anaesthetic nurse who was not otherwise involved in the care of the patient, and were covered by a non-transparent plastic bag. The anaesthesiologist did not enter the operating room until the study solution had been given.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel were blinded to treatment allocation, except for the anaesthetic nurse who prepared the solutions (who was not involved in the care of the patient).
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/55 excluded due to protocol violation (1 was given ephedrine despite a normal BP and the other could not go through the SST because of leg muscle spasm). Not specified which groups they were from
Selective reporting (reporting bias)	Low risk	Only maternal outcome reported was hypotension; no infant outcomes were reported
Other bias	Low risk	No apparent sources of other bias

Damevski 2011

Study characteristics

Methods	RCT
Participants	40 women *Inclusion criteria*: ASA I, women aged 21-28 years with normal pregnancies, elective caesarean for breech presentation, cephalopelvic disproportion, re-operation

Damevski 2011 *(Continued)*

	Exclusion criteria: body weight > 90 kg, women who refused caesarean *Setting*: Macedonia
Interventions	**Ephedrine infusion versus crystalloid preload** Group 1: ephedrine: continuous fast-drop infusion of 500 mL Ringer's solution with 50 mL ephedrine, commenced immediately after venous cannulation for spinal anaesthesia, and continued until the umbilical cord was clamped Group 2: crystalloid: 20 mL/kg Ringer's solution, warmed to room temperature, commenced 20-30 min prior to spinal anaesthesia, and continued until the umbilical cord was clamped All women received a standardised spinal anaesthetic technique and dose, standardised oxygen therapy, and standardised oxytocin regimen. Hypotension requiring intervention received 5 mg IV boluses of ephedrine in group 1 (ephedrine group) and 10 mg IV boluses of ephedrine in group 2 (crystalloid group).
Outcomes	*Maternal*: hypotension; quantity of crystalloid; quantity of ephedrine; nausea and vomiting *Neonatal*: Apgar scores
Notes	Hypotension defined as SBP < 100 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" – no further details reported
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Not all outcomes available (e.g. Apgar scores presented only as medians)
Other bias	Low risk	Similar baseline characteristics

Das Neves 2010

Study characteristics

Das Neves 2010 *(Continued)*

Methods	RCT
Participants	120 women *Inclusion criteria*: physical status ASA I, with an indication for elective CS, singleton term pregnancy *Exclusion criteria*: history of hypertension or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, fetal abnormalities, history of hypersensitivity to the drugs used in the study, and contraindications to spinal block *Setting*: Brazil
Interventions	**Phenylephrine: prophylactic infusion versus therapeutic dosing** Group 1: continuous IV infusion of phenylephrine, using a 1-channel "Baxter" volumetric infusion pump (containing a solution of 10 mL of NS with 10 mg phenylephrine (100 µg/mL)), at 0.15 µg/kg/min, which was started immediately after the spinal block Group 2: a single dose of phenylephrine, 50 µg IV, administered immediately after the spinal block. Baxter volumetric infusion pump connected, containing 100 mL NS Group 3: a single dose of phenylephrine, 50 µg IV, administered in case of hypotension, defined as a fall in SBP and/or DBP of up to 20% of mean baseline levels. Baxter volumetric infusion pump connected, containing 100 mL NS All women received a standardised spinal anaesthetic technique and dose followed by a standardised crystalloid infusion and standardised positioning. Hypotension treatment involved a bolus of 30 µg of phenylephrine IV repeated every 2 min if a drop in BP > 20% that was not controlled with the therapeutic regimen used. Bradycardia was treated when associated with hypotension with 0.5 mg of atropine IV.
Outcomes	*Maternal*: hypotension; reactive hypertension; bradycardia; nausea and vomiting *Neonatal*: Apgar score < 8 at 5 min
Notes	Hypotension defined as a drop in SBP and/or DBP > 20% of mean baseline levels Reactive hypertension defined as BP 20% > mean baseline levels after the use of the vasopressor Bradycardia defined as heart rate lower than 50 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	Sequential sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind." Patients, and physicians responsible for collecting and analysing the data were blinded; anaesthetist administering the anaesthesia was not blinded. This anaesthetist was not involved in data collection and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Those collecting and analysing the data were blinded

Das Neves 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up occurred
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Unclear risk	No apparent sources of other bias

Davies 2006

Study characteristics	
Methods	RCT
Participants	70 women *Inclusion criteria*: ASA physical status I or II, women scheduled for elective CS under spinal anaesthesia, > 37 weeks' gestation *Exclusion criteria*: pregnancy-induced hypertension, multiple pregnancy, fetal compromise, diabetes mellitus, polyhydramnios, weight > 100 kg, renal or hepatic disease, anaemia (haemoglobin < 10 g/dL), clotting *Setting*: UK
Interventions	**Colloid: 5 mL/kg versus 10 mL/kg preload** Group 1: 5 mL/kg pentastarch, volume preload before spinal anaesthesia (infused over 10 min) Group 2: 10 mL/kg pentastarch, volume preload before spinal anaesthesia (infused over 10 min) All women received standardised aspiration prophylaxis, a standardised spinal anaesthetic technique and dose, and standardised positioning. Hypotension requiring intervention was treated with 6 mg increments of ephedrine until resolution; smaller decreases in BP were similarly treated if accompanied by nausea, vomiting or dizziness.
Outcomes	*Maternal*: hypotension; ephedrine use *Neonatal*: Apgar score at 1 min
Notes	Hypotension was defined as a decrease in SBP to < 70% baseline or < 90 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation according to sealed envelopes"; no further details
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Low risk	"A technician prepared the calculated volume of pentastarch and covered it with a black bag to blind the anaesthetist to the volume administered."

Davies 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses reported
Selective reporting (reporting bias)	Unclear risk	Not all expected outcomes were reported
Other bias	Low risk	Similar baseline characteristics

Doherty 2012

Study characteristics	
Methods	RCT
Participants	69 women *Inclusion criteria*: ASA physical status I/II; aged 18 years and older; weight 50-100 kg; height between 150 and 180 cm *Exclusion criteria*: allergy or hypersensitivity to phenylephrine; hypertension; cardiovascular or cerebrovascular disease; fetal abnormalities; diabetes (excluding gestational diabetes); or contraindications to spinal anaesthesia *Setting*: Canada
Interventions	**Phenylephrine infusion versus phenylephrine bolus** Group 1: infusion: fixed rate phenylephrine infusion 120 µg/min; infusion was started immediately on completion of intrathecal injection, at a rate of 1 mL/min and continued for a minimum of 2 min, and continued if maternal SBP was equal to or lower than baseline. If maternal BP was higher than baseline, the infusion was discontinued and the BP reassessed after 2 min Group 2: bolus: intermittent phenylephrine bolus of 120 µg; women received 1 mL of bolus solution every time SBP was equal to or lower than baseline. A bolus was not administered when SBP was above baseline All women received an IV infusion of Ringer's lactate started at a minimal rate in the holding area, with subsequent standardised crystalloid coload on administration of spinal anaesthetic. No antiemetic premedication was given. All women received a standardised spinal anaesthetic technique, dose and positioning. Hypotension requiring intervention received rescue dose of 5 mg ephedrine. Bradycardia requiring intervention received 0.6 mg atropine if heart rate < 60 bpm for 2 consecutive readings and SBP equal to or lower than baseline (infusion was discontinued if bradycardia with SBP higher than baseline).
Outcomes	*Maternal*: BP; cardiac output; heart rate, hypotension; hypertension; nausea/vomiting; bradycardia; total dose of phenylephrine *Neonatal*: umbilical blood gases; neonatal weight; Apgar score at 1 min and 5 min

Doherty 2012 *(Continued)*

Notes	Hypotension was defined as SBP < 80% baseline. Hypertension was defined as SBP > 120% baseline. Bradycardia was defined as heart rate < 60 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind": women and attending anaesthetists were blinded to the group allocation. 2 syringes, 1 20 mL bolus and 60 mL infusion were prepared for each woman. 1 syringe contained 120 µ/mL phenylephrine and the second syringe contained saline. Both syringes were labelled 'phenylephrine/placebo' and 'bolus syringe' and 'infusion syringe' respectively. The anaesthetist then received 1 syringe of infusion solution and 1 syringe of bolus solution (but did not know which syringe contained the phenylephrine). Each was administered according to the protocol for bolus and infusion as described above.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated, but probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/69 were lost to follow-up: 4/35 from the intervention group (3 pump errors; 1 unable to calibrate properly) and 5/35 from the bolus group (2 required additional anaesthesia (ketamine), 2 pump errors and 1 unable to calibrate properly)
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes were reported, although blood gases reported only as mean and SD, and not specified if maternal hypertension required intervention
Other bias	Low risk	Baseline characteristics were similar

Dyer 2004

Study characteristics

Methods	RCT
Participants	50 women *Inclusion criteria*: less than 90 kg, ASA I and II, singleton pregnancy, presenting for elective caesarean under spinal anaesthesia *Exclusion criteria*: pre-eclamptic women *Setting*: South Africa
Interventions	**Crystalloid: preload versus rapid infusio**n

Dyer 2004 *(Continued)*

	Group 1: preload – modified Ringer's lactate, 20 mL/kg preload 20 min before spinal Group 2: coload – rapid infusion of an equivalent volume of modified Ringer's lactate immediately after induction of spinal All women received a standardised spinal anaesthetic technique and dose. Hypotension < 80% of baseline treated with 5 mg boluses of ephedrine; < 70% of baseline treated with 10 mg ephedrine until a return to within 80% of baseline
Outcomes	*Maternal*: hypotension; BP; heart rate; time to block; induction to incision times; incision to birth times; anaesthesia and surgery times; blood loss; urine output; nausea; ephedrine dose *Neonatal*: birthweight; Apgar scores; umbilical arterial pH; umbilical arterial base deficit
Notes	Hypotension defined as BP < 80% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" – methods not described
Allocation concealment (selection bias)	Unclear risk	"Allocation card contained within a sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Since there were clearly pre-defined target MAPs for vasopressor administration for each individual, the study was not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

El-Mekawy 2012

Study characteristics

Methods	RCT
Participants	90 women *Inclusion criteria*: ASA I, singleton pregnancy, term gestation, non-life-threatening cause for emergency CS under spinal anaesthesia (prolonged labour or dystocia, failed labour induction or amniotic rupture)

El-Mekawy 2012 *(Continued)*

	Exclusion criteria: patient refusal, fetal distress, known fetal abnormalities, cardiovascular, renal or liver diseases, chronic hypertension or gestational hypertension, coagulation disorders, and those with total or partial spinal anaesthesia failure *Setting*: Egypt
Interventions	**Crystalloid co/postload versus colloid co/postload versus ephedrine infusion** Group 1: 0.5 mL/kg/min Ringer's lactate via infusion pump: co/post loading started at time of spinal injection and continued after spinal injection with until fetus delivery (clamping of umbilical cord) Group 2: 0.5 mL/kg/min Voluven (6% HES 130/0.4 in isotonic NaCl solution) via infusion pump: co/post loading started at time of spinal injection and continued after it with until fetus delivery Group 3: ephedrine infusion at 1 mg/min via infusion pump commenced immediately after spinal anaesthesia until fetus delivery. Accompanied by infusion of Ringer's lactate at minimal infusion rates required to keep vein open Hypotension treated by 5 mg bolus of IV ephedrine every 2 min until SBP returned to normal value in all groups Bradycardia treated immediately using 0.5 mg atropine IV Nausea and vomiting treated with 10-20 mg IV metoclopramide when unrelated to hypotension or not corrected by ephedrine bolus alone
Outcomes	*Maternal*: BP, heart rate, adverse effects (nausea, vomiting, dizziness, chest symptoms, dyspnoea, tachypnoea), total IV fluid given, total ephedrine dose, time from spinal anaesthesia to delivery of fetus (clamping of umbilical cord) *Neonatal*: heart rate was monitored by CTG continuously until delivery; Apgar scores at 1 min and 5 min; arterial blood gas sample taken from umbilical cord for blood gas analysis (pH, pCO_2) within 2 min after delivery
Notes	Hypotension was defined as 20% decrease in SBP from the baseline. Maternal bradycardia was defined as heart rate < 60 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither participants nor personnel were blinded, however this was unlikely to have impacted upon the measured results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor not blinded; however this was unlikely to have impacted upon the measured results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported

El-Mekawy 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	Non apparent

Eldaba 2015

Study characteristics	
Methods	RCT
Participants	200 women Inclusion criteria: ASA I/II, aged 18-30 years, elective CS Exclusion criteria: patient refusal, contraindication to spinal anaesthesia, known allergy to granisetron, patients receiving serotonin agonists or antagonists, ischaemic heart disease, chronic hypertension or pregnancy-induced hypertension *Setting*: Egypt
Interventions	**Granisetron versus control** Group 1: 1 mg granisetron diluted in 10 mL normal saline IV administered slowly over 1 min, 5 min prior to spinal anaesthesia Group 2: 10 mL normal saline IV administered slowly over 1 min, 5 min prior to spinal anaesthesia (placebo) All women received a crystalloid preload (500 mL Ringer's lactate), standardised positioning, standardised spinal anaesthetic technique and dose, standardised maintenance IVT. Hypotension was managed with a rapid bolus of 100 mL of Ringer's lactate. Vasopressors administered if MABP < 70 mmHg: ephedrine 5 mg IV bolus if heart rate was < 90 bpm, phenylephrine 0.1 mg IV bolus if heart rate > 90 bpm. Bradycardia (if not associated with hypotension) was treated with 0.5 mg atropine.
Outcomes	*Maternal*: incidence of hypotension, heart rate *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as MAP < 70 mmHg. Bradycardia defined as heart rate < 50 bpm.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based randomisation
Allocation concealment (selection bias)	Unclear risk	Assignment in sealed envelopes

Eldaba 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Syringed were prepared by an anaesthetist who was blinded to the study protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	5 excluded (3 from group 1 and 2 from group 2) due to conversion to GA No statement with respect to 'intention-to-treat'
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	None evident

Embu 2011

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: ASA I-II, singleton pregnancy, elective CS under SAB *Exclusion criteria*: patients with pre-existing hypertension or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, autonomic neuropathy, spinal deformities, infections in the lumbar area, coagulopathies, hypovolaemia from any cause and SBP < 100 mmHg. Patients aged < 18 or > 40 years, weighing < 50 kg or > 100 kg, taller than 180 cm or shorter than 140 cm, and patients with placental complications, cord complications, fetal malformations and those babies whose birthweights were < 2.5 kg or > 4.5 kg by ultrasound *Setting*: Nigeria
Interventions	**Colloid preload versus crystalloid preload** Group 1: 500 mL HES IV IV 10 min before SAB Group 2: 1000 mL of Ringer's lactate IV 10 min before SAB All patients: standardised preparation, monitoring, positioning, spinal anaesthetic dose and technique, IV fluids, oxygen delivery Hypotension treated with (unspecified) rapid infusion of IV fluids, followed by IV ephedrine 5 mg if not responding
Outcomes	*Maternal*: incidence of hypotension, nausea and vomiting, dizziness and breathlessness, interval between preload-to-spinal injection and delivery and uterine incision-to-delivery *Neonatal*: Apgars at 1 min and 5 min
Notes	Hypotension defined as SBP < 80% of baseline or absolute value of SBP < 100 mmHg
Risk of bias	

Embu 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated by drawing sealed envelopes which were shuffled
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Bag placed over fluid to conceal identity
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	None apparent
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Farid 2016

Study characteristics	
Methods	RCT
Participants	74 women *Inclusion criteria*: healthy patients; elective CS *Exclusion criteria*: patients who experienced complications during the surgery *Setting*: Pakistan
Interventions	**Crystalloid preload versus crystalloid coload** Group 1 (P): received crystalloid preload 15 mL/kg Hartmann's solution 20 min prior to spinal anaesthesia Group 2 (C): received crystalloid coload 15 mL/kg Hartmann's solution at time of administration of spinal anaesthesia All women received standardised monitoring, standardised cannulation, standardised spinal anaesthetic technique and dose Hypotension was treated with vasopressor (phenylephrine or ephedrine)
Outcomes	*Maternal*: incidence of hypotension
Notes	Hypotension was defined as reduction in MAP by > 20% from baseline

Farid 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned by trainee anaesthesia or anaesthetist in charge of case"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Patients going into complications during surgery were excluded" – unspecified how many patients (if any) this involved. No further details provided
Selective reporting (reporting bias)	Low risk	Not evident
Other bias	Low risk	Not evident

Faydaci 2011

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA1-2, elective CS under SAB *Exclusion criteria*: not stated *Setting*: Turkey
Interventions	**Crystalloid preload: different doses** Group 1: 10 mL/kg Ringer's lactate Group 2: 15 mL/kg Ringer's lactate Group 3: 20 mL/kg Ringer's lactate All preloads administered over 15 min before SAB with subsequent ephedrine infusion commenced immediately after SAB All women received standardised premedication/fasting, spinal dose and technique, position, monitoring Hypotension was treated with 10 mg IV bolus ephedrine
Outcomes	*Maternal*: incidence of hypotension, nausea and vomiting, total amount ephedrine

Faydaci 2011 *(Continued)*

	Neonatal: cord blood gas analysis, Apgars at 1 min and 5 min
Notes	Hypotension defined as decrease in MAP of > 20%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	"Enclosed system" presumably means covered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

French 1999

Study characteristics	
Methods	RCT
Participants	160 women *Inclusion criteria*: ASA I or II undergoing elective caesarean under spinal anaesthesia
Interventions	**Colloid preload versus crystalloid preload** Group 1: pentastarch 10% in 0.9% saline 15 mL/kg Group 2: Hartmann's solution 15 mL/kg All women received a standardised anaesthetic technique with variable anaesthetic dose, followed by standardised surgical positioning.
Outcomes	*Maternal*: BP; hypotension; block height; uterine incision to birth interval *Neonatal*: Apgar scores at 1 min and 5 min; cord pH
Notes	Hypotension was defined as SBP below 90 mmHg or < 70% below baseline.

French 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Low risk	Adequate: randomisation code by pharmacy and study drugs "covered with a black plastic bag to ensure blinding"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: not specifically stated but anaesthetist and women presumably were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Gomaa 2003

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: healthy pregnant women (25 to 40 years) undergoing elective caesarean under spinal anaesthesia *Exclusion criteria*: women known to be hypertensive *Setting*: Egypt
Interventions	**Ephedrine versus phenylephrine versus control** Group 1: ephedrine, 50 mg IM Group 2: phenylephrine, 4 mg IM Group 3: 2 mL saline IM All study drugs given 10 min before spinal anaesthesia All women received a standardised crystalloid preload and a standardised spinal anaesthetic technique and dose followed by standardised surgical positioning.
Outcomes	*Maternal*: hypotension

Gomaa 2003 *(Continued)*

	Neonatal: cord/neonatal blood (reported as mean and SD); Apgar < 8 at 5 min (reported as mean and SD)
Notes	Hypotension was defined as 25% decrease in MAP from baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: drugs were prepared by an anaesthetic assistant not involved in the study and injected by an anaesthetist not involved in data collection or care of the women
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: not stated but losses unlikely
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Grubb 2004

Study characteristics	
Methods	RCT
Participants	24 women *Inclusion criteria*: pregnant women scheduled for elective caesarean
Interventions	**Ephedrine versus control** Group 1: ephedrine, 50 mg IM Group 2: saline IM Study drugs administered prior to spinal anaesthetic All women received standardised volume loading and a standardised spinal anaesthetic technique and dose followed by standardised surgical positioning.
Outcomes	*Maternal*: hypotension; nausea
Notes	Hypotension was defined as defined as SBP < 70% baseline or < 90 mmHg

Grubb 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described
Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: described as "double-blind placebo-controlled" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated but losses unlikely
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Gulhas 2012

Study characteristics	
Methods	RCT
Participants	105 women *Inclusion criteria*: ASA I-II, aged 18-45 years, elective CS under SAB *Exclusion criteria*: contraindication to regional anaesthesia, ASA score III-IV, < 18 years of age, multiple gestation, < 150 cm tall or > 170 cm tall, pre-eclampsia, eclampsia, diabetes mellitus, intrauterine anomalities, using medications containing ephedrine or phenylephrine, failed SAB requiring conversion to general anaesthesia *Setting*: Turkey
Interventions	**Various doses of ketamine versus control** Group 1: 0.25 mg/kg IV ketamine administered immediately following intrathecal injection Group 2: 0.5 mg/kg IV ketamine administered immediately following intrathecal injection Group 3: placebo control: 2 mL physiological saline administered immediately following intrathecal injection All women received a standardised crystalloid preload, a standardised spinal anaesthetic technique and dose), standardised monitoring and standardised surgical positioning. Hypotension was managed with 10 mg ephedrine IV.

Gulhas 2012 *(Continued)*

	Atropine was administered if heart rate was < 45 bpm.
Outcomes	*Maternal*: hypotension, ephedrine use, sedation score, shivering, pruritus, nausea and vomiting, hallucinations *Neonatal*: Apgars, cord blood pH
Notes	Hypotension defined as > 20% reduction in SBP from baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers (Excel) by anaesthetist not involved in study
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded outcome data assessors and "ward staff"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome data assessors and "ward staff"
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients excluded with failed blocks, flow diagram does not actually make sense from protocol as patients would have received placebo/Ketamine before exclusion
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Gunaydin 2009

Study characteristics

Methods	RCT
Participants	60 women *Inclusion criteria*: ASA 2 women undergoing elective CS *Exclusion criteria*: starch allergies, history of anaphylaxis
Interventions	**Colloid preload versus crystalloid preload** Group 1: IV infusion of 1000 mL Ringer's lactate preloading Group 2: IV infusion of 500 mL colloid Voluven 6% (6% HES 130/0.4 in isotonic NaCl solution) preloading All women received standardised cannulation, aspiration prophylaxis, spinal anaesthesia technique and dose and surgical positioning.

Gunaydin 2009 *(Continued)*

	Hypotension treated with 10 mg IV ephedrine
Outcomes	*Maternal*: time for block onset and maximum sensory block level, maximum motor block time, block regression time, motor block duration, first analgesic requirement, mobilisation and onset of bowel sounds, the incidence of hypotension, total used ephedrine amount, nausea and vomiting *Neonatal*: 1 min and 5 min Apgar scores
Notes	Hypotension defined as a decrease in mean BP to 20% below baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified. Reported as "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Closed envelope method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personel were blinded, participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not data loss, no losses to follow-up
Selective reporting (reporting bias)	Low risk	Not reported
Other bias	Low risk	Not reported

Gunusen 2010

Study characteristics	
Methods	RCT
Participants	120 women *Inclusion criteria*: healthy women aged 20-40 years scheduled for elective caesarean delivery under spinal anaesthesia who had uncomplicated singleton, term pregnancy *Exclusion criteria*: chronic or pregnancy-induced hypertension, cardiac disease, diabetes mellitus, height < 155 cm, a contraindication to spinal anaesthesia, or known fetal abnormality *Setting*: Turkey
Interventions	**Colloid preload versus crystalloid preload versus ephedrine infusion plus crystalloid co-load**

Gunusen 2010 *(Continued)*

	Group 1: crystalloid preload: rapid infusion of Ringer's lactate 20 mL/kg, within 15-20 min of the spinal block. Following anaesthesia, placebo infusion solution administered at a rate of 2.5 mL/min using an infusion pump. Ringer's lactate 1000 mL administered at minimal maintenance rate via 2nd cannula Group 2: colloid preload: 4% succinated gelatine solution (Gelofusine) 500 mL, within 15-20 min of the spinal block Following anaesthesia, placebo infusion solution administered at a rate of 2.5 mL/min using an infusion pump. Ringer's lactate 1000 mL administered at minimal maintenance rate via 2nd cannula Group 3: ephedrine infusion plus crystalloid co-load: no fluid preload given Following anaesthesia, infusion solution of ephedrine 50 mg in 100 mL (1.25 mg/mL) administered at rate of 2.5 mL/min using an infusion pump. Ringer's lactate1000 mL, administered rapidly via 2nd cannula All women received standardised aspiration prophylaxis, a standardised spinal anaesthetic technique and dose, standardised surgical positioning and standardised oxytocin administration. Hypotension (requiring intervention) was treated immediately with an IV bolus of ephedrine 5 mg from a separate syringe, repeated when necessary, every 2 min if hypotension persisted or recurred Hypertension treatment: infusion was stopped if the SBP and heart rate increased above the baseline values Bradycardia treatment consisted of IV atropine 0.5 mg.
Outcomes	*Maternal*: moderate hypotension; severe hypotension; maternal bradycardia requiring intervention; maternal tachycardia; hypertension; nausea and vomiting *Neonatal*: acidosis (cord/neonatal blood with pH < 7.2); neonatal Apgar score < 8 at 5 min
Notes	Moderate hypotension was defined as a decrease of 20% from baseline, or an SBP < 95 mmHg. Severe hypotension was defined as a decrease of 30% from baseline. Bradycardia was defined as heart rate < 50 bpm. Tachycardia was defined heart rate > 120 bpm. Hypertension was defined as an increase in SBP > 30% above baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	"Randomly allocated" – concealment method not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Pre-load fluid in groups CO and CR was administered by an anaesthetic nurse who was not otherwise involved in the care of the patients. Co-load fluids were prepared by an anaesthetic nurse who was independent of the study. Ringer's lactate in all groups were covered by a similar non-transparent plastic bag in the perioperative period. The anaesthetist did not enter the operating room until the study solutions had been given, so that those recording data were unaware of the study group allocation.

Gunusen 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Those recording data were unaware of the study group allocation." Attending paediatrician assessed Apgar scores – unclear if blinded to allocated treatment Umbilical blood samples were taken by the same midwife in the operating room – likely to have been blinded to allocated treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1/120 – 1 patient in crystalloid preload group was excluded from the study due to an inadequate spinal block
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Hall 1994

Study characteristics	
Methods	RCT
Participants	30 women *Inclusion criteria*: elective CS, singleton fetus *Exclusion criteria*: placental pathology, pregnancy exceeded 37 weeks' gestation *Setting*: UK
Interventions	**Variable ephedrine infusions versus phenylephrine infusion** Group 1: infusion of ephedrine 1 mg/mL at 60 mL/h (1 mg/min) Group 2: infusion of ephedrine 2 mg/mL at 60 mL/h (2 mg/min) Group 3: infusion of phenylephrine at 10 µg/mL at 60 mL/h (10 µg/min) All women received the vasopressor for 30 min via Graseby pump All women received standard aspiration prophylaxis, IV cannulation, crystalloid preloading, surgical positioning, invasive arterial and non-invasive BP monitoring, and standardised spinal anaesthetic technique and dose. Hypotension was managed with a 2 mL bolus of the vasopressor infusion. If pressure was > 20% above baseline for 3 min, the infusion was stopped.
Outcomes	*Maternal*: incidence of hypotension, time for anaesthesia to reach T4 and maximum height of sensory loss, time between insertion of spinal needle and delivery of fetus, time from uterine incision to delivery of fetus, incidence of complications, total drug dose *Neonatal*: Apgar score 1 min and 5 min, umbilical arterial and venous blood samples
Notes	Hypotension was defined as SAP decrease > 20% below baseline Bradycardia was defined as heart rate < 40 bpm

Hall 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthetist who produced infusion not involved in anaesthetic. Blinding: women and anaesthetists blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 1 woman excluded from group 2 due to data corruption
Selective reporting (reporting bias)	Low risk	None reported
Other bias	Low risk	None reported

Hartley 2001

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: ASA I or II undergoing elective CS *Exclusion criteria*: weight > 90 kg, height < 150 cm or > 175 cm, multiple pregnancy, diabetes or hypertension
Interventions	**Lateral versus supine wedged** Group 1: right-lateral position adopted 2 min after spinal injection for 10 min, then turned to supine wedged (right hip) position Group 2: supine-wedged (right hip) position adopted 1 min after spinal injection and maintained throughout Intervention occurred after spinal injection. All women received a standardised crystalloid preload and anaesthetic technique and dose. Bradycardia was managed with atropine. Hypotension was managed with ephedrine.

Hartley 2001 *(Continued)*

Outcomes	*Maternal*: hypotension; heart rate; block height; time to maximum block; time to birth; duration of hypotension; nausea/dizziness; ephedrine requirements
Notes	Hypotension was defined as SBP < 80% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation and allocation concealment: sealed envelope
Allocation concealment (selection bias)	Unclear risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Hasan 2012

Study characteristics

Methods	RCT
Participants	90 women *Inclusion criteria*: ASA I-II, age 20-35 years, weight 45-60 kg, height 153-165 cm *Exclusion criteria*: pregnancy-induced hypertension, chronic hypertension, pre-eclampsia, twin pregnancy, fetal compromise, diabetes mellitus, polyhydramnios, renal, liver or heart disease, coagulopathy *Setting*: Bangladesh
Interventions	**Crystalloid preload versus colloid preload versus combination preload** Group 1: Ringer's lactate 20 mL/kg preloading Group 2: HES 6% 8 mL/kg preloading Group 3: combination of RL 10 mL/kg and HES 6% 4 mL/kg preloading

Hasan 2012 *(Continued)*

	All women received standardised cannulation, standardised spinal anaesthetic technique and dose, standardised surgical positioning, standardised oxygen therapy and standardised oxytocin dose after delivery Hypotension was treated with IV boluses of ephedrine 5 mg and rapid infusion of Ringer's lactate in all 3 groups
Outcomes	*Maternal*: systolic, diastolic and mean BP measurements; total dose of ephedrine; total volume of IV fluid given *Neonatal*: Apgar scores
Notes	Hypotension defined as SBP less than 100 mmHg AND less than 20% of the baseline BP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear method. "Randomisations were done using card sampling"
Allocation concealment (selection bias)	Low risk	Anaesthetist who generated the random sequence infused the allocated fluid behind a screen set, separate from the outcome assessor.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and outcome assessors were blinded; however, the personnel who generated the random sequence and infused the fluid were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in final analysis
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Hwang 2012

Study characteristics

Methods	RCT
Participants	86 women *Inclusion criteria*: elective CS *Exclusion criteria*: pre-existing hypertension, pre-eclampsia, cardiovascular disease, diabetes, obesity, multiple pregnancy *Setting*: South Korea

Hwang 2012 *(Continued)*

Interventions	**(R) lateral positioning versus wedged supine positioning** Group 1: maintain the right lateral position for 6 min after spinal anaesthesia before assuming the wedged supine position Group 2: assumed the wedged supine position immediately after the spinal injection Wedging positioning was achieved with an air balloon (1500 mL) was inserted under the right upper buttock in the supine position in both groups. All women received standardised cannulation, standardised crystalloid preload, standardised oxygen therapy and standardised spinal anaesthetic technique and dose. Ephedrine was given if BP decreased > 30% from baseline ("severe hypotension") with increments of 5 mg at 2 min intervals
Outcomes	*Maternal*: hypotension, nausea and vomiting, ephedrine requirement, maximum block height *Neonatal*: Apgar scores at 1 min and 5 min after birth, umbilical arterial blood gas analysis
Notes	Hypotension defined as a decrease in MAP of > 20% from baseline Severe hypotension defined as a decrease in MAP of > 30% from baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (6 subjects per block)
Allocation concealment (selection bias)	Low risk	Opaque covers – removed immediately after intrathecal injection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind due to different positions but unlikely to affect observation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women were in different positions for 6 minutes therefore assessor was unblinded. After the women were put in the supine position, another observer who was blinded to patient group recorded the measurements.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1: 1 excluded due to hypertension at baseline Group 2: 1 excluded due to inadequate block Excluded women not analysed in final results
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Idehen 2014

Study characteristics	
Methods	RCT
Participants	70 women *Inclusion criteria*: elective CS, ASA I or II *Exclusion criteria*: multiple pregnancy, weight > 115 kg, height < 150 cm, diabetes mellitus, hypertensive diseases in pregnancy intra-uterine death, age < 18 years or > 40 years, patients on diuretics, contraindication to central neuraxial blockade *Setting*: Nigeria
Interventions	**Combination crystalloid/colloid preload versus crystalloid preload** Group 1: 1000 mL crystalloid/colloid (6% pentastarch/Ringer's lactate, 750 mL/250 mL) combination IV preload Group 2: 500 mL colloid (6% pentastarch) IV preload Women in both groups received the same aspiration prophylaxis, IV cannulation, spinal anaesthesia technique and dose. Hypotension treated with 3 mg aliquots of ephedrine and rapid infusion of fluid.
Outcomes	*Maternal*: incidence of hypotension, ephedrine requirement, nausea and vomiting, maximum block height, blood loss, urine output *Neonatal*: Apgar scores at 1 min and 5 min, birth asphyxia, meconium aspiration
Notes	Hypotension defined as SBP < 80% of baseline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blind balloting
Allocation concealment (selection bias)	Unclear risk	Not reported, but double-blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Syringes were preloaded and wrapped
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator who assessed the outcomes was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Low risk	None apparent

Idehen 2014 *(Continued)*

Other bias	Low risk	None apparent

Imam 2012

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA I-II, elective CS under spinal anaesthesia *Setting*: Pakistan
Interventions	**Crystalloid preload versus ephedrine alone versus combination of preload + ephedrine** Group 1 (crystalloid group): fluid preload with Ringer's solution 20 mL/kg over 10-15 min prior to intrathecal injection Group 2 (ephedrine group): IV ephedrine 0.25 mg/kg immediately after intrathecal injection Group 3 (combination group): fluid preload with Ringer's solution 20 mL/kg over 10-15 min preceding intrathecal injection plus ephedrine 0.25 mg/kg immediately after intrathecal injection Spinal anaesthesia technique was not described.
Outcomes	*Maternal*: hypotension, nausea and vomiting
Notes	Hypotension was not defined. It was not clear if they were assessing systolic, diastolic or mean BPs.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "randomised" but no elaboration
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States "blind" but no elaboration
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States "blind" but no elaboration
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None reported
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Inglis 1995

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: women who presented for elective CS at term with a singleton pregnancy receiving spinal anaesthesia *Exclusion criteria*: women less than 150 cm in height, more than 170 cm in height, or whose babies showed evidence of fetal compromise
Interventions	**Right lateral position versus sitting position during spinal anaesthesia** Group 1: right lateral (when anaesthesia induced) Group 2: sitting (when anaesthesia induced) All women received a preload of IV Hartmann's solution (1000 mL), a standardised spinal anaesthetic technique and dose, and standardised surgical positioning.
Outcomes	*Maternal*: hypotension; nausea and vomiting; time to block; women's satisfaction; ephedrine requirements
Notes	Hypotension was defined as systolic pressure decreased to < 70% of baseline or < 100 mmHg.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" – method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Block assessed by an investigator who was unaware of the women's original position
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 from lateral group removed from study (in 1, the spinal needle could not be inserted in the lateral position, but was successfully placed in the sitting position and for the other, a repeat block was needed)
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Jabalameli 2011

Study characteristics	
Methods	RCT
Participants	150 women *Inclusion criteria*: singleton pregnancy with ASA physical status I or II scheduled for elective caesarean under spinal anaesthesia, without pre-existing systemic disease or pregnancy-induced hypertension, preterm labour or signs of onset of labour, known fetal abnormalities, or without contraindications to spinal anaesthesia *Exclusion criteria*: any significant history of maternal medical or obstetric illness and any fetal compromise in current pregnancy *Setting*: Iran
Interventions	**Crystalloids versus colloids versus ephedrine** Group1: crystalloid preload: Ringer's lactate solution (15 mL/kg) infused in 30 min before spinal injection. Group 2: colloid preload: colloid solution (Hexamel 7 mg/kg) infused in 30 min before spinal injection. Group 3: ephedrine: ephedrine (15 mg IV bolus) immediately after spinal injection, infused in 45 s. All women received a standardised spinal anaesthetic technique and dose, a standardised crystalloid coload, standardised leg wrapping and standardised surgical positioning. Hypotension (requiring intervention) received rescue boluses of 5 mg ephedrine given each 5 min
Outcomes	*Maternal*: hypotension (SBP); hypotension, bradycardia; BP; heart rate; ephedrine requirement; vomiting; nausea; hypertension *Neonatal*: Apgar at 1 min and 5 min, umbilical cord blood pH, NACS
Notes	Hypotension was defined as SBP < 90 mmHg or > 20% below baseline. Bradycardia was defined as heart rate < 50 bpm. Hypertension was defined as SBP > 140 mmHg or > 20% baseline values.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	"Randomised" – not further specified except that sampling method was "consecutive"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported that women and all staff involved in the study were blind to the protocol used; however, colloid and crystalloids were preloads while ephedrine was given immediately after the spinal injection.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nurse assessing the severity of nausea and physician measuring neonatal outcomes were blinded

Jabalameli 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported (although nausea was only reported as a continuous measure).
Other bias	Low risk	Similar baseline characteristics

Jacob 2012

Study characteristics	
Methods	RCT
Participants	100 women *Inclusion criteria*: age 20-40 years, ASA I-II, singleton uncomplicated pregnancy, scheduled for elective caesarean under spinal anaesthesia *Exclusion criteria*: chronic hypertension, pregnancy-induced hypertension, eclampsia, known cardiovascular disease, haematocrit < 30%, any contraindication to spinal anaesthesia, height < 150 cm *Setting*: India
Interventions	**Crystalloid preload versus crystalloid coload** Group 1: 15 mL/kg over 20 min before placement of spinal block Group 2: 15 mL/kg of Ringer's lactate over 20 min starting as soon as CSF was tapped All women received standardised aspiration prophylaxis, standardised cannulation, standardised spinal anaesthetic technique and dose, standardised surgical positioning and standardised oxytocin regimen after delivery. Hypotension was treated with crystalloid boluses and 6 mg of ephedrine given intravenously every 3 min until SBP recovered to baseline value. The choice of crystalloid and the volume administered was left to the judgement of the attending anaesthetist. Bradycardia was treated with IV atropine 0.6 mg bolus.
Outcomes	*Maternal*: hypotension, ephedrine requirement for hypotension, nausea and vomiting, pruritus, headache, hypertension, shivering, time from induction-delivery and uterine incision to delivery, total IV fluid, blood loss *Neonatal*: Apgar scores at 1 min and 5 min, umbilical artery and vein blood gas measurements
Notes	Hypotension was defined as decrease in SBP to < 80% of baseline or SBP < 90 mmHg (whichever was lower). Bradycardia was defined as heart rate less than 50 bpm.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Jacob 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Neonatologist blinded Anaesthetist – not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

James 1973

Study characteristics	
Methods	RCT
Participants	79 women *Inclusion criteria*: normotensive women undergoing repeat or primary CS for cephalopelvic disproportion
Interventions	**Lower limb compression versus control** Group 1: plastic inflatable boots applied from toes to upper thighs and inflated immediately after spinal Group 2: control All women received a standardised crystalloid preload, a standardised spinal anaesthetic technique with dose adjusted according to subject's height and standardised surgical positioning.
Outcomes	*Maternal*: hypotension *Neonatal*: Apgar scores at 1 min and 5 min (expressed as mean score)
Notes	Hypotension was defined as SBP < 100 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

James 1973 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding: not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Jorgensen 1996

Study characteristics	
Methods	RCT
Participants	30 women *Inclusion criteria*: healthy, ASA I women undergoing elective CS *Exclusion criteria*: pre-eclampsia, pregnancy-induced hypertension, fetal abnormality, uteroplacental dysfunction
Interventions	**Lower limb compression versus control** Group 1: compression stockings (pressure equivalent to 54 mmHg) in place before spinal Group 2: control Intervention administered before spinal anaesthetic. All women received a standardised crystalloid preload, a standardised spinal anaesthetic technique with dose adjusted according to subject's height and standardised surgical positioning.
Outcomes	*Maternal*: hypotension; nausea; total ephedrine dose *Neonatal*: Apgar scores at 1 min, 5 min, and 10 min; umbilical cord blood pH (expressed as mean and SD)
Notes	Hypotension was defined as SBP < 100 mmHg or 80% baseline.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by "lottery", otherwise not described

Jorgensen 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding: not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 2 participants excluded from control group (1 failed spinal, 1 found to have pregnancy-induced hypertension)
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Jorgensen 2000

Study characteristics	
Methods	RCT
Participants	120 women *Exclusion criteria*: pre-eclampsia, arterial hypertension or multiple pregnancy *Setting*: Denmark
Interventions	**Warm versus cold crystalloid preload** Group 1: cold (21 degrees centigrade 0.9% saline preload) Group 2: warm (37 degrees centigrade saline preload) All women received a standardised spinal anaesthetic technique and dose as well as 5 mg IV ephedrine after spinal injection.
Outcomes	*Maternal*: hypotension; heart rate; arm discomfort; shivering; nausea; vomiting
Notes	Hypotension was defined as < 70% decrease in SAP from baseline or 100 mmHg or less.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation: "computer generation"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment: "sealed envelopes"

Jorgensen 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: not double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding: not double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 7/120 women were withdrawn from study, 2 because of failed spinal anaesthesia, 1 because of violation of selection criteria, and 5 because of protocol violations
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Karinen 1995

Study characteristics	
Methods	RCT
Participants	26 women *Inclusion criteria*: term parturients undergoing elective CS, healthy, uncomplicated singleton, non-labouring
Interventions	**Colloid versus crystalloid preload** Group 1: 500 mL 6% HES Group 2: 1000 mL Ringer's lactate Study drug infused over 10 min prior to spinal anaesthesia All women received standardised aspiration prophylaxis, standardised spinal anaesthetic technique and dose and standardised crystalloid infusion after spinal anaesthetic.
Outcomes	*Maternal*: hypotension; uterine artery pulsatile index; CVP; induction-delivery time *Neonatal*: Apgar scores at 1 min, 5 min, and 15 min (incomplete data); umbilical artery pH (expressed as mean and range)
Notes	Hypotension defined as SBP < 80% baseline or < 90 mmHg
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes" – no further details provided

Karinen 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: obstetrician performing ultrasound blinded to allocation, other blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	Not apparent

Khan 2013

Study characteristics	
Methods	RCT
Participants	100 women *Inclusion criteria*: ASA I-II, age 20-35, single pregnancy, elective caesarean under spinal anaesthesia *Exclusion criteria*: hypertension, congestive cardiac failure, cardiovascular disease, fetal distress, any contraindication to spinal anaesthesia, > 800 mL blood loss in theatre *Setting*: India
Interventions	**Crystalloid preload versus crystalloid coload** Group 1: preload of 20 mL/kg of Ringer's lactate over 20 min Group 2: coload of 20 mL/kg of Ringer's lactate at the maximal possible rate by pressurise giving set All women received no premedication, standardised cannulation, no further IV fluid except to keep IV line patent, standardised spinal anaesthetic technique and dose and standardised oxytocin postdelivery. Hypotension was treated with boluses of ephedrine 5 mg
Outcomes	*Maternal*: incidence of hypotension, height of sensory block, systolic/diastolic/mean BP, ephedrine requirement *Neonatal*: Apgar sores at 1 min and 5 min
Notes	Hypotension was defined as decrease in SBP > 20% from baseline or decrease of systolic pressure to < 90-100 mmHg
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Khan 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but protocol well defined and seems unlikely to have affected results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but protocol well defined and seems unlikely to have affected results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

King 1998

Study characteristics	
Methods	RCT
Participants	30 women *Inclusion criteria*: undergoing elective CS *Exclusion criteria*: hypertension, pre-eclampsia, preterm labour, juvenile diabetes, cocaine and methamphetamine use and cardiac disease
Interventions	**Ephedrine versus ephedrine + crystalloid versus crystalloid** Group 1: ephedrine infusion group: 10 mL saline bolus followed by ephedrine infusion 1 mg/mL, i.e. 20 mg in 12 min Group 2: ephedrine bolus group: 10 mg ephedrine followed by saline infusion 5 mL/min for 2 min followed by 1 mL/min for 10 min Group 3: saline bolus 2 mL followed by infusion 5 mL/min for 2 min followed by 1 mL/min for 10 min All women received a standardised crystalloid preload followed by standardised infusion, a standardised spinal anaesthetic technique and dose and standardised positioning.
Outcomes	*Maternal*: hypotension; time to first ephedrine rescue dose; number of hypotensive participants; total ephedrine dose *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as SBP < 80% baseline
Risk of bias	

King 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Low risk	Adequate: study drugs prepared by a third party (pharmacy)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: anaesthetist blinded to interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Kohler 2002

Study characteristics	
Methods	RCT
Participants	100 women *Inclusion criteria*: healthy women (ASA I or II) scheduled for elective CS under spinal anaesthesia *Exclusion criteria*: pre-eclampsia, arterial hypertension, gestational age less than 38 weeks or multiple pregnancy
Interventions	**Supine versus sitting positioning after spinal anaesthesia** Group 1: modified supine (tilted 10 degrees to left) after spinal Group 2: sitting position for 3 min after spinal before modified supine (n = 52) All women received 200-300 mL isotonic saline given before spinal, then an additional 15 mL/kg after a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; BP; nausea; vomiting; pain; level of anaesthesia; rescue with ephedrine; time from injection to birth; time from incision to birth *Neonatal*: umbilical arterial and venous blood; Apgar scores at 1 min and 5 min; time to sustained respiration; birthweight
Notes	Hypotension was defined as SBP < 70% of baseline or < 100 mmHg
Risk of bias	

Kohler 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Low risk	Adequate: "assignments were kept in sealed sequentially-numbered opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding: "haemodynamic data were transferred to a database by a person blind to which group the woman had been allocated"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/100 – 1 because of electrical power failure and 1 because of violation of selection criteria
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Kohli 2013

Study characteristics	
Methods	RCT
Participants	80 participants *Inclusion criteria*: age 18-35 years, ASA I-II, CS under spinal anaesthesia *Exclusion criteria*: contraindication to central neuraxial block, chronic hypertension, multiple pregnancy, diabetes mellitus, pregnancy-induced hypertension, BMI > 30 kg/m^2 *Setting*: India
Interventions	**Mechanical compression versus control** Group 1: sequential compression device used. The chambers of the device sequentially inflated from ankle to knee to a maximum pressure of 45-50 mmHg at the ankle and 35 mmHg at the calf; the duration of compression was 12 s with a 60 s relaxation period between compressions Group 2: no sequential compression device used All women received "adequate" crystalloid preload, standardised monitoring, standardised spinal anaesthetic technique and dose. All women had SCD put on legs, but only group 1 had their SCDs turned on. Hypotension treated with 6 mg boluses of IV ephedrine.
Outcomes	*Maternal*: incidence of hypotension, ephedrine use

Kohli 2013 *(Continued)*

	No neonatal outcomes
Notes	Hypotension was defined as decrease in SBP by > 20% from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Kuhn 2016

Study characteristics

Methods	RCT
Participants	120 women *Inclusion criteria*: healthy pregnant women, term pregnancy, elective caesarean delivery, aged 18-40 years, height 160-180 cm, pre-pregnancy BMI < 31 kg/m^2 *Exclusion criteria*: pre-existing or gestation hypertension/pre-eclampsia/cardiovascular or cerebrovascular disease/psychiatric or somatic disease (other then well-treated mild asthma/thyroid hypofunction) or contraindications to spinal anaesthesia *Setting*: Norway
Interventions	**Phenylephrine versus leg wrapping versus control** Group 1: phenylephrine (initial bolus 0.25 µg/kg followed by infusion 0.25 µg/kg/min) + sham leg-wrapping Group 2: leg wrapping + IV placebo infusion Group 3: no treatment consisting of sham leg wrapping + IV placebo infusion

Kuhn 2016 *(Continued)*

	All women received no premedication or IV prehydration, standardised IV cannulation, standardised monitoring (via LiDCOplus monitor including arterial line), standardised positioning, standardised spinal anaesthesia technique and dose, standardised crystalloid co-hydration, standardised oxygen therapy, standardised oxytocin regimen. Leg wrapping or sham leg wrapping performed prior to spinal anaesthesia (refer to below for method of blinding) Study medicine infusion commenced at time of spinal anaesthesia, and ceased if SAP > 150 mmHg for > 3 min Hypotension was treated with IV bolus of 30 µg phenylephrine If hypotension was combined with bradycardia, or MAP < 60 mmHg, an IV bolus of 5 mg ephedrine was administered.
Outcomes	*Maternal*: extent of decrease in SBP; change in cardiac output, systemic vascular resistance, stroke volume; heart rate; nausea and vomiting, pruritus *Neonatal*: umbilical artery and vein pH and BE, Apgar score
Notes	Hypotension was defined as SAP < 80% of mean SAP or SAP < 90 mmHg Bradycardia was defined as heart rate < 55 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Hospital pharmacy performed block randomisation into 3 groups of equal size using a pool of sealed and shuffled envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes for leg wrapping, neutral syringes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded Study medicine prepared in 50 mL syringes containing either phenylephrine or placebo, marked with randomisation number and neutral study information Instructions for therapeutic or sham wrapping placed into a sealed envelope for each patient Leg wrapping performed by specifically trained technical assistants after visual shielding between head of bed and lower extremities. Subsequently, legs were covered prior to positioning in lateral for spinal anaesthesia.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation codes not revealed until all measurements recorded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1 Ph: 2 excluded (1 GA, 1 low-quality data) Group 2 LW: 2 excluded (2 low-quality data) Group 3 Con: 4 excluded (4 low-quality data)
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported

Kuhn 2016 *(Continued)*

Other bias	Low risk	Funding from South-Eastern Norway Regional Authority through government research grant

Kundra 2007

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA physical status I or II, with full-term singleton pregnancies and scheduled to undergo elective or emergency lower segment CS under subarachnoid block; without maternal or fetal complications *Exclusion criteria*: essential or pregnancy-induced hypertension, diabetes, pre-eclampsia, heart disease, placental abruption, prematurity (< 37 weeks' gestation), obesity, haemoglobin < 7g/dL, intrauterine growth restriction, fetal distress, fetal anomalies *Setting*: India
Interventions	**Left lateral tilt versus left manual uterine displacement** Group 1: left lateral tilt: women received 15 degree left lateral tilt immediately following administration of anaesthetic Group 2: left manual uterine displacement: women received manual displacement of the uterus immediately following anaesthetic; positioned supine without left lateral tilt All women received standardised aspiration prophylaxis, standardised crystalloid preload, standardised spinal anaesthetic technique and dose. Hypotension (requiring intervention) was treated with IV boluses of ephedrine (6 mg) until SBP was restored to > 90 mmHg.
Outcomes	*Maternal*: hypotension; ephedrine requirement *Neonatal*: Apgar at 1 min, 5 min, and 10 min
Notes	Hypotension was defined as SBP < 90 mmHg or < 80% of baseline value Bradycardia defined as heart rate < 60 bpm

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope technique."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Manual displacement of the uterus was provided by a person other than the attending anaesthetist who was blinded to the haemodynamic parameters being displayed by screen separation."

Kundra 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apgar scores were assessed by a clinician who was blinded to group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Selective reporting (reporting bias)	Unclear risk	Not all expected outcomes were reported or reported completely
Other bias	Low risk	Baseline characteristics were similar

Kundra 2008

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: ASA class I and II, single term pregnancies, scheduled for elective caesarean under spinal anaesthesia *Exclusion criteria*: pre-existing or pregnancy-induced hypertension, known cardiovascular disease or contraindications to spinal anaesthesia *Setting*: India
Interventions	**Ephedrine versus crystalloid preload** Group 1: ephedrine: ephedrine infusion prepared in 0.9% NS (1 mg/mL), started prophylactically at a rate of 5 mg/min for the first 2 min and then at a rate of 1 mg/min for the next 18 min, following administration of spinal anaesthetic Group 2: crystalloid preload: Ringer's lactate 500 mL, infused rapidly over 15-20 min before institution of spinal anaesthetic All women received a standardised spinal anaesthetic technique and dose followed by a standardised crystalloid infusion. Hypotension requiring intervention received 5 mg IV bolus ephedrine, repeated if necessary.
Outcomes	*Maternal*: hypotension; induction to birth time; total ephedrine dose; adverse effects; heart rate *Neonatal*: Apgar scores; umbilical venous gases
Notes	Hypotension was defined as a > 20% fall in SBP

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly divided into two groups"

Kundra 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "single-blinded" but unlikely that blinding was possible as women in the ephedrine group had 2 separate IV lines established, while those in the crystalloid group had only 1 line
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Unclear risk	Neonatal outcomes not reported in a form that could be used in this review
Other bias	Low risk	Similar baseline characteristics

Lin 1999

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: healthy parturients undergoing primary or repeat CS, gestation 33-41 weeks, uncomplicated singleton, not in labour, ASA I
Interventions	**Colloid preload versus crystalloid preload** Group 1: 500 mL dextran 40 (n = 30) Group 2: 1000 mL Ringer's lactate (n = 30) Study drug administered over 20 min prior to spinal All women received a standardised spinal anaesthetic technique with variable dose (1.8-2.2mL 0.5% bupivacaine).
Outcomes	*Maternal*: hypotension; uterine incision-delivery time; estimated blood loss; urine output; nausea *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension defined as SBP < 70% baseline
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

Lin 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not apparent

Loke 2002

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: ASA I women presenting for elective caesarean under spinal anaesthesia
Interventions	**Head-down tilt versus control:** Group 1: anaesthesia induced in right lateral position (woman's spine inclined at 5 to 6 degrees from horizontal with head slightly lower); anaesthesia induced in right lateral position 10 degree head-up tilt Group 2: anaesthesia induced in right lateral position (woman's spine inclined at 4 to 5 degrees from horizontal with head slightly higher). All women received a standardised preload of 1 litre crystalloid IV and a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; sensory block; ephedrine requirement; nausea; pain *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension defined as SBP < 90 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

Loke 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Sealed envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding: outcome assessors were only admitted to the operating room once the position of the operating table had been readjusted
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none reported but losses unlikely
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Loo 2002

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: undergoing elective CS, ASA I, age 18 to 40 years, height > 150 cm, weight < 100 kg, full-term singleton fetus with no congenital abnormalities, no polyhydramnios, no intrauterine growth retardation, and estimated fetal weight > 2500 g
Interventions	**Ephedrine + crystalloid co-load versus crystalloid preload** Group 1: prophylactic ephedrine 6 mg IV and 1000 mL Ringer's lactate commenced immediately after spinal anaesthesia Group 2: preload of 1000 mL Ringer's lactate All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension (defined as SBP < 100 mmHg); BP; heart rate; time to block; ephedrine dose *Neonatal*: Apgar scores
Notes	Hypotension defined as SBP < 100 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

Loo 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment: "divided into two groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: described as "double-blinded" but no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Low risk	None apparent

Loughrey 2002

Study characteristics	
Methods	RCT
Participants	67 women (= 68 neonates due to 1 twin pregnancy in the control group) *Inclusion criteria*: term and peri-term women presenting for elective CS *Exclusion criteria*: moderate to severe pre-eclampsia, history of essential hypertension, contraindication to spinal anaesthesia
Interventions	**Ephedrine (different doses) versus control** Group 1: 6 mg ephedrine Group 2: 12 mg ephedrine Group 3: 0.9% saline IV bolus (control) The study drug was given simultaneously with the anaesthetic. All women received a standardised crystalloid preload and thromboembolic stockings were not worn. All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; doses of ephedrine; heart rate; hypertension; nausea or vomiting *Neonatal*: cord arterial pH; Apgar score at 5 min
Notes	Hypotension was defined as a reduction in SAP > 30% from baseline or < 90 mmHg.
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Loughrey 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Computer-generated"
Allocation concealment (selection bias)	Low risk	Adequate: study drugs coded by hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: "double-blind" – all observers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/67 – 1 woman in the saline group was excluded because an infusion of ephedrine was administered following the spinal injection and another because of administration of IV fentanyl to supplement analgesia
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Loughrey 2005

Study characteristics	
Methods	RCT
Participants	43 women *Inclusion criteria*: ASA I and II non-labouring women undergoing scheduled elective caesareans; term uncomplicated singleton pregnancies, women taking only prenatal vitamins and weighing less than 100 kg *Exclusion criteria*: cardiac, pulmonary or renal diseases or systemic diseases that could influence haemodynamic responses, including pre-eclampsia, hypertension and diabetes; if women were taking or had a history of taking any medications that could influence haemodynamic responses, including magnesium sulphate, terbutaline or B-blockers
Interventions	**Phenylephrine versus control** Group 1: 10 mg ephedrine IV Group 2: 40 µg phenylephrine + 10 mg ephedrine The IV bolus of study drug was administered simultaneously with the intrathecal anaesthetic injection. All women received a standardised crystalloid preload, did not wear thromboembolic stockings and received a standardised spinal anaesthetic technique and dose. IV preload with 10 mL/kg of Ringer's lactate; and 10mg IV ephedrine administered simultaneously with study drug For rescue from hypotension, women in the ephedrine only group were given 5 mg ephedrine and women in the ephedrine + phenylephrine group were given 5 mg ephedrine + 20 µg phenylephrine.

Loughrey 2005 *(Continued)*

Outcomes	*Maternal*: hypotension; heart rate; nausea; rescue boluses; total mean ephedrine dose; total mean phenylephrine dose *Neonatal*: umbilical artery pH (mean and SD); umbilical vein pH (mean and SD); Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as SBP < 100 mmHg or a decrease in SBP of 20% from baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: "double-blinded"; anaesthetist remained blinded to the study solution throughout
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 3/43 – 1 woman in the ephedrine only group and 2 in the ephedrine/phenylephrine group were excluded from analysis due to improper data collection before unblinding
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Madi-Jebara 2008

Study characteristics

Methods	RCT
Participants	120 women *Inclusion criteria*: non-labouring ASA I and II women having non-urgent CS *Exclusion criteria*: obesity (> 115 kg), height < 152 cm, diabetes, pregnancy-induced hypertension, chronic hypertension, heart disease, multiple gestation, age < 18 or > 40 years *Setting*: Lebanon
Interventions	**Colloid versus crystalloid** Group 1: HES (500 mL) Group 2: Ringer's lactate (1000 mL)

Madi-Jebara 2008 *(Continued)*

	All women received study fluid administered as preload before spinal. No IV fluids were administered prior to anaesthesia. Standardised spinal anaesthetic technique and dose. Hypotension (requiring intervention) received IV boluses of 3 mg ephedrine; repeated every 2 min if hypotension persisted or recurred
Outcomes	*Maternal*: hypotension; nausea and/or vomiting *Neonatal*: Apgar scores; umbilical arterial and venous pH
Notes	Hypotension defined as SBP < 100 mmHg or 20% decrease from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" – no further details given
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	None of the neonatal outcomes were reported in a form that could be used in this review.
Other bias	Low risk	Baseline characteristics were similar.

Magalhaes 2009

Study characteristics

Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I or II, term pregnancy, of single fetus, indication for CS *Exclusion criteria*: refusal to participate in study, patients aged < 18 years, pre-existing or pregnancy-induced systemic hypertension, presence of cardiovascular or cerebrovascular diseases, fetal abnormalities, history of allergy to drugs used in the study, contraindications to spinal block *Setting*: Brazil
Interventions	**Prophylactic ephedrine versus prophylactic phenylephrine**

Magalhaes 2009 *(Continued)*

	Group 1: prophylactic IV dose of 10 mg ephedrine immediately after spinal block Group 2: prophylactic IV dose of 80 µg phenylephrine immediately after spinal block Standardised monitoring and positioning, standardised spinal anaesthetic technique (at L2-L3 or L3-L4) and dose, standardised crystalloid coload and maintenance No significant baseline differences between groups Hypotension was managed with a bolus dose of 50% of study drug Bradycardia was treated with 0.75 mg atropine
Outcomes	*Maternal*: level of block, time from blockade at T5 to incision of skin, incision of uterus and removal of fetus was recorded, incidence of maternal hypotension, reactive hypertension, bradycardia, nausea/vomiting, total dose of vasopressor *Neonatal*: Apgar scores at 1 min and 5 min, pH < 7.2
Notes	Hypotension was defined as BP less than or equal to 80% baseline. Reactive hypertension was defined as BP > 20% baseline values after the use of the vasopressor. Bradycardia was defined as heart rate < 50 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sequential sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind": syringes of study drugs prepared by a physician who was not involved with data collection and analysis
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Result of allocation was ignored by both patients & physicians responsible for collecting & analysing study parameters."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported
Other bias	Unclear risk	No apparent sources of other bias

Marciniak 2013

Study characteristics

Methods	RCT

Marciniak 2013 *(Continued)*

Participants	60 women *Inclusion criteria*: ASA I-II, elective CS *Exclusion criteria*: patient refusal to participate in study, contraindication to perineural anaesthesia, multiple pregnancies, body weight > 115 kg, height < 152 cm, age < 18 or > 40 years old, diabetes, pregnancy-induced hypertension, chronic hypertension, heart disease *Setting*: Poland
Interventions	**Comparison of 2 different colloid solutions as preload: Voluven versus Tetraspan** Women were transfused 1 of the following solutions prior to spinal anaesthesia: Group 1: 500 mL transfusion of 6% HES 130/0.4 with 0.9% NaCl prior to anaesthesia (Voluven) over 15 min Group 2: 500 mL of 6% HES 130/0.42 in a physiological electrolyte solution (Tetraspan) over 15 min All women received standardised aspiration prophylaxis, standardised spinal anaesthetic technique and dose, standardised oxygen therapy and standardised oxytocin administration after delivery. Until the birth of the child, the patient did not receive any further IV fluid. Hypotension was managed with 5-10 mg of IV ephedrine. During delivery 40% O_2 given via mask. 10 units oxytocin IV given after delivery
Outcomes	*Maternal*: BP, time to skin incision/delivery/uterine incision *Neonatal*: Apgar scores 1, 3, 5, 10 min after birth, pH of venous and arterial umbilical blood
Notes	Hypotension defined as a drop in SBP of 20% below the baseline pressure (or below 100 mmHg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	5 patients from Group 1 and 4 patients from Group 2 were removed from the study due to problems with cord blood collection for gaso-metric tests (e.g. in-

Marciniak 2013 *(Continued)*

	ability to perform dual collection of blood samples from the same vessel or no collection). Successful tests were conducted in the remaining 51 patients (25 in Group 1 and 26 in Group 2)

Marciniak 2015

Study characteristics	
Methods	RCT
Participants	72 women *Inclusion criteria*: ASA I/II, elective CS due to cephalopelvic disproportion, post-C-section condition, gluteal position, ophthalmic indications and those without medical indications *Exclusion criteria*: lack of consent, contraindications to spinal anaesthesia, multiple pregnancy, body weight > 155 kg, height < 152 cm, age < 18 years or > 40 years, diabetes mellitus, pregnancy-induced hypertension, chronic hypertension, cardiac diseases, use of selective serotonin reuptake inhibitors *Setting*: Poland
Interventions	**Ondansetron versus control** Group 1 (O): 8 mg ondansetron in 10 mL 0.9% NaCl IV Group 2 (P): 10 mL 0.9% NaCl IV Syringe content administered over 1 min, after colloid preload and 5 min prior to spinal anaesthesia. All women received standardised aspiration prophylaxis, standardised monitoring, standardised cannulation and colloid prehydration, standardised spinal anaesthetic technique and dose. Hypotension was managed with fractionated IV ephedrine boluses. Bradycardia was managed with 0.5 mg atropine.
Outcomes	*Maternal*: hypotension, bradycardia *Neonatal*: Apgar scores at 1 min and 5 min, baby's weight, umbilical vein acid-base status
Notes	Hypotension was defined as a 20% decrease in systolic pressure or decrease in systolic pressure < 90 mmHg Bradycardia was defined as heart rate < 60 bpm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Online randomisation programme
Allocation concealment (selection bias)	Low risk	Study drug prepared by anaesthetist otherwise uninvolved in study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The anaesthetist preparing the solution was on call, and the anaesthetist administering the solution was blinded.

Marciniak 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients in placebo group received IV opioids due to insufficient analgesia and were thus excluded from the study
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported
Other bias	Low risk	None evident

Mathru 1980

Study characteristics	
Methods	RCT
Participants	87 women *Inclusion criteria*: healthy parturients undergoing elective caesarean under spinal anaesthesia
Interventions	**Colloid + crystalloid versus crystalloid versus ephedrine + crystalloid versus ephedrine + colloid + crystalloid** Group 1: 5% albumin in Ringer's lactate with 5% dextrose solution (15 mL/kg) Group 2: Ringer's lactate with 5% dextrose solution (15 mL/kg) Group 3: Ringer's lactate with 5% dextrose solution (15 mL/kg) plus ephedrine 25 mg IM Group 4: 5% albumin in Ringer's lactate with 5% dextrose solution (15 mL/kg) plus ephedrine 25 mg IM Fluids were administered as a preload over 15-20 min before spinal anaesthesia. All women received a standardised anaesthetic technique with variable local anaesthetic dose (6-8 mg 0.5% hyperbaric tetracaine).
Outcomes	*Maternal*: hypotension; MAP; heart rate *Neonatal*: Apgar scores
Notes	Hypotension defined as a decrease in SBP below 90 torr

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not stated

Mathru 1980 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Inadequate reporting
Other bias	High risk	Variable dose of local anaesthetic used for spinal anaesthesia

Mercier 2014

Study characteristics	
Methods	RCT
Participants	167 women *Inclusion criteria*: ASA I-II, elective caesarean under spinal anaesthesia, aged > 18 years, weight > 60 kg and < 95 kg, term singleton pregnancy (> 37 weeks' gestation) *Exclusion criteria*: concomitant diseases (e.g. pregnancy-induced hypertension, diabetes mellitus, cardiovascular or cerebrovascular disease, coagulation disorders), fetal complications, contraindications to spinal anaesthesia or HES administration, emergency CS, women who received IV fluid prior to admission to theatre *Setting*: multicentre, France
Interventions	**Colloid versus crystalloid preload** Group 1: HES: 500 mL 6% HES 130/0.4, followed by 500 mL Ringer's lactate Group 2: RL: 500 mL of Ringer's lactate, followed by second infusion of 500 mL Ringer's lactate All women received standardised aspiration prophylaxis, standardised monitoring, standardised anaesthetic technique and dose. Maternal bradycardia treated with atropine 0.5-1 mg IV Hypotension treatment: SBP > 95% baseline – no treatment, SBP 94-80% baseline received 50 µg phenylephrine, SBP 79%-90% of baseline received 100 µg phenylephrine, SBP < 70% of baseline received 150 µg phenylephrine. Sustained nausea and vomiting was treated with ondansetron 4 mg IV.
Outcomes	*Maternal*: incidence of hypotension; time of onset of hypotension; symptomatic hypotension; nausea and vomiting; dizziness; minimum heart rate; bradycardia; atropine and phenylephrine requirement *Neonatal*: Apgar scores at 1 min and 5 min, umbilical arterial and venous pH
Notes	Hypotension defined as SBP < 80% of baseline Bradycardia defined as heart rate < 50 bpm
Risk of bias	

Mercier 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence using SAS software; blocks of 4
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind: "study fluids were provided in indistinguishable 500 mL bottles in both groups with randomisation code, as previously pictured."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly reported in study results 11 protocol violations in HES group, and 10 in the Ringer's group Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	High risk	Fully funded by Fresenius Kabi, the company that produces HES

Miyabe 1997

Study characteristics	
Methods	RCT
Participants	34 women *Inclusion criteria*: term parturients undergoing elective CS, ASA I *Exclusion criteria*: not specified
Interventions	**Head-up versus control** Group 1: horizontal Group 2: 10 degree head-down tilt All women received a standardised anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; block height; fluid; ephedrine doses *Neonatal*: none stated
Notes	Hypotension defined as SBP < 100 mmHg

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Miyabe 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Mohta 2010

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I or II women with term uncomplicated pregnancies, scheduled to undergo elective CS under subarachnoid block *Exclusion criteria*: pregnancy-induced hypertension, cardiovascular disease, cerebrovascular disease, placental or fetal abnormalities, absolute or relative contraindication to spinal anaesthesia and women with SBP < 100 mmHg *Setting*: India
Interventions	**Phenylephrine versus mephentermine** Group 1: infusion of phenylephrine (50 µg/mL); administered immediately following spinal anaesthesia, at a rate of 60 mL/h (50 µg/min) Group 2: infusion of mephentermine s (600 µg/mL); administered immediately following spinal anaesthesia, at a rate of 60 mL/h (600 µg/min) All women received a standardised fluid preload and standardised spinal anaesthetic technique. Spinal anaesthetic dose was 2.2 mL of hyperbaric 0.5% bupivacaine unless patient's height was < 150 cm, in which case the dose was 2 mL. Hypotension was managed with a 2 mL bolus dose of respective vasopressor solution (100 µg phenylephrine or 1.2 mg mephentermine). Hypertension was managed with stepwise reduction in infusion by 6 mL/h. Bradycardia was managed with 0.3 mg boluses of atropine.
Outcomes	*Maternal*: hypotension; reactive hypertension; bradycardia; nausea; vomiting; dizziness

Mohta 2010 *(Continued)*

	Neonatal: umbilical arterial and venous blood gases; Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as fall of ≥ 20% from baseline or an absolute value of < 100 mmHg SBP, whichever was higher. Hypertension was defined as a rise in SBP > 20% above baseline. Bradycardia was defined as heart rate < 50 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided into two groups of 30 each"
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind: "the solution of vasopressor for infusion was prepared by an assistant who was not involved in the study, and the investigator, as well as the patient, were thus blinded to the identity of vasopressor used" However, it was not possible for the anaesthetist to be blinded as treatment of hypotension with "the respective vasopressor solution" would have required knowledge of which vasopressor was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported
Other bias	Low risk	Similar baseline characteristics except for a lower mean baseline heart rate in the phenylephrine group

Morgan 2000

Study characteristics

Methods	RCT
Participants	185 women *Inclusion criteria*: healthy women with uncomplicated term pregnancies undergoing elective CS *Exclusion criteria*: not specified
Interventions	**Variable ephedrine infusions versus crystalloid preload alone versus crystalloid preload + variable ephedrine infusions** Group 1: ephedrine infusion alone at 1 mg/min from spinal injection until birth

Morgan 2000 *(Continued)*

	Group 2: ephedrine infusion alone at 2 mg/min from spinal injection until birth Group 3: ephedrine infusion alone at 3-4 mg/min from spinal injection until birth Group 4: Ringer's lactate 1000 mL over 20 min before spinal injection Group 5: Ringer's lactate 1000 mL over 20 min before spinal injection plus ephedrine infused at 1 mg/min from spinal injection until birth Group 6: Ringer's lactate 1000 mL over 20 min before spinal injection plus ephedrine infused at 2 mg/min from spinal injection until birth Group 7: Ringer's lactate 1000 mL over 20 min before spinal injection plus ephedrine infused at 3-4 mg/min from spinal injection until birth All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; heart rate; hypertension *Neonatal*: umbilical artery pH (expressed as means ± SD), BE
Notes	Hypotension defined as decrease in SBP > 30% from baseline Tachycardia defined as heart rate > 130 bpm Hypertension defined as SBP > 150 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: "double blinded" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Moslemi 2015

Study characteristics

Moslemi 2015 *(Continued)*

Methods	RCT
Participants	90 recruited, 83 completed analysis *Inclusion criteria*: healthy pregnancy of gestational age 36 weeks or higher, non-emergency CS *Exclusion criteria*: below 36 weeks' gestation, emergence CS, high-risk pregnancies (multiple gestations, intrauterine growth retardation, pre-eclampsia, maternal cardiovascular or respiratory diseases), any contraindication of spinal anaesthesia (patient refusal, coagulopathy, haemorrhage or hypovolaemic shock), unexpected events during surgery (haemorrhage, sensory block higher or lower than T4-T5 after spinal anaesthesia) *Setting*: Iran
Interventions	**Phenylephrine versus ephedrine versus crystalloid** Group 1: 450 µg phenylephrine in 250 cc normal saline administered over 30 min after preload Group 2: 45 mg ephedrine in 250 cc normal saline administered over 30 min Group 3: 250 cc normal saline infused over 30 min All women received standardised monitoring, standardised crystalloid preload and standardised spinal anaesthetic technique and dose. Hypotension was treated with study vasopressor (clinician blinded to which vasopressor): Group 1 received 50-100 µg phenylephrine Group 2 and 3 received 5-10 mg ephedrine.
Outcomes	*Maternal*: incidence and degree of hypotension, heart rate and rhythm, nausea/vomiting, number of vasopressor therapy and total dose, "any other intra or post-operative complication". *Neonatal*: arterial blood gas, Apgar at 1 min and 5 min
Notes	Hypotension defined as drop in BP > 20% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs labelled with numerical codes and investigators were blinded Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1: 4 excluded due to very high or very low sensory block Group 2: 3 excluded due to very high or very low block

Moslemi 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	Group 1: 4 excluded due to very high or very low sensory block Group 2: 3 excluded due to very high or very low block
Other bias	Low risk	None apparent Funded by: University of Medical Sciences and Women's Reproductive Health Research Centre

Muzlifah 2009

Study characteristics	
Methods	RCT
Participants	80 women *Inclusion criteria*: ASA I or II women scheduled for elective CS under spinal anaesthesia, normal singleton pregnancy; > 36 weeks' gestation; BMI 20-38 kg/m^2; height > 145 cm *Exclusion criteria*: contraindications for spinal anaesthesia and failed spinal necessitating conversion to GA *Setting*: Malaysia
Interventions	**Crystalloids: different preload volumes** Group 1: low volume crystalloid 10 mL/kg of Ringer's lactate infusion preload Group 2: high volume crystalloid 20 mL/kg of Ringer's lactate infusion preload All women received standardised aspiration prophylaxis, standardised anaesthetic technique and dose, standardised fluid maintenance. Hypotension was managed with 6 mg boluses of ephedrine.
Outcomes	*Maternal*: hypotension; BP; ephedrine requirement; nausea; vomiting; oxygen saturation; respiratory rate
Notes	Hypotension was defined as a > 20% fall in MAP from baseline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	Unclear risk	"Randomly allocated" – no further details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "single blinded" – no further details reported
Blinding of outcome assessment (detection bias)	Unclear risk	As above

Muzlifah 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported
Selective reporting (reporting bias)	High risk	No neonatal outcomes were reported
Other bias	Low risk	Similar baseline characteristics

Nazir 2012

Study characteristics	
Methods	RCT
Participants	100 women *Inclusion criteria*: ASA grade I women undergoing elective CS under spinal anaesthesia with a normal singleton pregnancy beyond 36 weeks' gestation *Exclusion criteria*: pregnancy-induced hypertension, diabetes, cardiovascular or cerebrovascular disease, fetal abnormalities, contraindication to spinal anaesthesia *Setting*: India
Interventions	**Prophylactic ephedrine versus phenylephrine** Group 1: prophylactic bolus of ephedrine 10 mg IV 1 min after intrathecal injection Group 2: prophylactic dose of phenylephrine 100 µg IV 1 min after intrathecal injection All women received standardised premedication, a standardised fluid preload, a standardised spinal anaesthetic technique (in either lateral or seated position) and dose, standardised surgical positioning. Hypotension managed with rescue boluses of ephedrine 5 mg IV (group 1) or phenylephrine 50 µg IV (group 2) whenever maternal SBP was recorded as less than 90 mmHg. Bradycardia was treated with atropine 300 µg IV bolus.
Outcomes	*Maternal*: BP (systolic, diastolic, mean); heart rate; need for rescue bolus(es); need for atropine *Neonatal*: Apgar scores at 1 min and 5 min; umbilical cord blood pH (unclear as to venous or arterial); results for Apgar and pH < 7.2
Notes	Definition of hypotension is a SBP measurement < 90 mmHg. Bradycardia was defined as heart rate < 60 bpm.
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**
Random sequence generation (selection bias)	Unclear risk — "Randomly allocated into two groups of 50 each" – method not specified

Nazir 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Randomly allocated into two groups of 50 each" – method not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind" – the vasopressor solutions were prepared in identical syringes by an anaesthetist or investigator who was not involved in subsequent patient care
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but outcomes probably recorded by staff involved in care
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	None evident

Ngan Kee 2000

Study characteristics	
Methods	RCT
Participants	80 women *Inclusion criteria*: ASA I or II Asian women with term singleton pregnancies having elective CS *Exclusion criteria*: pre-existing or pregnancy-induced hypertension, known cardiovascular or cerebrovascular disease, or contraindications to spinal anaesthesia *Setting*: Hong Kong, China
Interventions	**Ephedrine + crystalloid preload (different doses) versus crystalloid preload alone** Group1: ephedrine 10 mg Group 2: ephedrine 20 mg Group 3: ephedrine 30 mg Group 4: saline control All were diluted to 10 mL with saline and injected intravenously over 30 s. All women received a standardised crystalloid preload with Ringer's lactate followed by a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; hypertension; heart rate; total ephedrine dose; nausea or vomiting; upper sensory level; skin incision to birth and uterine incision to birth time *Neonatal*: Apgar scores at 1 min and 5 min; umbilical arterial and venous blood gas and pH; cardiotocograph
Notes	Hypotension defined as SBP < 80% baseline or < 100 mmHg

Ngan Kee 2000 *(Continued)*

	Hypertension defined as SBP > 120% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Coded, opaque shuffled envelopes – randomisation method not described
Allocation concealment (selection bias)	Low risk	Adequate: coded, opaque shuffled envelopes, study drugs were prepared by an anaesthetist not involved in assessing women
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind (participants and anaesthetists) – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: maternal heart rate data lost in 1 woman (out of 20) from 10 mg group; cord blood samples incomplete in 2 each from control (n = 20), 20 mg (n = 20) and 30 mg (n = 20) groups
Selective reporting (reporting bias)	Low risk	Appears to report all outcomes
Other bias	Low risk	None evident

Ngan Kee 2004a

Study characteristics

Methods	RCT
Participants	50 women *Inclusion criteria*: term singleton pregnancies scheduled for elective caesarean under spinal anaesthesia *Exclusion criteria*: pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormality or contraindication to spinal anaesthesia *Setting*: Hong Kong, China
Interventions	**Phenylephrine versus control** Group 1: phenylephrine IV immediately after intrathecal injection; 100 µg/min for 3 min Group 2: control (saline infusion plus rescue IV bolus of phenylephrine (100 µg) when SAP < 80% baseline Note: women in the phenylephrine group were given phenylephrine 100 µg/min whenever SAP was less than baseline. All women received a standardised spinal anaesthetic technique and dose.

Ngan Kee 2004a *(Continued)*

Outcomes	*Maternal*: hypotension; BP; nausea and vomiting; bradycardia requiring intervention; phenylephrine dose; incision to birth time *Neonatal*: umbilical arterial blood gases; umbilical venous blood gases; Apgar scores
Notes	Hypotension defined as SAP < 80% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization codes"
Allocation concealment (selection bias)	Low risk	"Codes contained in sealed, sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind"; "two identical syringes"; investigators and women were blinded to the contents of the syringes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none (although there was insufficient cord blood to measure pH in 1 neonate)
Selective reporting (reporting bias)	Low risk	Appears to report all
Other bias	Low risk	None evident

Ngan Kee 2013a

Study characteristics

Methods	RCT
Participants	104 participants *Inclusion criteria*: ASA I-II, age > 18 years, term singleton pregnancy, elective caesarean under spinal anaesthesia *Exclusion criteria*: pre-existing or gestational hypertension, abnormality of fetus, onset of uterine contraction, coagulopathy, thrombocytopenia, cerebrovascular or cardiovascular disease, any contraindication to the use of spinal anaesthesia, height > 180 cm or < 140 cm, weight > 100 kg or < 50 kg *Setting*: Hong Kong, China
Interventions	**Prophylactic glycopyrrolate versus control** Group 1: single IV bolus of glycopyrrolate 4μg/kg diluted in saline to 2 mL administered at commencement of spinal injection

Ngan Kee 2013a *(Continued)*

	Group 2: single IV bolus 2 mL saline placebo administered at commencement of spinal injection All women received standardised aspiration prophylaxis, standardised monitoring, standardised positioning, standardised cannulation, a standardised spinal anaesthetic technique and dose, and standardised crystalloid coload. BP maintained using infusion of phenylephrine 100 µg/mL using a computer controlled closed-loop feedback infusion.
Outcomes	*Maternal*: total dose and median rate of phenylephrine infusion, total amount of IV fluid given, number of episodes of hypotension, nausea and vomiting *Neonatal*: Apgar scores, umbilical cord gases
Notes	Hypotension was defined as SBP < 80% of baseline. Hypertension was defined as SBP > 120% of baseline. Bradycardia was defined as heart rate < 50 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random codes
Allocation concealment (selection bias)	Low risk	Sealed opaque sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes, both blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1 – 5 excluded due to severe shivering, infusion tubing fault, computer cable fault Group 2 – 6 excluded due to severe shivering, infusion tubing fault
Selective reporting (reporting bias)	Low risk	Appears all reported
Other bias	Low risk	None evident

Nishikawa 2007

Study characteristics

Methods	RCT
Participants	54 women *Inclusion criteria*: ASA I-II status women, between 20 to 40 years, undergoing elective caesarean

Nishikawa 2007 *(Continued)*

	Exclusion criteria: women with BMI > 30 kg/m^2, anaemia (Hb < 10 g/dL), history of neurological or psychiatric diseases *Setting*: Japan
Interventions	**Colloid preload versus colloid coload versus crystalloid alone** Group 1: colloid preload: after Ringer's lactate was started at a rate of 5 mL/kg, this was changed to HES 6% (molecular weight 70 kDa, degree of substitution 0.5) and infusion rate was increased to 15 mL/kg for 10 min *before* spinal anaesthesia. Infusion rate was returned to Ringer's lactate at 5 mL/kg Group 2: colloid coload: after Ringer's lactate was started at a rate of 5 mL/kg, this was changed to HES 6% (molecular weight 70 kDa, degree of substitution 0.5) and infusion rate was increased to 15 mL/kg for 10 min *after* spinal anaesthesia. Infusion rate was returned to Ringer's lactate at 5 mL/kg Group 3: crystalloid alone: Ringer's lactate at 5 mL/kg All women received standardised leg wrapping, no sedative premedication, and a standardised spinal anaesthetic technique and dose. Hypotension requiring intervention was managed with IV bolus of 4 mg of ephedrine to maintain BP at 80% of baseline. Bradycardia was managed with IV atropine 0.5 mg.
Outcomes	*Maternal*: hypotension; need for ephedrine; BP; bradycardia *Neonatal*: pH, BE, Apgar scores
Notes	Hypotension was defined as a decrease in SBP < 80% baseline Bradycardia was defined as heart rate < 50 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; "both the patient and the researcher who recorded the data were blinded as to the type of colloid loading"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported (except for nausea/vomiting)

Nishikawa 2007 *(Continued)*

Other bias	Unclear risk	Similar baseline characteristics except that women in the HES coload group had lower mean BMI

Nivatpumin 2016

Study characteristics

Methods	RCT
Participants	168 women *Inclusion criteria*: age > 18 years, ASA I-II, term singleton pregnancy, elective caesarean delivery under spinal anaesthesia *Exclusion criteria*: diabetes mellitus other than gestational diabetes, hypertension, BMI > 40 kg/m², complicated pregnancy, allergy to study drugs, long QT syndrome, contraindications to spinal anaesthesia *Setting*: Thailand
Interventions	**Ondansetron versus ephedrine versus control** Group 1: ephedrine 10 mg IV Group 2: ondansetron 8 mg IV Group 3: normal saline IV Above interventions were diluted in 10 mL 0.9% saline and administered immediately after spinal anaesthesia. All women received the same aspiration prophylaxis, monitoring, crystalloid preload, anaesthetic technique and dose. If hypotension developed, women received ephedrine 5-10 mg or noradrenalin 4-8 µg IV (choice of agent was up to the attending anaesthetist). Bradycardia was treated with IV atropine 0.6 mg.
Outcomes	*Maternal*: hypotension, nausea and vomiting, incidence of vasopressor and dose of vasopressor used *Neonatal*: Apgar scores
Notes	Hypotension defined as decrease in SBP > 20% of baseline or SBP < 90 mmHg. Bradycardia defined as heart rate < 50 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Nivatpumin 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 women were excluded due to protocol violations
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Oh 2014

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I, elective CS under spinal anaesthesia *Exclusion criteria*: gestational age < 37 weeks, multiple gestation, fetal distress, pre-eclampsia, cardiovascular disease, diabetes *Setting*: South Korea
Interventions	**Comparison of crystalloid preload versus coload** Group 1: rapid infusion of 15 mL/kg Hartmann's preloading Group 2: rapid infusion of 15 mL/kg Hartmann's just after intrathecal injection All women had same monitoring, IV access, spinal anaesthetic technique and dose. Hypotension treated with 5 mg IV ephedrine.
Outcomes	*Maternal*: incidence of hypotension, nausea and vomiting *Neonatal*: Apgar scores at 1 min and 5 min, umbilical cord gases
Notes	Hypotension defined as a decrease of SBP > 20% from baseline
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**
Random sequence generation (selection bias)	Low risk — Computer-generated random allocation (block randomisation, block size 4)

Oh 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, but unlikely to have affected incidence of hypotension
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to have affected incidence of hypotension
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1: 1 woman excluded due to surgical delay by other operation Group 2: 1 woman excluded due to inadequate spinal anaesthesia
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Olsen 1994

Study characteristics	
Methods	RCT
Participants	28 women *Inclusion criteria*: healthy parturients at term scheduled for elective CS due to disproportion or breech presentation
Interventions	**Prophylactic ephedrine + crystalloid preload versus crystalloid preload alone** Group 1: 750 mL isotonic saline plus 20 mL/kg preload Group 2: 750 mL isotonic saline plus 500 mL preload followed by ephedrine bolus (0.15 mg/kg) and ephedrine infusion (0.4 mg/kg/h); ephedrine commenced after spinal anaesthetic All women received standardised positioning, and a standardised spinal anaesthetic technique and dose followed by standardised surgical positioning.
Outcomes	*Maternal*: hypotension; BP; level of block; induction to incision/incision to birth times; ephedrine dose *Neonatal*: umbilical pH; Apgar scores
Notes	Hypotension was defined as > 10 mmHg decrease in MAP (reported only as dose of ephedrine)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

Olsen 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apgar scores were blinded – no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 2/28 women were excluded due to technical difficulties with the ephedrine infusion pump and the Dinamap respectively
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	unclear reporting

Ortiz-Gomez 2014

Study characteristics	
Methods	RCT
Participants	128 women *Inclusion criteria*: ASA I, elective caesarean under spinal anaesthesia *Exclusion criteria*: patient refusal to participate, contraindication to spinal anaesthesia, age < 20 or > 45 years, BMI > 30 kg/m^2, history of allergy or side effects to ondansetron *Setting*: Spain
Interventions	**Comparison of different doses of prophylactic ondansetron with placebo** Group 1: placebo 0.9% saline 10 mL Group 2: 2 mg ondansetron with 0.9% saline to total volume of 10 mL Group 3: 4 mg ondansetron with 0.9% saline to total volume of 10 mL Group 4: 8 mg ondansetron with 0.9% saline to total volume of 10 mL The above 10 mL preparation was injected IV over 60 s, 5 min before the spinal anaesthesia was performed All women received the same IV cannulation, monitoring, spinal anaesthetic technique with dose adjusted according to height, and 8 mL/kg of colloid coloading Hypotension was treated with IV ephedrine 10 mg, or phenylephrine 50 µg if maternal heart rate > 95 beat/min Bradycardia was treated with IV atropine 0.01 mg/kg
Outcomes	*Maternal*: incidence of hypotension, adverse effects, need for atropine or ephedrine or phenylephrine

Ortiz-Gomez 2014 *(Continued)*

Notes	Hypotension defined as SBP < 75% of baseline Bradycardia was defined as heart rate < 45 beat/min

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by local statistical department
Allocation concealment (selection bias)	Low risk	Ondansetron/placebo syringes were prepared by the anaesthetic nurse with no label indicating the group allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Querghi 2010

Study characteristics

Methods	RCT
Participants	62 women *Inclusion criteria*: ASA physical status 1 and 2, term singleton pregnancy undergoing elective CS under spinal anaesthesia *Exclusion criteria*: pre-existing or pregnancy-induced hypertension, women with cardiac, renal or other end-organ disease, women in active labour, placenta praevia, contraindications to neuraxial block, emergency delivery *Setting*: Tunisia
Interventions	**Crystalloid preload versus control** Group 1: rapid preload infusion of 20 mL/kg Ringer's lactate, 15 min before the spinal block Group 2: no preload All women received a standardised spinal anaesthetic technique and dose with standardised surgical positioning.

Querghi 2010 *(Continued)*

	Hypotension (requiring intervention) was treated immediately with rapid fluid infusion and ephedrine 6 mg IV and repeated whenever necessary.
Outcomes	*Maternal*: hypotension; nausea; vomiting; pruritus; dizziness; time to hypotension; heart rate *Neonatal*: Apgar at 1 min and 5 min
Notes	Hypotension was defined as 20% or more fall below the pre-induction level, or systolic pressure < 100 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned"; no further details given
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	An independent investigator who recorded all variables was blinded to the anaesthetic technique used (however the paper did not report how this blinding was achieved)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above; plus Apgar score was assessed by a paediatrician who was unaware of group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/62 – 1 from each group (both due to inadequate sensory level (< T6))
Selective reporting (reporting bias)	Unclear risk	Some maternal outcomes not reported completely; only 1 neonatal outcome reported
Other bias	Unclear risk	Similar baseline characteristics

Ozkan 2004

Study characteristics

Methods	RCT
Participants	150 women *Inclusion criteria*: absence of any systemic illness or fetal pathology, undergoing CS under spinal anaesthesia
Interventions	**Crystalloid preload versus colloid preload versus crystalloid preload + prophylactic ephedrine versus colloid preload + prophylactic ephedrine** Group1: Ringer's lactate IV 1000 mL Group 2: Ringer's lactate IV 1000 mL + ephedrine 15 mg Group 3: Ringer's lactate IV 1000 mL + ephedrine 30 mg

Ozkan 2004 *(Continued)*

	Group 4: gelatine 500 mL solution Group 5: gelatine 500 mL + ephedrine 15 mg Group 6: gelatine 500 mL + ephedrine 30 mg Unclear whether standardised spinal anaesthetic technique and dose Hypotension treated with additional Ringer's lactate infusions while hypotensive periods longer than 3 min were treated with 5 mg ephedrine IV
Outcomes	*Maternal*: hypotension; heart rate; nausea; vomiting; vasopressor requirement *Neonatal*: stated that there were no significant differences in neonatal outcomes, but these outcomes were not described
Notes	Hypotension defined as < 20% of baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	High risk	Variable dose of local anaesthetic used for spinal anaesthesia

Perumal 2004

Study characteristics

Methods	RCT
Participants	40 women *Inclusion criteria*: healthy term women awaiting elective caesarean under spinal anaesthesia
Interventions	**Colloid preload versus crystalloid preload**

Perumal 2004 *(Continued)*

	Group 1: HES preload, 1000 mL over 15 min Group 2: Ringer's lactate preload, 1500 mL over 15 min All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; heart rate; Doppler measures; ephedrine use
Notes	Hypotension was defined as 20% reduction in SBP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described
Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none reported but losses unlikely
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	Unclear risk	Not apparent, but not well reported

Pouliou 2006

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: ASA I-II women aged 18-45 having elective LSCS under spinal anaesthesia No exclusion criteria mentioned in abstract *Setting*: Greece
Interventions	**Pre-spinal anaesthesia IM ephedrine versus delayed IV ephedrine** Group 1: ephedrine IM 37.5 mg 15 min before spinal Group 2: ephedrine 15 mg IV 2 min after spinal anaesthesia

Pouliou 2006 *(Continued)*

	All women received a standardised crystalloid preload followed by a standardised spinal anaesthetic technique and dose
Outcomes	*Maternal*: incidence/severity of hypotension
Notes	Hypotension classified as "mild" (decrease of 20% from baseline) or "severe" (decrease of < 30% from baseline)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Double-randomised" but no details as to how
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Pouta 1996

Study characteristics

Methods	RCT
Participants	22 women *Inclusion criteria*: healthy women undergoing elective CS at term, indications being breech presentation, contracted pelvis or previous CS *Exclusion criteria*: multiple gestation, fetal and maternal complications and contraindications to spinal anaesthesia, active labour
Interventions	**Colloid preload versus crystalloid preload** Group 1: 500 mL 6% HES prior to spinal anaesthesia Group 2: 1000 mL Ringer's lactate prior to spinal anaesthesia

Pouta 1996 *(Continued)*

	All women received standardised aspiration prophylaxis, standardised crystalloid coload, standardised spinal anaesthetic and dose, and standardised surgical positioning.
Outcomes	*Maternal*: hypotension; data expressed as mean (SD) rather than discrete incidence of hypotension; heart rate; CVP; haematocrit; ANP; endothelin-1 (ET-1) assays (central and peripheral); blood loss *Neonatal*: birthweight; umbilical arterial ANP; ET-1 assays; pH (expressed as mean (SEM))
Notes	Hypotension defined as SBP < 90 mmHg or less than 80% of baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described
Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Ramin 1994

Study characteristics

Methods	RCT
Participants	32 women *Inclusion criteria*: healthy pregnant women undergoing elective caesarean at term (38 to 40 weeks' gestation) with spinal anaesthesia *Exclusion criteria*: women in labour, hypertension, diabetes, platelet counts < 100,000 mm3, prolonged thromboplastin time, fetal distress, cardiac or pulmonary disease, any medical illness, or a known history of drug abuse
Interventions	**Prophylactic angiotensin versus prophylactic ephedrine versus control** Group 1: angiotensin II (1000 ng/mL in 0.9% sodium chloride)

Ramin 1994 *(Continued)*

	Group 2: ephedrine (1 mg/mL) Group 3: control (no prophylactic intervention) All women received a standardised crystalloid preload and a standardised spinal anaesthetic technique with slight variation in spinal anaesthetic doses.
Outcomes	*Maternal*: hypotension (defined as decrease of > 30% from baseline); arterial BP (mean and SD); angiotensin levels *Neonatal*: Apgar scores at 1 min and 5 min (mean and SD); pH < 7.2; umbilical artery pH (mean and SD); umbilical venous pH (mean and SD); pCO_2; BE
Notes	Hypotension was defined as a decrease in BP of > 30% from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" but method otherwise not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/32 – 1 woman in the control group with a fetal death; 1 woman (group not specified) gave birth before her scheduled procedure
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Rees 2002

Study characteristics

Methods	RCT
Participants	60 women *Inclusion criteria*: healthy women undergoing elective caesarean *Exclusion criteria*: women with symptoms or signs of labour, prematurity (< 37 weeks' gestation), multiple pregnancy, hypertension, pre-eclampsia, obesity, intrauterine growth retardation, fetal distress or any other factor contraindicating a standard spinal anaesthetic technique

Rees 2002 *(Continued)*

	Setting: UK
Interventions	**Left lateral versus left lateral tilt** Group 1: full left lateral after spinal Group 2: 15 degree left lateral table tilt from supine after spinal Women remained in the study position for 15 min after spinal anaesthesia; women in the left lateral group were then turned into the 15 degree tilt position. All women received a standardised crystalloid preload, a standardised spinal anaesthetic technique and dose, and 6 mg ephedrine IV immediately after insertion of spinal anaesthetic.
Outcomes	*Maternal*: hypotension; block height; ephedrine dose; nausea; vomiting; bradycardia; maximum percentage decrease in arm SAP; maximum percentage decrease in leg SAP; fetal heart traces *Neonatal*: Apgar scores (presented as means and ranges); venous cord gases (presented as means only); arterial cord gases (presented as means only)
Notes	Hypotension was defined as SAP of either less than 100 mmHg or less than 80% of baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by cephalic or breech presentation (separate random-number lists)
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes prepared in advance by a third party
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/60 – 1 from each group: in 1 woman, the anaesthetist was unable to site the spinal in the lateral position and the spinal was subsequently successfully inserted in the sitting position; another withdrawal (from the lateral group) was due to inadequate spread of spinal blockade
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Riley 1995

Study characteristics

Methods	RCT

Riley 1995 *(Continued)*

Participants	40 women *Inclusion criteria*: non-labouring ASA I and II women having non-urgent CS *Exclusion criteria*: obesity (weight over 115 kg), height less than 152 cm, diabetes, pregnancy-induced hypertension, chronic hypertension, heart disease, multiple gestation and age less than 18 or more than 40 years
Interventions	**Colloid + crystalloid preload versus crystalloid preload** Group 1: 500 mL 6% hetastarch administered prior to induction of spinal anaesthesia Group 2: 1000 mL Ringer's lactate administered prior to induction of spinal anaesthesia All women received a standardised crystalloid infusion after the study drug, a standardised spinal anaesthetic technique and dose, and ephedrine 10 mg IV.
Outcomes	*Maternal*: hypotension; heart rate; block height; ephedrine dose; nausea and/or vomiting; additional IV fluid prior to birth. *Neonatal*: Apgar scores < 7; umbilical arterial and venous blood gas (expressed as mean and SD); pH (expressed as mean and SD).
Notes	Hypotension was defined as SBP less than 100 mmHg and less than 80% of baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and providers blinded – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Romdhani 2014

Study characteristics

Romdhani 2014 *(Continued)*

Methods	RCT
Participants	105 patients undergoing elective caesarean section *Inclusion criteria*: term singleton pregnancies, not in labour, elective caesarean, appropriate for spinal anaesthesia *Exclusion criteria*: pre-eclampsia, weight > 110 kg, < 150 cm tall, allergy to HES, known fetal abnormalities, contraindication for spinal anaesthesia, sensitive block height that exceeded T4, haemodynamic instability caused by a surgical complication, failed spinal anaesthesia *Setting*: Tunisia
Interventions	**HES vs crystalloid preload** Group 1: 500 mL of 6% HES 130/0.4 Group 2: 1500 mL of 9% normal saline solution Both groups received bolus 30 min prior to spinal anaesthesia Both groups received rescue ephedrine
Outcomes	*Maternal*: hypotension; heart rate; dose of ephedrine; nausea and vomiting *Neonatal*: umbilical blood pH; Apgar at 1 min and 5 min
Notes	Hypotension defined as a 20% drop in systolic blood pressure from baseline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported
Other bias	Low risk	Not apparent

Rout 1992

Study characteristics	
Methods	RCT
Participants	20 women *Inclusion criteria*: healthy parturients undergoing elective CS, term, singleton pregnancies, cephalic presentation, not more than 90 kg *Exclusion criteria*: medical or obstetric complications or evidence of placental dysfunction
Interventions	**Crystalloid preload: comparison of different rates of infusion** Group 1: plasmalyte-L 20 mL/kg infused over 20 min prior to spinal anaesthesia Group 2: plasmalyte-L 20 mL/kg infused over 10 min prior to spinal anaesthesia All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; heart rate; CVP; spinal to birth time; uterine incision to birth time; block height at 5 min; ephedrine dose *Neonatal*: Apgar scores (minus colour) at 2 and 5 min; umbilical arterial and venous blood gas and pH (data incomplete)
Notes	Hypotension was defined as SBP less than 100 mmHg and less than 80% of baseline.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Rout 1993a

Study characteristics	
Methods	RCT
Participants	100 women *Inclusion criteria*: ASA I parturients undergoing elective repeat CS with uncomplicated singleton pregnancy and weight less than 90 kg at term *Exclusion criteria*: not specified
Interventions	**Lower leg compression versus leg elevation versus control** Group 1: legs horizontal but wrapped from toe to mid-thigh with rubber Esmarch bandages with preservation of pedal pulses Group 2: legs elevated on 4 pillows at 30 degrees to horizontal Group 3: control – neither wrapped nor raised All women received a standardised crystalloid preload and a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; diastolic BP; heart rate; onset of hypotension; ephedrine dose; spinal to birth time; uterine incision to birth time *Neonatal*: umbilical arterial and venous blood gas; pH < 7.25; Apgar scores minus colour at 2 min and 5 min
Notes	Hypotension defined as defined as SBP less than 100 mmHg and less than 80% baseline

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 3/100 – 2 women had an inadequate block and 1 woman had a high block (groups not specified)
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Sahoo 2012

Study characteristics	
Methods	RCT
Participants	56 women *Inclusion criteria*: ASA I, age 20-40, elective LSCS *Exclusion criteria*: contraindications to SAB, patient refusal, unstable haemodynamics, coagulopathy, history of hypersensitivity to ondansetron or local anaesthetic agents, hypertensive disorders of pregnancy, cardiovascular insufficiency, receiving selective serotonin reuptake inhibitors or migraine medications *Setting*: India
Interventions	**Pretreatment with ondansetron versus placebo** Group 1: IV ondansetron 4 mg diluted in 10 mL of normal saline given over 1 min, 5 min before spinal anaesthesia Group 2: 10 mL of normal saline IV given over 1 min, 5 min before spinal anaesthesia
Outcomes	*Maternal*: hypotension, decrease in BP, decrease in heart rate, nausea and vomiting *Neonatal*: none
Notes	Hypotension: SBP < 90 mmHg or DBP < 60 mmHg Bradycardia: heart rate < 50 bpm

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation chart
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded anaesthetist assessing outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not apparent
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Selvan 2004

Study characteristics	
Methods	RCT
Participants	60 women *Inclusion criteria*: healthy women awaiting elective caesarean under spinal anaesthesia
Interventions	**Colloid vs crystalloid preload** Group 1: HES 6% w/v 500 mL Group 2: HES 6% w/v 1000 mL Group 3: Hartmann's solution 1500 mL All women were placed in the left lateral position and fluid was then preloaded over 15 min. All women received a standardised anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; heart rate; BP; ephedrine use *Neonatal*: cord gases
Notes	Hypotension defined as 20% reduction in SBP

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" – no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	Unclear risk	Not apparent, but not well reported

Siddik 2000

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: non-labouring ASA class I and II women scheduled for elective caesarean *Exclusion criteria*: obesity (> 115 kg), height > 152 cm, diabetes, pregnancy-induced hypertension, chronic hypertension, heart disease, multiple gestation, breech presentation, age < 18 or > 40 and SBP < 100 mmHg *Setting*: Lebanon
Interventions	**Colloid v crystalloid preload** Group 1: HES 10%, 500 mL Group 2: Ringer's lactate 1000 mL Preload was administered 10 min before spinal anaesthesia; women were placed in left supine wedged position. All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; block height; ephedrine dose; heart rate; BP; nausea; vomiting *Neonatal*: Apgar scores; venous and arterial blood gases
Notes	Hypotension was defined as SBP < 80% baseline or < 100 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	"Drawing shuffled sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: nurses placed a brown paper bag over the IV solution to conceal its identity from the anaesthetist
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Siddik-Sayyid 2009

Study characteristics	
Methods	RCT
Participants	183 women *Inclusion criteria*: non-labouring women, > 37 weeks' gestation, ASA I or II scheduled for elective caesarean *Exclusion criteria*: pregnancy-induced hypertension, chronic hypertension, multiple gestation, known fetal compromise, diabetes mellitus, polyhydramnios, weight > 100 kg, major systematic disease, anaemia (haemoglobin concentration < 10 g/dL), or clotting diathesis *Setting*: Lebanon
Interventions	**Colloid preload versus colloid coload** Group 1: colloid preload: preload of 500 mL HES (6% HES 130/0.4), administered by gravity at a wide open rate over 15-20 min before spinal anaesthesia Group 2: colloid coload: coload of 500 mL of HES (6% HES 130/0.4) administered using a pressure infusion system at the maximum possible rate, commenced at the time of identification of CSF All women received a standardised spinal anaesthetic technique and dose, a standardised crystalloid infusion after spinal anaesthetic, and a standardised oxytocin regimen after delivery. Hypotension requiring intervention was managed with 6 mg IV bolus of ephedrine if heart rate < 90 bpm or 0.1 mg phenylephrine IV bolus if heart rate > 90 bpm.
Outcomes	*Maternal*: hypotension; minimum SBP; maximum heart rate; time to hypotension; ephedrine dose; phenylephrine dose; nausea and/or vomiting; metoclopramide administration; total Ringer's lactate; duration of infusion; duration of surgery; sensory block level; duration of anaesthesia *Neonatal*: birthweight; Apgar score; umbilical vein pH, pO_2, pCO_2, BE; umbilical artery pH, pO_2, pCO_2, BE
Notes	Hypotension was defined as the administration of at least 1 dose of vasopressor. Severe hypotension was defined as SBP < 80 mmHg.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	"Randomised" – no further details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Woman, anaesthetist performing the spinal block, collecting the data and treating adverse effects, and the paediatrician assessing neonatal outcomes were all unaware of group allocation. The infusion bag was prepared and hidden behind a drape and administered by a nurse who was not involved in anaesthetic management (and who decided when the woman should sit up for spinal anaesthesia). To maintain blinding, this occurred after completion of colloid administration in the preload group (lasting ~15-20 min) or 15-20 min from starting the Ringer's lactate in the coload group.

Siddik-Sayyid 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/183 women were excluded after randomisation due to protocol violations (2 from the preload group and 3 from the coload group)
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes reported but some (all neonatal outcomes) not reported in a form that could be used in this review (e.g. medians, and average for Apgar scores)
Other bias	Low risk	No apparent risk of other sources of bias

Singh 2009

Study characteristics	
Methods	Randomised, quasi-experimental observational cohort study
Participants	60 patients *Inclusion criteria*: ASA I, elective LSCS *Exclusion criteria*: pregnancy-induced high BP, high-risk pregnancy, fetal distress, moderate to severe anaemia, patient refusal, infection at site of injection, bleeding diathesis, severe hypovolaemia, elevated intracranial pressure, spine deformity and patients with major systemic illness *Setting*: India
Interventions	**Crystalloid versus colloid preload** Group 1: 20 mL/kg Ringer's lactate preloading over 20 min just prior to SAB Group 2: 10 mL/kg HES 130/0.4 (up to a max 500 mL) preloading over 20 min just prior to SAB All women received standardised premedication, positioning, monitoring, IV cannulation/urinary catheter, SAB and technique, oxygen delivery, intra-operative fluids, oxytocin. Hypotension treated with IV bolus of crystalloid up to 200 mL, further hypotension treated with mephentermine 3 mg IV bolus every 1 min until SBP> 90 mmHg achieved. Bradycardia treated with atropine 300 µg aliquots.
Outcomes	*Maternal*: haemodynamics/observations, urine output, duration of surgery, uterine incision-delivery time, SAB complications, "undesirable effects" from HES including "anaphylactoid" reactions, pruritis, bleeding *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as a fall in SAP > 30% of baseline or SAP < 90 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Singh 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Singh 2014

Study characteristics		
Methods	RCT	
Participants	60 women *Inclusion criteria*: singleton uncomplicated pregnancy, ASA I-II, elective caesarean under spinal anaesthesia *Setting*: unknown	
Interventions	**Leg wrapping versus no leg wrapping** Group 1: no leg wrapping Group 2: leg wrapping with crepe bandage (15 cm width, 4 m stretched length) from ankle to mid-thigh level over both legs. During wrapping, lower extremities were lifted at a 45 degree angle Crepe bandages were wrapped tightly enough that the woman felt the tightness, yet it was comfortable and not painful. All patients had their legs wrapped by the same person in 3 min to eliminate bias introduced by method or altered force of wrapping. Legs were hidden to ensure blinding. All women received the same aspiration prophylaxis, monitoring, 20 mL/kg IV Ringer's lactate fluid preloading over 15-20 min prior to spinal anaesthesia, spinal anaesthetic technique and dose. Hypotension was treated with 50 µg IV phenylephrine bolus and an increase in rate of IV fluid infusion.	
Outcomes	*Maternal*: incidence of hypotension	
Notes	Hypotension was defined as a fall in SBP to < 90 mHg.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of random sequence not reported

Singh 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Singh 2016

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: primiparous, full-term parturients, aged 18-40 years, ASA I, scheduled for elective CS *Exclusion criteria*: refusal of regional anaesthesia, contraindications to spinal anaesthesia, fetal abnormalities, known allergy to any of the drugs used in the study, pregnancy-induced hypertension or parturients with SBP > 140 mmHg, history of diabetes mellitus, cardiovascular or cerebrovascular and any chronic diseases *Setting*: India
Interventions	Ephedrine versus control Group 1: 1 mL 5 mg ephedrine IV immediately after SAB Group 2: 1 mL 0.9% NaCl IV immediately after SAB All women received standardised monitoring, standardised crystalloid IV fluid, standardised spinal anaesthetic technique and dose. Treatment of hypotension involved rapid infusion of Ringer's lactate and 5 mg IV ephedrine. Bradycardia treated with 0.6 mg IV atropine sulfate.
Outcomes	*Maternal*: incidence of hypotension, reactive hypertension, number of patients requiring rescue ephedrine, total dose of rescue ephedrine (mg), bradycardia, nausea/vomiting, average time to delivery *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as a decrease in SBP of > 20%

Singh 2016 *(Continued)*

	Bradycardia was defined as heart rate < 60 bpm Reactive hypertension: SBP > 140 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Study solution prepared by person not involved in the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study staff recorded outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed protocol
Selective reporting (reporting bias)	Low risk	Not evident
Other bias	Unclear risk	None evident

Sood 1996

Study characteristics

Methods	RCT
Participants	50 women *Inclusion criteria*: ASA I or II parturients undergoing elective CS at term *Exclusion criteria*: history of cardiovascular disease or contraindication to spinal, body weight > 90 kg and/or thigh circumference > 62 cm
Interventions	**Lower limb compression versus control** Group 1: TED stockings applied 1 hour preoperatively from toes to mid-thigh according to manufacturer's guidelines Group 2: no compression All women received standardised crystalloid preload, standardised spinal anaesthetic technique with dose adjusted according to subject's height.
Outcomes	*Maternal*: hypotension; diastolic BP and MAP; heart rate; SpO_2

Sood 1996 *(Continued)*

	Neonatal: Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as a SBP < 90 mmHg or a decrease in SBP more than 20% from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Stein 1997

Study characteristics

Methods	RCT
Participants	75 women *Inclusion criteria*: healthy women (55 of whom had experienced at least 1 previous birth) undergoing elective CS during spinal anaesthesia *Exclusion criteria*: history of nausea and vomiting associated with previous surgery or anaesthesia; nausea or vomiting within 24 h prior to caesarean, history of diabetes mellitus, or morbid obesity
Interventions	**Acupressure versus metoclopramide versus placebo** Group 1: acupressure bands + 2 mL IV saline Group 2: placebo wrist bands + 10 mg metoclopramide Group 3: placebo wrist bands + 2 mL IV saline Acupressure defined as pressure on the Neiguan (P6) acupuncture points of the wrist.

Stein 1997 *(Continued)*

	All women received a standardised preload of 1500-2000 mL Ringer's lactate in addition to a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; nausea (score > 2); vomiting; anxiety *Neonatal*: Apgar score < 7 at 5 min
Notes	Hypotension was defined as a decrease in SBP more than 20% from baseline or < 100 mmHg.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	"Envelope system" – no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: wrist bands were placed bilaterally by an anaesthetist not directly involved in the women's care. The acupressure bands were lightly covered with gauze and tapes so they could not be distinguished from the placebo bands.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Sujata 2012

Study characteristics

Methods	RCT
Participants	100 women *Inclusion criteria*: ASA I-II, elective CS under SAB *Exclusion criteria*: contraindication to SAB, peripartum bleeding > 1 L, multiple gestation, polyhydramnios, gestation < 37 weeks, any patient considered at high risk of DVT *Setting*: India
Interventions	**Mechanical lower limb compression versus contro**l Group 1: mechanical pump with thigh-level cuff applied to lower limbs in all subjects and switched on Group 2: mechanical pump with thigh-level cuff applied to lower limbs in all subjects but not switched on

Sujata 2012 *(Continued)*

	All women received standardised aspiration prophylaxis, standardised monitoring, standardised spinal anaesthetic technique and dose, standardised crystalloid coloading and maintenance, standardised positioning and standardised oxytocic administration. Hypotension was treated with IV ephedrine 6 mg, repeated every 3 min as needed.
Outcomes	*Maternal*: BP, heart rate, SpO_2 recorded every 3 min for 1 h. Total volume of IV fluid given, total ephedrine dose *Neonatal*: Apgar scores
Notes	Hypotension defined as a decrease in SBP > 20% baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaethetist caring for women during caesarean blinded. Possible that blinding may have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1 – 3 women excluded due to pregnancy-induced hypertension Group 2 – 5 women excluded due to pregnancy-induced hypertension
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Sutherland 2001

Study characteristics

Methods	RCT
Participants	100 women *Inclusion criteria*: ASA I or II women undergoing elective CS *Exclusion criteria*: contraindication to spinal anaesthesia or thigh circumference > 64 cm
Interventions	**Lower limb compression versus control** Group 1: TED stockings applied before arrival in theatre and lower limb sequential compression device inflated immediately after spinal injection

Sutherland 2001 *(Continued)*

	Group 2: no mechanical prophylaxis All women received a standardised spinal anaesthetic technique with dose adjusted according to subject's height. Hypotension was managed with a standardised ephedrine regimen.
Outcomes	*Maternal*: hypotension; systolic, diastolic and mean BP; level of sensory block; ephedrine requirement; time to first episode of hypotension *Neonatal*: Apgar scores at 1 min and 5 min (expressed as n with score < 9); umbilical artery pH (expressed as mean (SD))
Notes	Hypotension defined as SBP < 100 mmHg or fall of > 20% from baseline Lack of blinding acknowledged Protocol violations acknowledged

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: no dropouts but 46/100 protocol violations (ephedrine administered in error on 17 occasions (9 intervention, 8 control), ephedrine omitted in error on 29 occasions (10 intervention, 19 control)
Selective reporting (reporting bias)	Unclear risk	Not apparent
Other bias	Unclear risk	Not apparent

Tawfik 2014

Study characteristics

Methods	RCT
Participants	210 women *Inclusion criteria*: elective caesarean, ASA I-II, singleton pregnancy *Exclusion criteria*: age < 19 or > 40 years, height < 150 or > 185 cm, weight < 60 or > 100 kg, BMI > 40 kg/m^2, chronic or pregnancy-induced hypertension, baseline SBP < 100 or > 140 mmHg, diabetes mellitus, cardiovascular, cerebrovascular or renal disease, haemoglobin < 100g/L, patients in labour, any con-

Tawfik 2014 *(Continued)*

	traindication to spinal anaesthesia, preterm (< 37 weeks gestation), multiple pregnancy, polyhydramnios or known fetal abnormalities *Setting*: Egypt
Interventions	**Colloid preload versus crystalloid coload** Group 1: colloid preload – 6% HES 130/0.4 in 0.9% sodium chloride 500 mL within 15 min before induction of spinal anaesthesia Group 2: crystalloid coload – 1000 mL of Ringer's acetate using a pressuriser as rapidly as possible starting at time of intrathecal injection All women received IV cannulation, routine monitoring, a standardised crystalloid infusion after administration of study solution, a standardised spinal anaesthetic technique and dose. Hypotension was treated with IV ephedrine 5 mg bolus. Severe hypotension was treated with 10 mg IV ephedrine. Bradycardia was treated with IV atropine 0.5 mg.
Outcomes	*Maternal*: hypotension, bradycardia, nausea and vomiting *Neonatal*: Apgar scores at 1 min and 5 min and umbilical cord gases
Notes	Hypotension defined as SBP < 80% baseline or < 90 mmHg Severe hypotension: SBP < 80 mmHg Maternal bradycardia defined as heart rate < 50 bpm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Anaesthetists, women, and neonatologists blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded. Outcomes recorded by anaesthetists and neonatologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients excluded due to failed spinal or protocol violation
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Tercanli 2005

Study characteristics	
Methods	RCT
Participants	22 women *Inclusion criteria*: healthy women with uncomplicated singleton pregnancies at 36-40 weeks' gestation, not in labour, undergoing elective caesarean under spinal anaesthesia
Interventions	**Crystalloid: high versus low volume preload** Group 1: 15 mL/kg Ringer's lactate Group 2: 150 mL Ringer's lactate All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; ephedrine dose *Neonatal*: pulsatility indices; pH (mean and SD); Apgar score at 1 min, 5 min, and 10 min (mean and SD); NACS
Notes	Hypotension was defined as decrease in SBP of more than 20% from baseline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Low risk	Adequate: drawing of sealed consecutive opaque sealed envelopes a day before surgery
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: not stated but losses unlikely
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Terkawi 2015

Study characteristics	
Methods	RCT
Participants	91 women *Inclusion criteria*: elective CS *Exclusion criteria*: diabetes, chronic hypertension, gestational hypertension, pre-eclampsia, cardiac disease, patients with long QT syndrome and known contraindications to spinal anaesthesia *Setting*: USA
Interventions	**Ondansetron versus control** Group 1: received 8 mg ondansetron diluted in 10 mL in 0.9% NaCl Group 2: received 10 mL of 0.9% NaCl Study drug was administered over a period of 5 min whilst in sitting position, prior to SAB. All women received standardised aspiration prophylaxis, standardised colloid preload, standardised crystalloid maintenance fluid, standardised monitoring, standardised spinal anaesthetic technique and dose, standardised positioning. Hypotension was managed with boluses of 100 µg of phenylephrine administered incrementally until SBP > 90 mmHg. Bradycardia was managed with 0.4 mg atropine or 0.2 mg glycopyrrolate.
Outcomes	*Maternal*: incidence of hypotension, incidence of bradycardia, amount of vasopressor and anticholinergic agents given, pruritus, nausea and vomiting, extent of sensory block, estimated blood loss, total fluid administered *Neonatal*: Apgar scores
Notes	Hypotension was defined as SBP < 90 mmHg or 20% drop in SBP from baseline. Bradycardia was defined as heart rate < 60 bpm.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drugs prepared by pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All research personnel were blinded.
Incomplete outcome data (attrition bias)	Low risk	Group 1: 4 excluded (3 due to protocol violation, 1 due to failed SAB)

Terkawi 2015 *(Continued)*

All outcomes		Group 2: 1 excluded (due to protocol violation)
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	None evident

Torres unpub

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: scheduled for elective CS *Exclusion criteria*: contraindications to spinal anaesthesia, fetal or maternal pathology and known allergy to the drugs being administered
Interventions	**Ephedrine versus control** Group 1: ephedrine IV 8 mg Group 2: placebo (saline) Study drugs were given at the same time as spinal anaesthetic. All women received a preload of 10 mL/kg Ringer's lactate, a prophylactic dose of 8 mg of ephedrine prior to intrathecal injection, a standardised spinal anaesthetic technique and dose, and standardised positioning for surgery.
Outcomes	*Maternal*: hypotension; dose of local anaesthetic; level of block; surgical time; BP; heart rate; nausea; vomiting; total ephedrine dose; postdural puncture headache *Neonatal*: Apgar score at 1 min and 5 min
Notes	Hypotension was defined as decrease in SBP of 20% or more.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind but details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind but details not reported

Torres unpub *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Not apparent
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Trabelsi 2015

Study characteristics	
Methods	RCT
Participants	80 women *Inclusion criteria*: ASA I, elective caesarean, primipara, term pregnancy *Exclusion criteria*: emesis gravidarum, contraindication to spinal anaesthesia (patient refusal, unstable haemodynamic, and coagulation abnormalities), chronic hypertension or pre-eclampsia, morbid obesity, and/or any study drugs allergy *Setting*: Tunisia
Interventions	**Prophylactic ondansetron versus control** Group 1: 4 mg IV ondansetron in 10 mL saline, 5 min before spinal puncture Group 2: 10 mL saline, 5 min before spinal puncture All women received the same monitoring, standardised crystalloid preload before spinal anaesthesia, spinal anaesthetic technique and dose. Hypotension was treated with 100 mL crystalloid and 6 mg ephedrine IV. Bradycardia was treated with fluids and ephedrine up to 25 mg, If did not resolve within 30 s of treatment, IV atropine 0.5 mg IV given every 30 s until resolution
Outcomes	*Maternal*: incidence of hypotension, nausea and vomiting *Neonatal*: Apgar scores, umbilical cord gases
Notes	Hypotension was defined as a decrease from baseline > 20% in systolic pressure. Bradycardia was defined as 30% drop in heart rate or < 45 bpm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generated by website: www.random.org
Allocation concealment (selection bias)	Low risk	Anaesthetic nurse prepared solution according to group allocation on above website

Trabelsi 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data loss
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Tsen 2000

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: ASA I and II women not in labour undergoing elective caesarean for term uncomplicated singleton pregnancies, taking only prenatal vitamins and weighing less than 100 kg *Exclusion criteria*: women with cardiac, pulmonary or renal diseases, or systemic diseases that could influence haemodynamic responses, including pre-eclampsia, hypertension and diabetes; if women were taking or had a history of taking any medications that could influence haemodynamic responses, including magnesium sulphate, terbutaline or beta-blockers
Interventions	**Ephedrine versus control** Group 1: ephedrine 2 mL IV (10 mg) given simultaneously with spinal anaesthetic Group 2: saline 2 mL IV given simultaneously with spinal anaesthetic All women received a standardised crystalloid preload and a standardised spinal anaesthetic technique and dose, followed by standardised surgical positioning. Hypotension was treated with 10 mg IV doses of ephedrine.
Outcomes	*Maternal*: hypotension; MAP; heart rate; tachycardia (ephedrine group only); hypertension (ephedrine group only); systemic vascular resistance index; stroke index; cardiac index *Neonatal*: Apgar score < 8 at 5 min
Notes	Hypotension was defined as 20% decrease in MAP
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Tsen 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: double-blind – Apgar scored by a paediatrician blinded to the study – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Turkoz 2002

Study characteristics		
Methods	RCT	
Participants	30 women *Inclusion criteria*: healthy women at term undergoing elective CS under spinal anaesthesia *Exclusion criteria*: active labour, rupture of amniotic membranes, chronic or pregnancy-induced hypertension, insulin-dependent diabetes mellitus, multiple gestation, oligohydramnios and preoperative diagnosis of small for gestational age fetus	
Interventions	**Ephedrine infusion versus ephedrine bolus** Group 1: ephedrine infusion IV 5 mg/min commenced immediately after intrathecal injection Group 2: control – ephedrine bolus 10 mg administered if hypotension developed All women received standardised positioning, standardised crystalloid preload, a standardised spinal anaesthetic technique with the dose adjusted according to subject's height.	
Outcomes	*Maternal*: hypotension); nausea and vomiting; BP; heart rate; arterial blood *Neonatal*: umbilical arterial blood; umbilical venous blood; heart rate; BP	
Notes	Hypotension defined as 20% decrease from baseline (measured prior to fluid preload)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Turkoz 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Ueyama 1992

Study characteristics	
Methods	RCT
Participants	100 women (60 non-labouring women scheduled for elective caesarean and 40 labouring women for emergency caesarean) *Exclusion criteria*: women with placenta praevia, abruptio placenta; toxaemia
Interventions	**Ephedrine (various doses) versus control** Group1: ephedrine 5 mg Group 2: ephedrine 10 mg Group 3: no ephedrine Ephedrine was administered with the spinal. All women received a standardised preload of 1000 mL Ringer's lactate, a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; SAP
Notes	Hypotension was defined as SAP lower than 80 mmHg
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Ueyama 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Methods not described
Allocation concealment (selection bias)	Unclear risk	Methods not describe
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Ueyama 1999

Study characteristics	
Methods	RCT
Participants	36 women *Inclusion criteria*: healthy full-term parturients scheduled for elective caesarean during spinal anaesthesia *Exclusion criteria*: abruptio placenta, placenta praevia, multiple gestation, pre-eclampsia, or women who were receiving ritodrine or other beta-tocolytics
Interventions	**Colloid preload versus crystalloid preload** Group 1: 500 mL HES 6% Group 2: 1000 mL HES 6% Group 3: 1500 mL Ringer's lactate All solutions were infused over 30 min before injection of spinal anaesthesia. All women received a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; blood volume; cardiac output
Notes	Hypotension defined as defined as decrease in SBP to less than 100 mmHg and less than 80% of baseline value
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Ueyama 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation by random envelope method
Allocation concealment (selection bias)	High risk	No allocation concealment. Infusion bottle shape different between study groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	Unclear risk	Not apparent, but not well reported

Ueyama 2002

Study characteristics	
Methods	RCT
Participants	20 women *Inclusion criteria*: healthy women scheduled for elective caesarean during spinal anaesthesia
Interventions	**Prophylactic ephedrine versus prophylactic phenylephrine** Group 1: 40 mg ephedrine Group 2: 250 µg phenylephrine All women were given Ringer's lactate at a rate of 100 mL/hour immediately after ephedrine or phenylephrine. All women received a standardised spinal anaesthetic technique and dose followed by standardised surgical positioning.
Outcomes	*Maternal*: hypotension; cardiac output
Notes	Hypotension defined as a drop in SBP of > 20% and < 100 torr

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods not described

Ueyama 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding: "in a double-blind fashion" – no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Unlugenc 2015

Study characteristics	
Methods	RCT
Participants	90 women *Inclusion criteria*: ASA I/II, singleton uncomplicated pregnancy at full term gestation undergoing elective CS under spinal anaesthesia *Exclusion criteria*: significant co-existing disease such as pre-eclampsia and hepato-renal disease, pregnancy pre-induced hypertension, being in active labour or requiring emergency CS, any contraindication to regional anaesthesia such as local infection or bleeding disorders *Setting*: Turkey
Interventions	**Rapid crystalloid coload versus rapid colloid coload versus slow crystalloid coload** Group 1: 1000 mL Ringer's lactate at maximum rate Group 2: 1000 mL 6% HES at maximum rate Group 3: 1000 mL Ringer's lactate at minimum rate All fluids were commenced immediately after induction of spinal anaesthesia. All women received standardised fasting regimen, standardised monitoring, standardised cannulation, standardised crystalloid coload (10 mL/kg/hour) via a separate cannula, standardised spinal anaesthetic technique and dose, standardised positioning, standardised oxygen therapy. Hypotension was treated with IV ephedrine 10 mg. If heart rate was < 50 bpm, 0.5 mg atropine was administered IV.
Outcomes	*Maternal*: incidence of hypotension, total fluid volumes, ephedrine requirements, bradycardia, hypoxaemia, excessive sedation, pruritis, dizziness, nausea and vomiting

Unlugenc 2015 *(Continued)*

	Neonatal: umbilical artery pH/PaO_2/$PaCO_2$/HCO_3-, Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as SBP < 80% of baseline (prenatal) or < 90 mmHg. Bradycardia was defined as heart rate < 50 bpm. Hypoxaemia was defined as SpO_2 < 95%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Fluid in non-transparent bag
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to patient group. "Demographic data (age, height, weight, parity and gravity) and duration of surgery were noted by an observer blinded to the treatment group. Systolic and diastolic blood pressures (SBP, DBP), heart rate and peripheral oxygen saturation (SpO_2) were recorded by an anaesthetist blinded to the patient group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	None identified

Upadya 2016

Study characteristics

Methods	RCT
Participants	50 women *Inclusion criteria*: non-labouring ASA I/II undergoing elective CS *Exclusion criteria*: patients aged < 18 years or > 40 years, weighing > 100 kg, height < 152 cm, associated diabetes mellitus, pregnancy-induced hypertension, chronic hypertension, heart disease, multiple gestation, breech presentation, SBP < 100 mmHg, patients who had received IV fluids prior to surgery *Setting*: India
Interventions	**Crystalloid preload versus colloid preload** Group 1 crystalloid preload: 1000 mL Ringer's lactate

Upadya 2016 *(Continued)*

	Group 2 colloid preload: 500 mL 6% hetastarch Fluids were administered 30 min prior to surgery. All women received standardised aspiration prophylaxis, standardised cannulation, standardised monitoring, standardised spinal anaesthetic technique and dose, standardised positioning, standardised oxygen therapy. Hypotension was managed with IV boluses of 5 mg of ephedrine, repeated every 2 min as required.
Outcomes	*Maternal*: incidence of hypotension, nausea/vomiting, interval between spinal injection and delivery *Neonatal*: Apgar scores
Notes	Hypotension was defined as SBP < 100 mmHg and < 80% baseline BP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of losses to follow-up
Selective reporting (reporting bias)	Low risk	Not evident
Other bias	Low risk	None apparent

Ure 1999

Study characteristics	
Methods	RCT
Participants	50 women *Inclusion criteria*: singleton pregnancy, ASA I or II, presenting for elective caesarean at term *Exclusion criteria*: height < 152 cm, multiple pregnancy, pregnancy-induced hypertension, placenta praevia, diabetes mellitus, maternal refusal, clotting disorder, fixed cardiac output disease, pre-existing neurological disease, local and systemic sepsis, and allergy to local anaesthetics

Ure 1999 *(Continued)*

Interventions	**Glycopyrrolate versus control** Group 1: glycopyrrolate 200 µg Group 2: saline (placebo) All women received the study drug with a standardised crystalloid preload (15 mL/kg). All women received a standardised spinal anaesthetic technique and dose followed by standardised surgical positioning.
Outcomes	*Maternal*: hypotension; nausea; nausea severity score; nausea episodes per woman; vomiting; ephedrine dose; heart rate; duration of operation; time to block; blood loss *Neonatal*: birthweight; Apgar score
Notes	Hypotension defined as decrease in SAP 20% or more from baseline or absolute decrease to less than 100 mmHg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: "double-blind"; "both glycopyrrolate and saline were given as 1 mL of clear fluid and therefore the participant and researcher were blinded to the randomization"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 1 woman in the glycopyrrolate group refused subarachnoid anaesthesia after the study drug had been given
Selective reporting (reporting bias)	Low risk	Not apparent
Other bias	Low risk	Not apparent

Wang 2014a

Study characteristics

Methods	RCT
Participants	150 women

Wang 2014a *(Continued)*

	Inclusion criteria: primiparous, single fetus, elective caesarean, age 18-35 years, 37-40 weeks gestation, ASA I-II, normal prenatal exam, normal liver and renal function, normal fetal screening, no medical history of heart or lung disease *Setting*: China
Interventions	**Comparison of different doses of prophylactic ondansetron versus control** 5 min prior to spinal anaesthesia, women were given (all diluted to 5 mL with physiological saline): Group 1: 5 mL physiological saline Group 2: 2 mg ondansetron Group 3: 4 mg ondansetron Group 4: 6 mg ondansetron Group 5: 8 mg ondansetron All women received no premedication, routine monitoring, cannulation, a standardised crystalloid coload, and a standardised spinal anaesthetic technique and dose Treatment of hypotension consisted of administration of IV bolus of 100 µg phenylephrine
Outcomes	*Maternal*: hypotension, treatment for hypotension/bradycardia, nausea and vomiting *Neonatal*: cord gases, Apgar score at 1 min and 5 min
Notes	Hypotension defined as systolic pressure < 80% of baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Ondansetron and saline solutions were prepared by an anaesthetist who was blinded to this study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Wang 2014b

Study characteristics	
Methods	RCT
Participants	66 women *Inclusion criteria*: primiparous, singleton pregnancy, elective caesarean, age 18-35, 37-42 weeks' gestation, ASA I-II, normal prenatal examinations, normal renal and liver function, no medical history of heart or lung disease, no fetal abnormalities *Exclusion criteria*: hypertension, cardiovascular or cerebrovascular disease, placenta praevia, abnormal fetal development, contraindications to spinal anaesthesia, endocrine disorders, recent administration of 5-HT reuptake inhibitors or drugs for treatment of migraines *Setting*: China
Interventions	**Prophylactic ondansetron versus control** 5 min prior to spinal anaesthesia: Group 1: 4 mg IV ondansetron (diluted to 5 mL with physiological saline) Group 2: 5 mL IV physiological saline All women received the same standardised monitoring, cannulation, spinal anaesthetic technique and dose, standardised crystalloid coload and postdelivery oxytocin If hypotension occurred, 100 µg IV phenylephrine was administered, and repeated every 2 min as required until SBP > 80% baseline If bradycardia occurred, 0.5 mg IV atropine was administered If SpO_2 < 95%, mask assisted O_2 inhalation was given at 3 L/min If nausea or vomiting occurred, 12.5 mg IV promethazine was administered If intractable pain, assisted anaesthetics were added or GA performed and patient was excluded
Outcomes	*Maternal*: incidence of hypotension, bradycardia, nausea and vomiting, peak block height, total consumption of phenylephrine *Neonatal*: umbilical cord gases, Apgar scores at 1 min and 5 min
Notes	Hypotension was defined as maternal SBP < 80% baseline Bradycardia was defined as heart rate < 50 bpm Hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Opaque, sealed, sequentially numbered envelopes

Wang 2014b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs prepared by anaesthetist not directly involved in the patient scare or assessment. Solutions were in syringes of similar appearance, labelled study drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above, anaesthetist was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 1: 1 woman excluded from BP analysis due to intractable shivering preventing BP measurement, 2 women excluded from blood gas analysis due to insufficient samples Group 2: 1 woman completely excluded due to failed spinal anaesthesia, 2 women excluded from blood gas analysis because of insufficient samples
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent. Grant from Wuxi Municipal Health Bureau

Webb 1998

Study characteristics	
Methods	RCT
Participants	40 women *Inclusion criteria*: parturients receiving spinal anaesthesia for elective CS *Exclusion criteria*: impalpable lumbar spines, baseline BP > 150/90, coagulopathy, sepsis, hypovolaemia
Interventions	**Ephedrine versus control** Group 1: ephedrine 37.5 mg IM in 1.5 mL saline administered prior to spinal anaesthesia Group 2: placebo 1.5 mL saline IM in deltoid muscle administered prior to spinal anaesthesia All women received a standardised crystalloid preload, and a standardised spinal anaesthetic technique and dose.
Outcomes	*Maternal*: hypotension; hypertension; heart rate *Neonatal*: Apgar scores at 5 min; umbilical vein pH (expressed as mean and SD)
Notes	Hypotension was defined as a decrease in SBP < 100 mmHg OR > 70% baseline Hypertension was defined as SBP > 30% above baseline, but no intervention reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described

Webb 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not state
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Wilson 1998

Study characteristics		
Methods	RCT	
Participants	70 women *Inclusion criteria*: pregnant women (ASA I or II) undergoing elective CS	
Interventions	**Glucose versus crystalloid preload** Group 1: glucose 5% IV Group 2: normal saline IV Administered at 125 mL/h prior to spinal anaesthesia Unclear whether all women received the same anaesthetic technique and dose	
Outcomes	*Maternal*: hypotension; total study solution received; total IV preload; glucose levels *Neonatal*: Apgar scores; umbilical cord gases	
Notes	Hypotension was defined as SBP > 20% decrease	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described

Wilson 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: study solutions "were enclosed in an opaque bag to maintain blinding"; "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: not stated
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	High risk	Variable dose of local anaesthetic used for spinal anaesthesia

Wilson 1999

Study characteristics	
Methods	RCT
Participants	120 women *Inclusion criteria*: ASA I-II singleton pregnancy, able to speak English, undergoing elective CS *Exclusion criteria*: morbid obesity, glucose intolerance, taking vasoactive medication or that known to alter glucose metabolism
Interventions	**Comparison of dextrose 5% versus normal saline as a crystalloid preload** Group 1: dextrose 5% in normal saline at 125 mL/h IV for 2 hours before surgery Group 2: normal saline at same rate All women received a standardised crystalloid preload after the study drug (normal saline 15 mL/kg) followed by a standardised anaesthetic technique and dose, and standardised surgical positioning
Outcomes	*Maternal*: hypotension; serial blood glucose measurements; preoperative fasting time; total fluid volume administered; block height; spinal-birth time *Neonatal*: Apgar scores at 1 min, 5 min, and 10 min; umbilical venous and arterial blood gas; pH; lactate and glucose (generally expressed as mean (SD))
Notes	Hypotension defined as a decrease in SBP > 20% or BP less than 100 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated table
Allocation concealment (selection bias)	Unclear risk	Method not described

Wilson 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: intervention solutions in opaque bags – participants, anaesthetist and investigator unaware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 1 participant was excluded from saline only group due to incomplete maternal data; and neonatal data were incomplete due to technical problems with umbilical cord blood analysis
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias	Unclear risk	Unclear reporting

Yokoyama 1997

Study characteristics	
Methods	RCT
Participants	30 women *Inclusion criteria*: healthy women undergoing elective CS under spinal anaesthesia at term *Setting*: Japan
Interventions	**Dopamine versus control** Group 1: dopamine continuous infusion 5 µg/kg/min Group 2: non-dopamine infusion All women received a preload of 1000 mL of Ringer's lactate All women received a variable anaesthetic technique (L2-3 or L3-4) with variable 0.3% dibucaine doses (1.6-2.0 mL)
Outcomes	*Maternal*: hypotension; BP; heart rate *Neonatal*: Apgar scores
Notes	Hypotension was defined as 90% or less of baseline BP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Yokoyama 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	Unclear risk	Not apparent, but not well reported

Yorozu 2002

Study characteristics	
Methods	RCT
Participants	67 women *Inclusion criteria*: without toxaemia, undergoing caesarean under spinal anaesthesia *Setting*: Japan
Interventions	**Colloid preload versus crystalloid preload** Group 1: HES starch 1% dextrose (n = 32) Group 2: Ringer's lactate (n = 35) For all women IV infusion was commenced at arrival in the operating room and continued until delivery All women received a standardised spinal anaesthetic technique with dose adjusted according to subject's height, and standardised surgical positioning
Outcomes	*Maternal*: pain; time from incision to birth; hypotension; ephedrine dose; duration of hypotension; level of block; blood loss *Neonatal*: Apgar score; birthweight; blood pH; pO_2; pCO_2; BE; blood sugar; haemoglobin
Notes	Hypotension was defined as SBP < 90 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Yorozu 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paediatricians blinded for Apgar scores
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not apparent, but not well reported
Other bias	Unclear risk	Not apparent, but not well reported

ANP: atrial natriuretic peptide; **ASA**: American Society of Anesthesiologists Classification; **BE**: base excess; **BMI**: body mass index; **BP**: blood pressure; **bpm**: beats per minute; **cc**: cubic centimetre, equivalent to 1 mL; **CS**: caesarean section; **CSE**: combined spinal-epidural; **CSF**: cerebrospinal fluid; **CTG**: cardiotocography; **CVP**: central venous pressure; **DBP**: diastolic blood pressure; **DVT**: deep vein thrombosis; **ET-1**: enothelin-1; **GA**: general anaesthetic; **HES**: hydroxyethyl starch; **IDC**: in-dwelling catheter (urinary catheter); **IVT**: intravascular transfusion; **IM**: intramuscular; **IV**: intravenous; **LSCS**: lower segment caesarean section; **MAP**: mean arterial pressure; **NACS**: neurologic and adaptive capacity score; **NICU**: neonatal intensive care unit; **NS**: normal saline; **pO_2**: partial pressure of oxygen; **pCO_2**: partial pressure of carbon dioxide; **RCT**: randomised controlled trial; **SAB**: sub-arachnoid block; **SAP**: systolic arterial pressure; **SBP**: systolic blood pressure; **SCD**: sequential compression device; **SD**: standard deviation; **SEM**: standard error of mean; **SpO_2/SaO_2**: oximetry; **SST**: supine stress test; **TED**: thromboembolic deterrent; **w/v**: weight/volume; **0.9% NaCl/ 0.9% NS**: 0.9% sodium chloride, normal saline.

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

Study	Reason for exclusion
Adekanye 2007	Examines effect on combined spinal-epidural (not spinal anaesthesia alone)
Adigun 2010	Prevention of hypotension was not a study outcome, instead it examined effect of the interventions on restoration of BP. Aim was treatment not prophylaxis
Akhtar 2011	Inadequate information on number of women allocated to each group
Alahuhta 1994	Intervention aimed to treat hypotension not prevent
Amponsah 2011	Investigated prevention of hypotension resulting from combined spinal-epidural anaesthesia
Aragao 2014	Intervention aimed to treat hypotension not prevent
Arai 2008	Combined spinal-epidurals performed
Arboleda 2012	Investigated treatment, rather than prevention, of hypotension
Armstrong 2010	Inadequate reporting of study method. It is unclear if patients received spinal versus epidural versus combined spinal-epidural
Ashpole 2005	Phenylephrine and ephedrine used to maintain systolic arterial pressure (treating hypotension)
Atalay 2010	Anaesthetic regimen differed between groups

Study	Reason for exclusion
Atashkhoyi 2012	Investigated treatment, rather than prevention, of hypotension
Ayorinde 2001	Combined spinal epidural anaesthesia performed
Aziz 2013	Quasi-randomised study
Bach 2002	Intervention aimed to treat hypotension not prevent
Balcan 2011	Pharmacological treatment of maternal hypotension was studied. Prophylaxis was not studied
Basuni 2016	Comparison of different anaesthetic techniques
Belzarena 2006	Ephedrine or ethylphenylephrine (etilfrine) were used for treating, not preventing, hypotension
Benhamou 1998	Compared different spinal techniques – intervention was adding clonidine or fentanyl to bupivacaine
Bhar 2011	Incidence of hypotension not reported
Bhattarai 2010	Phenylephrine, ephedrine or mephentermine were used for treating, not preventing hypotension
Bjornestad 2009	Participants received epidural, not spinal anaesthesia
Borgia 2002	Participants underwent combined epidural-spinal anaesthesia
Bouchnak 2006	Compared different spinal anaesthetic techniques – different rates of anaesthetic administration
Bouslama 2012	Dose of the anaesthetic into spinal was not standardised between the study groups (low dose versus high dose). Comparisons between different anaesthetics techniques not included in this review
Bryson 2007	Compared different spinal anaesthetic techniques – different doses of local anaesthetic.
Butwick 2007	Incidence of hypotension not reported
Cai 2016	Combined spinal-epidurals performed
Campbell 1993	Compared different spinal anaesthetic techniques – intervention compared 2 different needles
Cardoso 2004b	Metaraminol was used to maintain BP
Cardoso 2005	Phenylephrine or metaraminol were used for treating, not preventing, hypotension
Carvalho 2015	Not a prospective randomised controlled trial (control group was retrospectively collected from case notes). Also incidence of hypotension not reported.
Cesur 2008	This study evaluated different anaesthetic techniques – hyperbaric bupivacaine alone versus sequential subarachnoid injection of plain bupivacaine followed by hyperbaric bupivacaine
Chanimov 2006	Investigation of effect of fluid preload on neonatal acid-base status (not maternal hypotension)
Choi 2005	Comparison of different anaesthetic techniques
Chung 1996	Compared different spinal anaesthetic techniques – intervention was volume of anaesthetic
Clark 1980	Dopamine was used for treating, not preventing, hypotension

Study	Reason for exclusion
Cohen 2002	Investigated prevention of hypotension for combined spinal-epidural anaesthesia for caesarean section
Cooper 2002	Phenylephrine and ephedrine used to maintain systolic arterial pressure (treating hypotension)
Cooper 2004	Phenylephrine and ephedrine used to maintain systolic arterial pressure (treating hypotension)
Cooper 2007	Intervention aimed to treat hypotension not prevent
Coppejans 2006	Combined spinal-epidurals performed
Das 2011	Inadequate data. This study investigates both the prevention and management of hypotension using a infusion which is commenced prior to spinal injection and then titrated according to BP using a predetermined algorithm. It is the initial prevention of hypotension (prior to titration of the vasopressor infusion) that this Cochrane review examines, however, this is impossible to examine based on the published data in this paper.
Datta 1982	Not randomised (allocated according to BP levels)
Davemski 2007	Intervention aimed to treat hypotension not prevent
Defossez 2007	Treatment rather than prevention
Desalu 2005	Ephedrine or saline used to maintain systolic arterial pressure (treating hypotension)
Doherty 2011	Investigated treatment, rather than prevention, of hypotension. Also incidence of hypotension was not reported
Dua 2013	Investigated treatment of hypotension, not prevention of hypotension
Dyer 2009	Phenylephrine and ephedrine used to maintain systolic arterial pressure (treating hypotension)
El-Hakeem 2011	Incidence of hypotension not reported
Evron 2007	Investigated prevention of hypotension following combined spinal-epidural anaesthesia (not spinal anaesthesia alone)
Fabrizi 1998	Inadequate data on specific numbers for incidence of hypotension in each group
Farber 2015	Techniques to prevent incidence of hypotension following spinal anaesthesia for caesarean section not investigated
Forkner 2012	Combined spinal-epidural anaesthesia performed
Foss 2014	Incidence of hypotension not reported
Frikha 2008	Inadequate data. The number of participants in each study group was not reported.
Frolich 2001	Study not adequately controlled with respect to fluid administration. Methods to prevent maternal hypotension was not a study outcome
Fuzier 2005	Treatment, not prevention, of hypotension
Gallo 1996	Compared different spinal anaesthetic techniques – 2 doses of bupivacaine

Study	Reason for exclusion
Gambling 2015	Combined spinal-epidural anaesthesia performed
Garrison 2005	Intervention was early identification of signs of hypotension so that women received prompt treatment
George 2015	Treatment, rather than prevention, of hypotension
Goudie 1988	Participants not randomised ('sequential allocation')
Guasch 2010	Investigated different anaesthetic techniques in prevention of maternal hypotension
Guillon 2010	Incidence of hypotension not reported
Gulec 2012	Investigated different doses of levobupivacaine into a combined spinal-epidural anaesthetic
Gulhas 2013	Only women who developed hypotension were randomised
Gunda 2010	Ephedrine or phenylephrine were used to treat, not prevent, hypotension
Gupta 2012	Women given combined spinal epidural anaesthesia
Gutsche 1976	No mention of randomisation
Hahn 1998	BP 'maintained', thus not prevention
Hamzei 2015	Different anaesthetic agent doses for spinal anaesthesia were compared
Hanss 2006	Quasi-randomised trial
Haruta 1987	Investigated treatment of hypotension; no definition of hypotension; no evidence of randomisation
Hennebry 2009	Combined spinal-epidurals performed
Higgins 2015	Investigated treatment of hypotension, not prevention
Housni 2004	Studied the effect of the rate of injection of bupivacaine on haemodynamic changes in elective caesarean
Husaini 1998	Hypotension treated not prevented - ephedrine manually regulated to keep BP in normal range
Iwama 2002	2 different anaesthetics used - not a randomised trial
Jackson 1995	BP was maintained by ephedrine infusion as well as treated according to rescue criteria for hypotension
Jain 2008	Maintenance, not prevention of hypotension
James 1996	Interventions were differing needle orientations
Javed 2014	Comparison of different anaesthetic techniques
John 2013	Inadequate data – incidence of hypotension following spinal anaesthesia was not reported
Kamrul 2012	Investigated methods of preventing oxytocin induced hypotension by co-administration of phenylephrine. Preventing of spinal anaesthesia induced hypotension was not investigated.

Study	Reason for exclusion
Kang 1982	BP 'maintained', thus not prevention
Kang 1996	Epidural anaesthesia used
Kangas-Saarela 1990	Despite adequate definition of hypotension, any fall in BP was treated with ephedrine boluses – not prevention
Kansal 2005	BP 'maintained', thus not prevention
Kaya 2007	Combined spinal epidural anaesthesia performed
Keera 2016	Different anaesthetic techniques compared
Kinsella 2012	Incidence of hypotension not reported
Ko 2007	Combined spinal-epidurals performed
Kumar 2013	Treatment rather than prevention of spinal hypotension was investigated
Kutlesic 2012	Different anaesthetic techniques investigated
Lal 2015	Intervention aimed to treat hypotension, not prevent
Langesaeter 2008	Combined spinal-epidurals performed
LaPorta 1995	Comparison of pressors used to treat hypotension, not prevention
Law 2003	Incidence of hypotension not reported
Lee 2005	Intervention aimed to treat hypotension not prevent.
Lee 2008	Investigated prevention of hypotension in combined spinal-epidural anaesthesia
Lee 2012	Prevention of hypotension was not investigated
Lee 2015	Combined spinal-epidural anaesthesia performed
Lee 2016	Combined spinal-epidural anaesthesia performed
Lewis 2004	Ephedrine and/or fluid used to maintain BP
Liu 2010	Epidural anaesthesia used
Luo 2016	Treatment, rather than prevention, of hypotension
Madi-Jebara 2007	Intervention aimed to treat hypotension not prevent
Mahajan 2009	Study meets criteria for inclusion but unable to interpret data/results presented in paper. Attempted to contact to resolve but no response.
Matorras 1998	Anaesthetist made decision of whether women had general anaesthetic or spinal anaesthesia. Different anaesthetic techniques used therefore excluded
Matsota 2013	Group allocation was not reported. It was not reported to be a "randomised" study

Study	Reason for exclusion
Matsota 2015	Combined spinal-epidural anaesthesia performed
McDonald 2011	Combined spinal-epidurals performed
McLeod 2010	Prevention of hypotension following spinal anaesthesia was not investigated.
Mebazaa 2010	This study investigates different spinal anaesthetic doses (i.e. reduction in bupivacaine dose) effect on incidence of hypotension
Mendonca 2003	Combined spinal-epidurals performed
Mercier 2001	Investigated treatment of hypotension
Miller 2000	Unclear how many women were allocated to each study group
Mitra 2014	This RCT was included in comparison 7 (colloid versus crystalloid) in the Cyna 2017 updated review. However, this study has since been retracted by the Saudi Journal of Anaesthesia and we have now reclassified this study from included to excluded.
Mohta 2008	Dose-finding comparison between ephedrine and phenylephrine, not a randomised trial
Mohta 2015	Investigated treatment rather than prevention of hypotension
Mohta 2016	Treatment, rather than prevention, of hypotension
Moore 2000	Investigates effect of speed of spinal local anaesthetic injection on incidence of hypotension
Moore 2014	Different anaesthetic agent doses for spinal anaesthesia were compared
Moran 1991	Comparison of pressors used to maintain BP, not used for prevention
Mowbray 2002	Phenylephrine and ephedrine were used for treating, not preventing, hypotension
Narejo 2012	Investigated 2 different types of local anaesthetic used in intrathecal injection and their effects on the incidence of hypotension
Nasir 2005	Comparison of different anaesthetic regimens
Negron 2010	Combined spinal-epidural anaesthesia performed
Ngan 2016	Treatment, rather than prevention, of hypotension
Ngan Kee 2001a	Metaraminol was used for treating, not preventing, hypotension
Ngan Kee 2001b	Metaraminol was used for treating, not preventing, hypotension
Ngan Kee 2001c	Metaraminol was used for treating, not preventing, hypotension
Ngan Kee 2004b	Thresholds of systolic arterial pressure randomised rather than prophylactic interventions
Ngan Kee 2005	Phenylephrine was used to maintain systolic arterial pressure (treating hypotension)
Ngan Kee 2008a	Treatment, not prevention
Ngan Kee 2008b	Treatment, not prevention

Study	Reason for exclusion
Ngan Kee 2009	Phenylephrine and ephedrine were used to maintain systolic arterial pressure (treating hypotension)
Ngan Kee 2011	Methods to maintain maternal BP was investigated, not methods to prevent hypotension
Ngan Kee 2013b	Methods to maintain maternal BP was investigated, not methods to *prevent* hypotension
Ngan Kee 2015	Investigated treatment of hypotension
Nishikawa 2004	Results not reported for all women who were randomised (5 emergency caesareans not reported in the groups to which they were randomised)
Norris 1987	Crystalloids used for maintaining BP
Norris 1989	Incidence of hypotension not reported
Nutangi 2013	This study investigates the efficacy of vasopressors in treatment (not prevention) of postspinal hypotension.
Nze 2003	Incidence of hypotension not reported
Ocio 2013	Combined spinal-epidural anaesthesia performed
Okutan 2006	Incidence of hypotension not reported
Osseyran 2011	Anaesthetic techniques varied among participants: spinal anaesthetic is not controlled and position of patient variable (variable bupivicaine dose according to height of patient, ± fentanyl, positioned in supine or side-lying for SAB).
Park 1996	Study was uncontrolled with respect to haemodynamics – "...ephedrine and additional fluid were given at the discretion of the anesthesiologist ... to maintain a systolic BP > 100 mmHg or 80% of baseline"
Peng 2013	Combined spinal-epidural anaesthesia conducted, not spinal anaesthesia alone
Pickford 2000	Despite adequate definition of hypotension, rescue ephedrine was also given for nausea and hypotension was not reported
Prakash 2010	Phenylephrine and ephedrine were used to treat, not prevent, hypotension
Quan 2013	Incidence of hypotension not reported
Quan 2014	Combined spinal epidurals performed
Quan 2015	Different anaesthetic agents for spinal anaesthesia were compared
Quan 2016	Different anaesthetic techniques compared
Quiney 1995	Study not adequately controlled – BP maintained within 20% of preoperative value of baseline by adjusting infusion rate of ephedrine in Hartmann's solution
Rashad 2013	Investigated treatment of hypotension
Reed 2006	Intervention aimed to manage hypotension not prevent

Study	Reason for exclusion
Rehman 2011	This study investigated the efficacy of prophylactic ephedrine given soon after spinal block compared to those women who were given treatment boluses of ephedrine only after they developed hypotension
Rewari 2015	Number of women allocated to each study group not reported
Ronenson 2014	Intervention was using different doses of anaesthetic
Rout 1993b	Quasi-randomised study
Rout 2000	Unclear definition of hypotension
Rucklidge 2002	Combined spinal-epidurals performed
Rucklidge 2005	Combined spinal-epidurals performed
Rumboll 2015	Prevention of oxytocin-induced hypotension rather than prevention of spinal-induced hypotension
Russell 2002	Combined spinal-epidurals performed
Sahin 2015	Number of women allocated to each study group not reported
Sakr 2014	Combined spinal epidurals performed
Sanwal 2008	Investigated effects of intrathecal midazolam in addition to bupivacaine on post-spinal hypotension
Saravanan 2006	Combined spinal-epidurals performed
Schofield 2011	Intervention aimed to treat hypotension not prevent
Seltenrich 2001	Comparison of injection rates of spinal anaesthetic
Seyedhejazi 2007	Investigated the effect of different doses of bupivacaine-fentanyl on postspinal hypotension
Sherif 2013	Investigated treatment not prevention of hypotension in women having spinal anaesthesia for caesarean section
Shifman 2007	Epidurals performed
Siddik-Sayyid 2013	Not reported as a randomised study
Siddik-Sayyid 2014	Techniques to treat, rather than prevent, hypotension
Siddiqui 2016	Compared different anaesthetic doses/regimens
Simon 1999	Compared fast and slow injection rates; no mention of randomisation
Sivevski 2006	Investigated effect of plain bupivacaine versus lower dose bupivacaine with fentanyl on the incidence of hypotension
Sng 2013	Investigated treatment, not prevention of hypotension
Sng 2014	Techniques to treat, rather than prevent, hypotension

Study	Reason for exclusion
Sprague 1976	Not randomised – allocation was sequential
Stewart 2010	Combined spinal-epidurals performed
Stewart 2011	Investigated the effect of differing rates of phenylephrine infusions (used for the treatment of maternal hypotension) on the incidence of maternal reactive hypertension
Stoneham 1999	Compared different spinal anaesthetic techniques – spinal given in different positions
Sumikura 2009	Investigated the effect of preloading with lactated or bicarbonate Ringer's solutions on fetal acid base balance. Maternal BP was not reported
Szmuk 2008	Treatment, not prevention
Tamilselvan 2009	Combined spinal-epidurals performed
Tanaka 2007	Not a randomised controlled trial
Tanaka 2008	Phenylephrine dose finding study, not randomised trial
Tang 2015	Combined spinal-epidural performed; compared different anaesthetic techniques
Tekyeh 2013	Different doses of spinal local anaesthetic compared
Teoh 2009	Not prophylaxis – arterial BP was maintained at 90% to 100% of baseline values
Thomas 2001	Thresholds of systolic arterial pressure randomised rather than prophylactic interventions
Thomas 2004	Given as treatment not prophylaxis
Thomas 2006	Treatment given as baby was born
Tolia 2008	Compared different spinal anaesthetic techniques – different doses of anaesthetics
Turker 2011	Incidence of hypotension not reported
Vallejo 2015	Incidence of hypotension not reported
Van Bogaert 1998	The method by which hypotension was treated was not clearly reported, and potentially inconsistent between study participants
Vercauteren 1996	Investigated CSE technique
Vercauteren 2000	Combined spinal-epidurals performed
Vincent 1998	Study not adequately controlled – BP maintained at 90% – 100% of baseline by adjusting infusions of intervention pressor
Vuffray 2005a	Treatment, rather than prevention, of hypotension
Vuffray 2005b	Treatment, rather than prevention, of hypotension
Wang 2011	Intervention aimed to treat hypotension not prevent
Wang 2015	Combined spinal epidurals performed

Study	Reason for exclusion
Williamson 2009	Comparison of different spinal anaesthetic techniques
Wojciechowski 2008	Incidence of hypotension not reported
Wollman 1968	No mention of randomisation of study participants. 'Control group' included 5 parturients having vaginal birth
Xiao 2015a	Combined spinal epidurals performed
Xiao 2015b	Combined spinal epidurals performed
Xu 2012	Not a randomised trial. This study aimed to determine the median effective volume of crystalloid in preventing hypotension in women undergoing caesarean delivery with spinal anaesthesia.
Xu 2014	Combined spinal-epidural anaesthesia performed
Yadav 2012	Intervention aimed to treat hypotension not prevent
Yentis 2000	Combined spinal-epidurals performed
Yokoyama 2004	Variable bupivicaine dosing was used: "The amount of 0.5% bupivacaine hyperbaric solution to be administered was adjusted to aim for a level of anaesthesia of T4, at 2.5ml, with reference to the weight of the patient."
Yoon 2012	Incidence of hypotension not reported
Young 1996	Intervention aimed to treat hypotension not prevent
Yun 1998	Combined spinal-epidurals performed
Yurtlu 2012	Investigated effect of hyperbaric, isobaric and combinations of bupivacaine for spinal anaesthesia
Zakowski 1992	Comparison of pressors to treat, not prevent, hypotension
Zasa 2015	Only randomised women at high risk of developing hypotension
Zhou 2008	Combined spinal-epidurals performed

BP: blood pressure; **CSE**: combined spinal-epidural; **SBP**: systolic blood pressure.

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

Abedinzadeh 2010

Methods	RCT
Participants	Women undergoing caesarean section *Inclusion criteria*: aged 20-40 years, ASA physical status I and II, single pregnancy, elective caesarean, gestational age ≥ 37 weeks *Exclusion criteria*: hypovolaemia, deformity of spinal column, increase of intracranial pressure, coagulopathy, infection of skin or soft tissue and dissatisfaction of patient
Interventions	**Atropine versus ephedrine versus phenylephrine**

Abedinzadeh 2010 *(Continued)*

	Group 1: 0.5 mg atropine (IV) before spinal anaesthesia (single dose)
	Group 2: 5 mg ephedrine before spinal anaesthesia (single dose)
	Group 3: 100 µg phenylephrine (mucosal) before spinal anaesthesia (single dose)
	All women receive 500 mL Ringer's lactate before spinal anaesthesia
Outcomes	*Maternal*: blood pressure; heart rate; oxygen saturation
	Neonatal: —
Notes	Full report published in 2012, in Arabic, abstract is in English
	Awaiting translation

Alday 2011

Methods	RCT
Participants	80 women undergoing caesarean section
	Inclusion criteria: absence of uterine activity or fetal risk
	Exclusion criteria: not specified
Interventions	**Ephedrine vs phenylephrine after spinal block**
	Group 1: IV bolus of 0.1 mg/kg plus continuous infusion at a rate of 0.5 mg/kg/h
	Group 2: IV bolus of 0.5 µg/kg plus continuous infusion at a rate of 1.5 µg/kg/min
Outcomes	*Maternal*: hypotension; hypertension; bradycardia
	Neonatal: umbilical cord blood parameters (pH, pCO_2, HCO_3); Apgar scores
Notes	Original article in Spanish
	Only abstract in English
	Awaiting translation; unclear if this intervention is for treatment or prevention of hypotension

Amiri 2013

Methods	RCT
Participants	100 pregnant women undergoing elective caesarean section
	Inclusion criteria: not specified
	Exclusion criteria: not specified
Interventions	**Phenylephrine vs ephedrine post spinal anaesthesia**
	Group 1: 100 µg bolus dose
	Group 2. 10 mg bolus dose

Amiri 2013 *(Continued)*

Outcomes	*Maternal*: heart rate; BP *Neonatal*: umbilical cord blood gases
Notes	Original article in Arabic Only abstract in English Awaiting translation

Ashpole 2006

Methods	RCT
Participants	40 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Ephedrine versus phenylephrine** Group 1: 5 mg/min ephedrine infusions Group 2: 100 µg/min phenylephrine infusions
Outcomes	*Maternal*: incidence of hypotension; incidence of hypertension; duration of infusion; spinal delivery *Neonatal*: fetal acidosis
Notes	Unclear whether intervention is for treatment or prevention of hypotension – first author contacted 26/06/2017, awaiting response.

Bennasr 2014

Methods	RCT
Participants	120 women undergoing elective caesarean section *Inclusion criteria*: ASA I and II *Exclusion criteria*: not specified
Interventions	**HES vs normal saline** Group 1: 500 mg of HES 130/0.4 (Voluven (R)) Group 2: 500 mL normal saline Both groups received ephedrine for hypotension
Outcomes	*Maternal*: hypotension; ephedrine requirement and consumption; nausea and vomiting; headache *Neonatal*: Apgar scores; umbilical blood gases
Notes	Original version in French

Bennasr 2014 *(Continued)*

	Only abstract available in English Awaiting translation

Boswell 2008

Methods	RCT
Participants	105 women undergoing elective caesarean section
Interventions	Group 1: received a 1-mg/min ephedrine infusion from the time of injection of the spinal solution until uterine incision Group 2: received a 9-mg ephedrine bolus at the time of injection of the spinal solution. Group 3: received no prophylactic ephedrine
Outcomes	*Maternal*: time of hypotension; volume of rescue fluid; dose of rescue ephedrine *Neonatal*: Apgar scores
Notes	If SBP fell below IBP, a 250-mL rescue bolus of normal saline and ephedrine 6 mg were given. If, after 2 min the SBP was still < IBP, a further 6-mg bolus of ephedrine was given. If, after a further 2 min, the SBP remained < IBP, another 250-mL bolus of saline with ephedrine 6 mg was given. This 4-min cycle would be repeated until the SBP was > IBP. The study continued until uterine incision. Abstract only. Unclear whether intervention is for treatment or prevention of hypotension – first author's institution contacted 26 June 2017, awaiting response

Bright 2003

Methods	RCT
Participants	40 women undergoing elective caesarean section
Interventions	**Ephedrine vs placebo** Group 1: ephedrine 30 mg Group 2: placebo Identical capsules taken by mouth 1 h before institution of the spinal anaesthetic. All participants then received Hartmann's solution 15 mL/kg before subarachnoid injection of 0.5% heavy bupivacaine 2.5 mL and diamorphine 0.25 mg, using a 25-gauge pencil-point needle with the patient in the sitting position on the operation table
Outcomes	*Maternal*: — *Neonatal*: —
Notes	Women were given bolus injections of rescue ephedrine 6 mg on each occasion their systolic blood pressure was less than 80% of that recorded before the spinal injection. Abstract only. Insufficient information to assess risk of bias – unable to find contact details of author

Golmohammadi 2013

Methods	RCT
Participants	112 women undergoing elective caesarean section *Inclusion criteria*: ASA I and II *Exclusion criteria*: not specified
Interventions	**HES prior to spinal anaesthesia vs HES after spinal anaesthesia** Both groups received 500 mg of 6% HES Both groups received rescue dose of combined ephedrine 5 mg/mL with phenylephrine 25 µg/mL
Outcomes	*Maternal*: hypotension; vVasopressor consumption *Neonatal*: not specified
Notes	Original article in Arabic Only abstract available in English Awaiting translation

Gonzalez 2014

Methods	RCT
Participants	26 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: age < 18 years, non-elective CS, BMI > 40 kg/m^2, hypertension, multiple pregnancy, high-risk patients, sepsis, insulin – dependent diabetes mellitus, spinal block level > T5, ongoing epidural anaesthesia
Interventions	**Intermittent pneumatic compression system (IPCS) versus control** Group 1: IPCS applied to legs Group 2: crystalloid cohydration with 0.9% saline 500 mL (given to women in both groups)
Outcomes	*Maternal*: diastolic, mean and diastolic arterial pressure; umbilical cord blood gas values; phenylephrine boluses and total dose; haemoglobin levels *Neonatal*: Apgar scores at 1 min and 5 min
Notes	Abstract only; unclear whether intervention is for treatment or prevention of hypotension – unable to find contact details of authors

Higgins 2009

Methods	Not known

Higgins 2009 *(Continued)*

Participants	Women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Coload with colloid versus crystalloid solutions** Group 1: 500 mL of Ringer's lactate Group 2: 1000 mL of Ringer's lactate Group 3: 500 mL of 6% hydroxyethyl starch All solutions given over 15 minutes immediately following intrathecal administration of hyperbaric bupivacaine 12 µg with fentanyl 15 mg and morphine 150 µg.
Outcomes	*Maternal*: hypotension; heart rate; stroke volume; cardiac index; systemic vascular resistance *Neonatal*: —
Notes	Abstract only. Insufficient information to assess risk of bias – first author contacted 26 June 2017, awaiting response

Hwang 1994

Methods	RCT
Participants	21 women undergoing elective caesarean section *Inclusion criteria*: ASA I *Exclusion criteria*: not specified
Interventions	**Crystalloid 20 min vs crystalloid 10 min prior to spinal** Both groups received 20 mL/kg
Outcomes	*Maternal*: CVP; hypotension *Neonatal*: not specified
Notes	Original article in Korean Only abstract available in English Awaiting translation

Jain 2013

Methods	RCT
Participants	92 women undergoing caesarean section *Inclusion criteria*: undergoing spinal anesthesia for emergency cesarean delivery indicated due to acute fetal compromise

Jain 2013 *(Continued)*

	Exclusion criteria: not specified
Interventions	Ephedrine versus phenylephrine Group 1: received prophylactic infusions of ephedrine at the rate of 2.5 mg/min Group 2: received prophylactic infusions of phenylephrine at the rate of 30 µg/min
Outcomes	*Maternal*: systolic blood pressure; umbilical artery pH; need for immediate resuscitation; haemodynamics; intra-operative nausea/vomiting *Neonatal*: cord blood gases; incidence of fetal acidosis; Apgar score
Notes	Abstract only. Unclear whether intervention is for treatment or prevention of hypotension – first author contacted 26/06/2017, awaiting response.

Jung 2006

Methods	RCT
Participants	900 women undergoing elective caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Ephedrine vs phenylephrine vs ephedrine plus phenylephrine** Group 1: ephedrine 2 mg/min infusion with 6 mg bolus Group 2: phenylephrine 33.3 µg/min infusion with 50 µg bolus Group 3: ephedrine plus phenylephrine combined at half the infusion doses and bolus
Outcomes	*Maternal*: number of boluses given; hypotension; bradycardia *Neonatal*: umbilical blood gas; Apgar score
Notes	Original article in Korean Only abstract available in English Awaiting translation; unclear if intervention is for treatment or prevention

Kashiwagi 2012

Methods	RCT
Participants	A non-specified number of women undergoing elective caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Left 15 degrees tilt vs uterine displacement by hand** Ephedrine (4 mg IV) administered in either case for hypotension, nausea or vomiting

Kashiwagi 2012 *(Continued)*

	Group 1: following spinal injection patients turn to 15 degrees left lateral supine position Group 2: following spinal injection patient had uterine displacement by hand
Outcomes	*Maternal*: arm systolic BP; leg systolic BP; mean ephedrine requirement *Neonatal*: Apgar scores; umbilical artery pH
Notes	Original article in Japanese Only abstract available in English Awaiting translation

Kiss 2012

Methods	RCT
Participants	102 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: fetal distress, severe comorbidities, urgent caesarean section for any cause
Interventions	Ringer's lactate versus balanced Ringer's solution
Outcomes	*Maternal*: mean arterial pressure; heart rate; oxygen saturation *Neonatal*: —
Notes	Abstract only. Unclear if intervention is treatment or prevention of hypotension – unable to find contact details of authors

Lang 1996

Methods	RCT
Participants	38 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	Ringer's lactate versus albumin solution Group 1: 50 mL/kg of Ringer's lactate before spinal anaesthesia with 12 mg of bupivacaine Group 2: 15 mL/kg of 5% albumin solution before spinal anaesthesia with 12 mg of bupivacaine
Outcomes	*Maternal*: mean arterial pressure; umbilical cord blood gases; arterial natriuretic peptide; cardiac output *Neonatal*: Apgar scores; fetal biochemical profiles
Notes	Abstract only. Insufficient information to assess risk of bias – unable to find contact details of authors

Lee 2011

Methods	Not known
Participants	45 women undergoing caesarean section *Inclusion criteria*: not clear *Exclusion criteria*: not clear
Interventions	Prehydration versus Wrapping of legs Group 1: prehydration with 10 mL/kg Group 2: prehydration with 10 mL/kg and wrapping of the legs Group 3: prehydration with 5 mL/kg and wrapping of the legs
Outcomes	*Maternal*: incidence of hypotension; systolic arterial pressure *Neonatal*: —
Notes	Full report is in Chinese while the abstract is in English Awaiting translation

Osazuwa 2015

Methods	RCT
Participants	Women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	Colloid versus crystalloid versus combination of both preloads Group 1: 500 mL of Ringer's lactate, preload, before spinal anaesthesia Group 2: 500 mL of 6% pentastarch, preload, before spinal anaesthesia Group 3: combination of 250 mL of 6% pentastarch and 750 mL of Ringer's lactate intravenous fluid preload, before spinal anaesthesia
Outcomes	*Maternal*: hypotension *Neonatal*: not specified
Notes	Abstract only. Insufficient information to assess risk of bias – first author contacted 26/06/2017, awaiting response.

Rahmoune 2009

Methods	RCT
Participants	62 women undergoing caesarean section

Rahmoune 2009 *(Continued)*

	Inclusion criteria: women with ASA I status *Exclusion criteria*: not specified
Interventions	**Colloid versus control** Group 1: preloading with 500 mL of a gelatine modified fluid (Gelofusine 4%) over 10 min before spinal anaesthesia Group 2: no preload
Outcomes	*Maternal*: systolic arterial blood pressure; incidence of nausea and vomiting; allergic reactions *Neonatal*: Apgar scores at 1 min and 5 minutes; cord blood gases
Notes	Abstract only. Insufficient information to assess risk of bias – unable to find contact details for authors.

Sahoo 2011

Methods	RCT
Participants	40 women undergoing caesarean section *Inclusion criteria*: full-term pregnant women of ASA grade I and II, posted for cesarean section *Exclusion criteria*: not specified
Interventions	**Phenylephrine versus colloids (hydroxyethyl starch)** Group 1: women received phenylephrine at 60 µg/min for 2 min unless SBP was > 120% of baseline immediately after intrathecal injection Group 2: women received rapid colloid infusion (12 mL/kg of hydroxyethyl starch 6%) immediately after intrathecal injection
Outcomes	*Maternal*: blood pressure; fall in BP below 80% of baseline; umbilical artery pH *Neonatal*: —
Notes	Abstract only. Unclear if intervention is for treatment or prevention of hypotension – first author's institution contacted 26 June 2017, awaiting response

Sakuma 2010

Methods	RCT
Participants	32 patients undergoing caesarean delivery *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Phenylephrine vs ephedrine** Both groups received drug after spinal

Sakuma 2010 *(Continued)*

	Group 1: phenylephrine continuous infusion – details not specified in abstract Group 2: ephedrine continuous infusion – details not specified in abstract
Outcomes	*Maternal*: block height; haemodynamic changes *Neonatal*: umbilical artery pH
Notes	Original article in Japanese Only abstract available in English Awaiting translation; unclear if intervention is for treatment or prevention of hypotension

Soltani 2009

Methods	RCT
Participants	300 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	Combination of 2 interventions Group 1: crystalloid and colloid: Ringer's lactate (15 mL/kg) and Hemaxel (7ml/kg) – both given before spinal anaesthesia (SA) Group 2: crystalloid and ephedrine: Ringer's lactate (15 mL/kg) given before SA and ephedrine 15 mg IV, after SA Group 3: crystalloid and bandage: Ringer's lactate (15 mL/kg) and lower limb bandage Group 4: colloid and ephedrine: hydroxyethyl starch (7ml/kg) given before SA, and ephedrine 15 mg IV, after SA Group 5: colloid and bandage: hydroxyethyl starch (7ml/kg) given before SA, and lower limb bandage Group 6: ephedrine and bandage: ephedrine 15 mg, IV after SA, and lower limb bandage
Outcomes	*Maternal*: pulse rate; systolic blood pressure *Neonatal*: Apgar score; neurological and adaptive capacity score (NACS)
Notes	Abstract only. Insufficient information to assess risk of bias – first author contacted 26 June 2017, awaiting response

Van Bogaert 2000

Methods	RCT
Participants	68 women undergoing caesarean section *Inclusion criteria*: not specified

Van Bogaert 2000 *(Continued)*

	Exclusion criteria: not specified
Interventions	**Hip flexion versus no flexion** Immediately after the administration of subarachnoid injection, women were placed in Fowler's position (30 degree raised head and shoulders, 15 degree lateral tilt) Group 1: hip flexed at 45 degree for 5 minutes Group 2: legs were straight
Outcomes	*Maternal*: systolic arterial pressure; incidence of hypotension *Neonatal*: Apgar scores
Notes	Brief communication only. Insufficient information to assess risk of bias – first author contacted 26 June 2017, email bounced, unable to find other contact

Van Treese 1996

Methods	RCT
Participants	60 women undergoing caesarean section *Inclusion criteria*: ASA physical status I and II *Exclusion criteria*: pregnancy-induced hypertension; pre-eclampsia or eclampsia; illegal drug use; fetal distress; nausea and vomiting; maternal coagulopathy; high/low blood pressure; diabetes
Interventions	All women in both the groups received 15-20 mL/kg Ringer's lactate 20-30 minutes prior to sub-arachnoid block (SAB), left uterine displacement (LUD), and ephedrine as needed Group 1: TED compression prior to fluid loading and SAB, and fluids Group 2: TED compression and foam wedge that elevates leg to 30 degree within 5 minutes following SAB prior to fluid loading and SAB, and fluids Group 3: received only fluids
Outcomes	*Maternal*: incidence of hypotension; blood loss *Neonatal*: not specified
Notes	Abstract only. Insufficient information to assess risk of bias – unable to find contact details.

Yoon 2009

Methods	RCT
Participants	32 women undergoing caesarean section *Inclusion criteria*: not specified *Exclusion criteria*: not specified
Interventions	**Ephedrine versus phenylephrine versus combination of both infusions**

Yoon 2009 *(Continued)*

Outcomes	*Maternal*: systolic blood pressure; pulse rate; systolic vascular resistance index; cardiac index; stroke volume index; nausea and vomiting scores; total fluid intake; phenylephrine rescues; umbilical vein pH *Neonatal*: Apgar scores
Notes	Full report is available in Korean Awaiting translation. Unclear if intervention is for treatment or prevention of hypotension.

BMI: body mass index; **BP**: blood pressure; **CVP**: central venous pressure; **HES**: hydroxyethyl starch solution; **IBP**: invasive blood pressure; **IM**: intramuscular; **IV**: intravenous; **RCT**: randomised controlled trial; **SAB**: sub-arachnoid block; **TED**: thromboembolic deterrent.

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

NCT01891175

Study name	Prevention of maternal hypotension during elective caesarean section performed with spinal anaesthesia, through intermittent pneumatic compression system in the lower extremities
Methods	RCT
Participants	*Inclusion criteria*: age > 18 years; elective caesarean section *Exclusion criteria*: emergency caesarean; epidural anaesthesia; caesarean section of multiple pregnancies; obstetric pathology (pre-eclampsia, eclampsia, HELLP syndrome (haemolysis elevated liver enzymes low platelet count), small-for-gestational age, preterm (< 32 weeks); valvular heart disease; hypertension; sepsis; BMI > 40 kg/m^2; insulin dependent diabetes mellitus; block level achieved with spinal anaesthesia > T5; patients that cannot meet the study protocol
Interventions	Phenylephrine infusion vs phenylephrine infusion with intermittent pneumatic compression
Outcomes	*Maternal*: vasopressor dose required; effectiveness of intermittent pneumatic compression system to decrease requirement of vasopressors *Neonatal*: not specified
Starting date	—
Contact information	—
Notes	Information obtained from trial registry

BMI: body mass index; **RCT**: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Crystalloid vs control

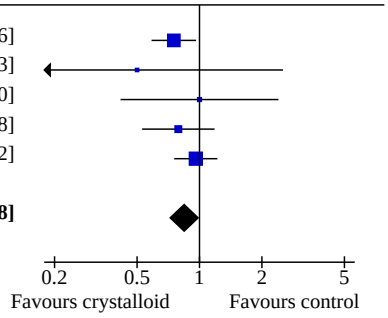
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Women with hypotension requiring intervention	5	370	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.72, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Nausea and/or vomiting	1	69	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.91]
1.3 Anaphylaxis	1	69	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Apgar < 8 at 5 min	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 1.1. Comparison 1: Crystalloid vs control, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Crystalloid Events	Crystalloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Idehen 2014	24	35	31	34	39.3%	0.75 [0.59 , 0.96]
Imam 2012	2	30	4	30	0.9%	0.50 [0.10 , 2.53]
King 1998	5	10	5	10	3.1%	1.00 [0.42 , 2.40]
Morgan 2000	26	78	35	83	14.9%	0.79 [0.53 , 1.18]
Ouerghi 2010	24	30	25	30	41.8%	0.96 [0.76 , 1.22]
Total (95% CI)		**183**		**187**	**100.0%**	**0.84 [0.72 , 0.98]**
Total events:	81		100			

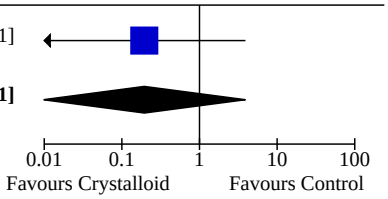
Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Crystalloid vs control, Outcome 2: Nausea and/or vomiting

Study or Subgroup	Crystalloid Events	Crystalloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Idehen 2014	0	35	2	34	100.0%	0.19 [0.01 , 3.91]
Total (95% CI)		**35**		**34**	**100.0%**	**0.19 [0.01 , 3.91]**
Total events:	0		2			

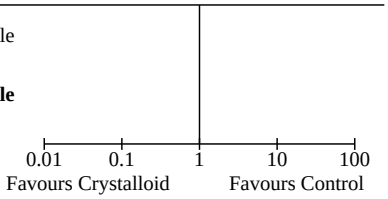
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



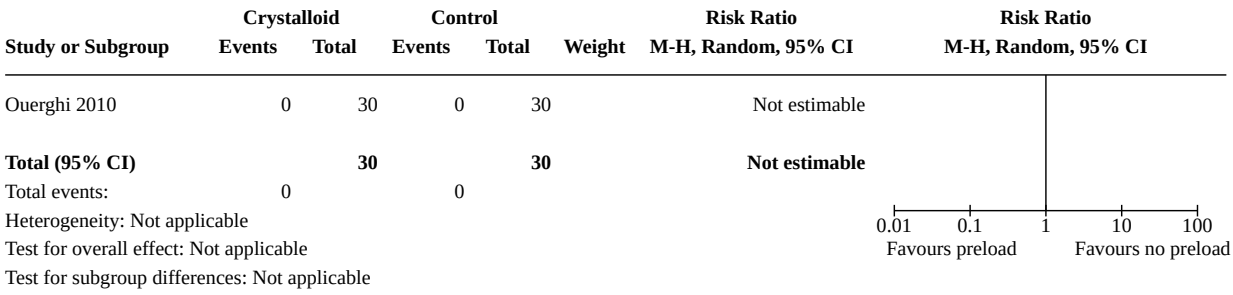
Analysis 1.3. Comparison 1: Crystalloid vs control, Outcome 3: Anaphylaxis

Study or Subgroup	Crystalloid Events	Crystalloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Idehen 2014	0	35	0	34		Not estimable
Total (95% CI)		**35**		**34**		**Not estimable**
Total events:	0		0			

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



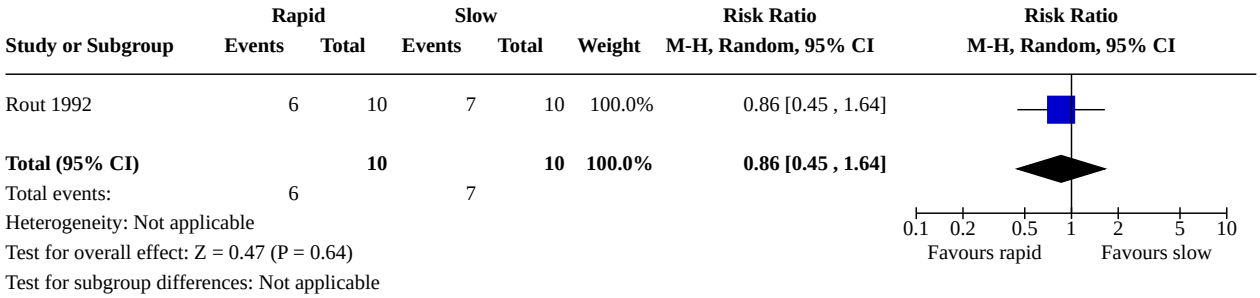
Analysis 1.4. Comparison 1: Crystalloid vs control, Outcome 4: Apgar < 8 at 5 min



Comparison 2. Crystalloid: rapid infusion vs slow infusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Women with hypotension requiring intervention	1	20	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.45, 1.64]

Analysis 2.1. Comparison 2: Crystalloid: rapid infusion vs slow infusion, Outcome 1: Women with hypotension requiring intervention



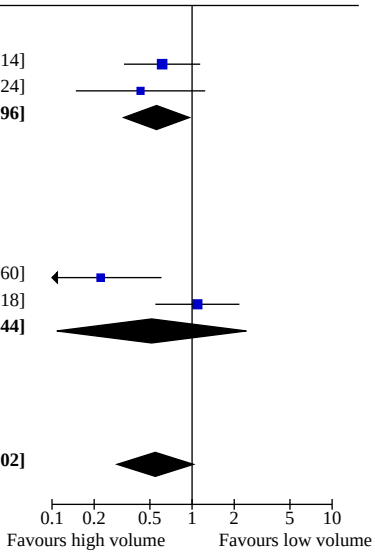
Comparison 3. Crystalloid: high vs low preload volume

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Women with hypotension requiring intervention	3	192	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.29, 1.02]
3.1.1 15 mL/kg crystalloid	2	67	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.33, 0.96]
3.1.2 20 mL/kg crystalloid	2	125	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.11, 2.44]
3.2 Nausea and/or vomiting	1	80	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.40, 3.62]
3.3 Apgar < 8 at 5 min	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 15 mL/kg crystalloid	1	45	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3.2 20 mL/kg crystalloid	1	45	Risk Ratio (M-H, Random, 95% CI)	Not estimable

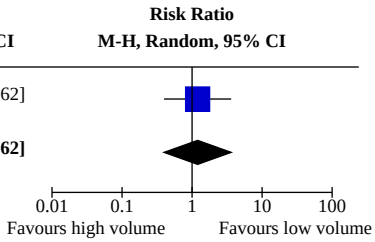
Analysis 3.1. Comparison 3: Crystalloid: high vs low preload volume, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	High volume preload Events	Total	Low volume preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 15 mL/kg crystalloid						
Faydaci 2011	11	30	9	15	30.8%	0.61 [0.33 , 1.14]
Tercanli 2005	3	11	7	11	19.5%	0.43 [0.15 , 1.24]
Subtotal (95% CI)		**41**		**26**	**50.3%**	**0.56 [0.33 , 0.96]**
Total events:	14		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
3.1.2 20 mL/kg crystalloid						
Faydaci 2011	4	30	9	15	20.8%	0.22 [0.08 , 0.60]
Muzlifah 2009	12	40	11	40	28.9%	1.09 [0.55 , 2.18]
Subtotal (95% CI)		**70**		**55**	**49.7%**	**0.51 [0.11 , 2.44]**
Total events:	16		20			
Heterogeneity: Tau² = 1.07; Chi² = 6.58, df = 1 (P = 0.01); I² = 85%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**111**		**81**	**100.0%**	**0.55 [0.29 , 1.02]**
Total events:	30		36			
Heterogeneity: Tau² = 0.23; Chi² = 7.05, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



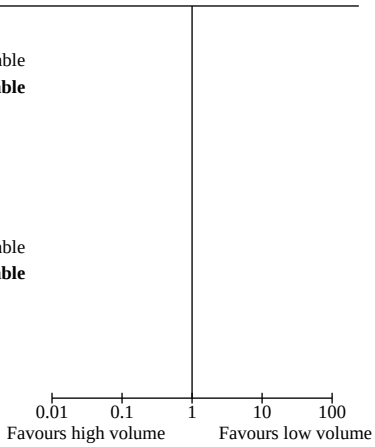
Analysis 3.2. Comparison 3: Crystalloid: high vs low preload volume, Outcome 2: Nausea and/or vomiting

Study or Subgroup	High volume preload Events	Total	Low volume preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Muzlifah 2009	6	40	5	40	100.0%	1.20 [0.40 , 3.62]
Total (95% CI)		**40**		**40**	**100.0%**	**1.20 [0.40 , 3.62]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Not applicable						



Analysis 3.3. Comparison 3: Crystalloid: high vs low preload volume, Outcome 3: Apgar < 8 at 5 min

Study or Subgroup	High volume preload Events	Total	Low volume preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 15 mL/kg crystalloid						
Faydaci 2011	0	15	0	30		Not estimable
Subtotal (95% CI)		**15**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.2 20 mL/kg crystalloid						
Faydaci 2011	0	15	0	30		Not estimable
Subtotal (95% CI)		**15**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



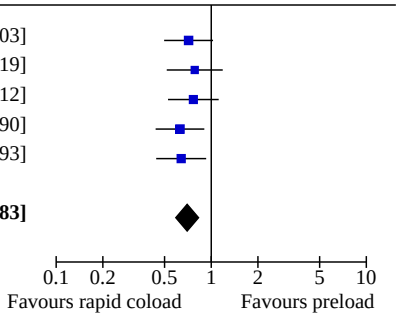
Comparison 4. Crystalloid: rapid coload vs preload

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Women with hypotension requiring intervention	5	384	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]
4.2 Hypertension requiring intervention	1	100	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.42, 6.60]
4.3 Women with bradycardia	1	100	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.59, 3.45]
4.4 Women with nausea or vomiting	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4.1 Women with nausea	3	210	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.26, 3.12]
4.4.2 Women with vomiting	2	160	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.98, 5.58]
4.5 Neonates with acidosis (pH < 7.2)	2	110	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.6 Apgar < 8 at 5 min	3	210	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 4.1. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Rapid coload Events	Rapid coload Total	Preload Events	Preload Total	Weight	Risk Ratio M-H, Random, 95% CI
Dyer 2004	15	25	21	25	21.5%	0.71 [0.50 , 1.03]
Farid 2016	18	37	23	37	16.4%	0.78 [0.52 , 1.19]
Jacob 2012	23	50	30	50	20.0%	0.77 [0.53 , 1.12]
Khan 2013	22	50	35	50	21.6%	0.63 [0.44 , 0.90]
Oh 2014	16	30	25	30	20.5%	0.64 [0.44 , 0.93]
Total (95% CI)		**192**		**192**	**100.0%**	**0.70 [0.59 , 0.83]**
Total events:	94		134			

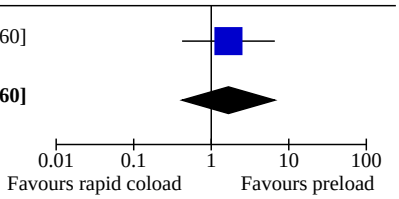
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 4.17 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 2: Hypertension requiring intervention

Study or Subgroup	Rapid coload Events	Rapid coload Total	Preload Events	Preload Total	Weight	Risk Ratio M-H, Random, 95% CI
Jacob 2012	5	50	3	50	100.0%	1.67 [0.42 , 6.60]
Total (95% CI)		**50**		**50**	**100.0%**	**1.67 [0.42 , 6.60]**
Total events:	5		3			

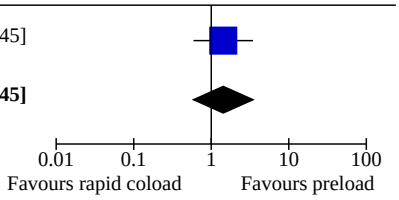
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 3: Women with bradycardia

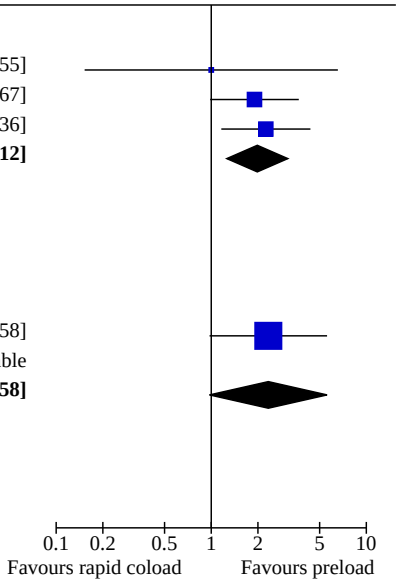
Study or Subgroup	Rapid coload Events	Rapid coload Total	Preload Events	Preload Total	Weight	Risk Ratio M-H, Random, 95% CI
Jacob 2012	10	50	7	50	100.0%	1.43 [0.59 , 3.45]
Total (95% CI)		**50**		**50**	**100.0%**	**1.43 [0.59 , 3.45]**
Total events:	10		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



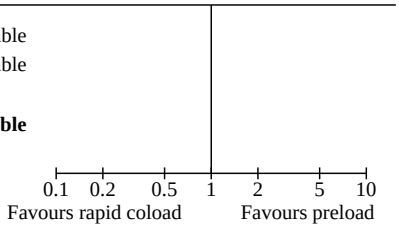
Analysis 4.4. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 4: Women with nausea or vomiting

Study or Subgroup	Rapid coload Events	Total	Preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Women with nausea						
Dyer 2004	2	25	2	25	5.8%	1.00 [0.15 , 6.55]
Jacob 2012	19	50	10	50	47.4%	1.90 [0.98 , 3.67]
Oh 2014	18	30	8	30	46.8%	2.25 [1.16 , 4.36]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**1.98 [1.26 , 3.12]**
Total events:	39		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.96 (P = 0.003)						
4.4.2 Women with vomiting						
Jacob 2012	14	50	6	50	100.0%	2.33 [0.98 , 5.58]
Oh 2014	0	30	0	30		Not estimable
Subtotal (95% CI)		**80**		**80**	**100.0%**	**2.33 [0.98 , 5.58]**
Total events:	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						



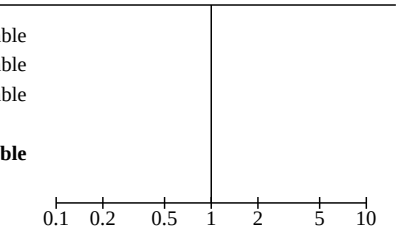
Analysis 4.5. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 5: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Rapid coload Events	Total	Preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dyer 2004	0	25	0	25		Not estimable
Oh 2014	0	30	0	30		Not estimable
Total (95% CI)		**55**		**55**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 4.6. Comparison 4: Crystalloid: rapid coload vs preload, Outcome 6: Apgar < 8 at 5 min

Study or Subgroup	Rapid coload Events	Total	Preload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dyer 2004	0	25	0	25		Not estimable
Jacob 2012	0	50	0	50		Not estimable
Oh 2014	0	30	0	30		Not estimable
Total (95% CI)		**105**		**105**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

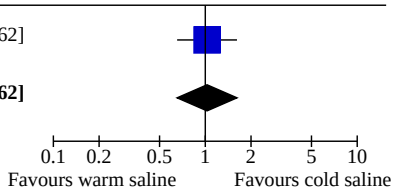


Comparison 5. Crystalloid: warm vs cold

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Women with hypotension requiring intervention	1	113	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.65, 1.62]
5.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.2.1 Nausea	1	113	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.97, 2.76]
5.2.2 Vomiting	1	113	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.12, 70.87]

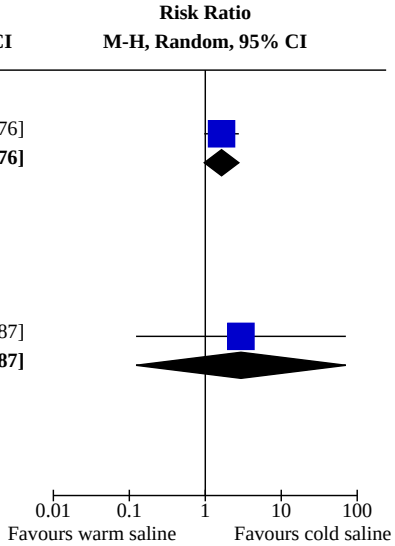
Analysis 5.1. Comparison 5: Crystalloid: warm vs cold, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Warm saline Events	Warm saline Total	Cold saline Events	Cold saline Total	Weight	Risk Ratio M-H, Random, 95% CI
Jorgensen 2000	23	57	22	56	100.0%	1.03 [0.65 , 1.62]
Total (95% CI)		**57**		**56**	**100.0%**	**1.03 [0.65 , 1.62]**
Total events:	23		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Not applicable						



Analysis 5.2. Comparison 5: Crystalloid: warm vs cold, Outcome 2: Women with nausea and/or vomiting

Study or Subgroup	Warm saline Events	Warm saline Total	Cold saline Events	Cold saline Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Nausea						
Jorgensen 2000	25	57	15	56	100.0%	1.64 [0.97 , 2.76]
Subtotal (95% CI)		**57**		**56**	**100.0%**	**1.64 [0.97 , 2.76]**
Total events:	25		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
5.2.2 Vomiting						
Jorgensen 2000	1	57	0	56	100.0%	2.95 [0.12 , 70.87]
Subtotal (95% CI)		**57**		**56**	**100.0%**	**2.95 [0.12 , 70.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						

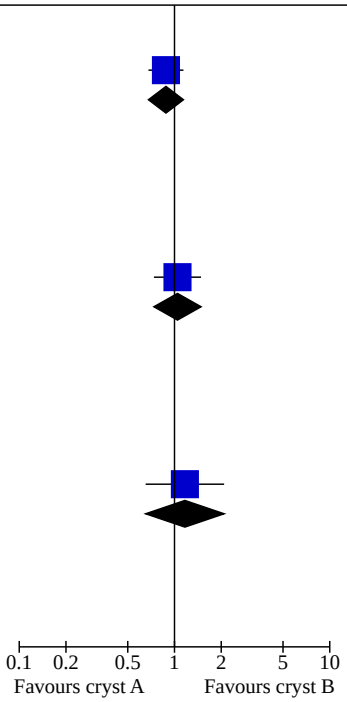


Comparison 6. Crystalloid vs another crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Women with hypotension requiring intervention	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 Dextrose + saline vs saline	1	120	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.68, 1.14]
6.1.2 Glucose vs saline	1	70	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.74, 1.48]
6.1.3 Ringer's lactate vs saline	1	60	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.65, 2.09]
6.2 Neonates with acidosis: Ringer's lactate vs saline	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Neonates with acidosis: dextrose vs saline	1	120	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.39, 3.72]
6.4 Neonates with Apgar score < 7 at 5 min	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.5 Neonates with Apgar score < 8 at 5 min	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

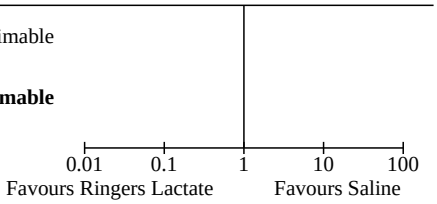
Analysis 6.1. Comparison 6: Crystalloid vs another crystalloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Crystalloid A Events	Crystalloid A Total	Crystalloid B Events	Crystalloid B Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Dextrose + saline vs saline						
Wilson 1999	37	60	42	60	100.0%	0.88 [0.68 , 1.14]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**0.88 [0.68 , 1.14]**
Total events:	37		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
6.1.2 Glucose vs saline						
Wilson 1998	23	35	22	35	100.0%	1.05 [0.74 , 1.48]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.05 [0.74 , 1.48]**
Total events:	23		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
6.1.3 Ringer's lactate vs saline						
Alimian 2014	14	30	12	30	100.0%	1.17 [0.65 , 2.09]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.17 [0.65 , 2.09]**
Total events:	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						



Analysis 6.2. Comparison 6: Crystalloid vs another crystalloid, Outcome 2: Neonates with acidosis: Ringer's lactate vs saline

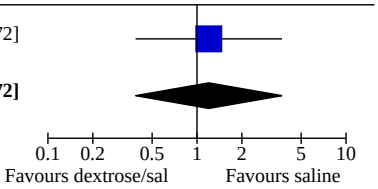
Study or Subgroup	Ringer's lactate Events	Ringer's lactate Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alimian 2014	0	30	0	30		Not estimable
Total (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 6.3. Comparison 6: Crystalloid vs another crystalloid, Outcome 3: Neonates with acidosis: dextrose vs saline

Study or Subgroup	Favours dextrose/sal Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Wilson 1999	6	60	5	60	100.0%	1.20 [0.39 , 3.72]
Total (95% CI)		**60**		**60**	**100.0%**	**1.20 [0.39 , 3.72]**
Total events:	6		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Crystalloid vs another crystalloid, Outcome 4: Neonates with Apgar score < 7 at 5 min

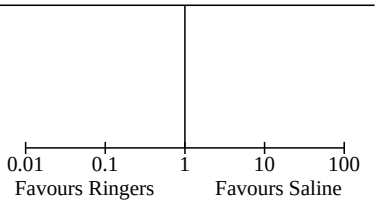
Study or Subgroup	Dextrose/saline Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Wilson 1999	0	60	0	60		Not estimable
Total (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			

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

Analysis 6.5. Comparison 6: Crystalloid vs another crystalloid, Outcome 5: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Ringer's lact Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alimian 2014	0	30	0	30		Not estimable
Total (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			

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



Comparison 7. Colloid vs crystalloid

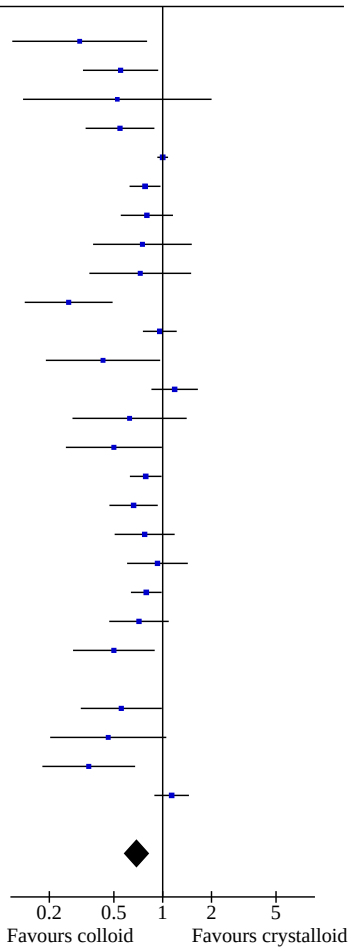
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Women with hypotension requiring intervention	27	2009	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.58, 0.81]
7.2 Women with hypertension requiring intervention	3	327	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.09, 4.46]
7.3 Women with cardiac dysrhythmia	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3.1 Tachycardia	1	60	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.53]
7.3.2 Bradycardia	5	413	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.54, 1.78]
7.4 Women with nausea and/or vomiting	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.4.1 Nausea and/or vomiting	14	1058	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.66, 1.19]
7.4.2 Nausea	5	390	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.77, 1.58]
7.4.3 Vomiting	4	320	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.55, 3.27]
7.5 Neonates with acidosis (pH < 7.2)	6	678	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.15, 4.52]
7.6 Neonates: Apgar score	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.6.1 Apgar < 7 at 5 min	2	127	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 2.90]
7.6.2 Apgar < 8 at 5 min	10	730	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 2.05]

Analysis 7.1. Comparison 7: Colloid vs crystalloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Alimian 2014	4	30	26	60	2.0%	0.31 [0.12 , 0.80]
Arora 2015 (1)	11	30	20	30	3.7%	0.55 [0.32 , 0.94]
Bottiger 2010	3	32	5	28	1.2%	0.53 [0.14 , 2.00]
Bouchnak 2012	12	30	22	30	3.9%	0.55 [0.33 , 0.89]
Cardoso 2004a	25	25	25	25	5.9%	1.00 [0.93 , 1.08]
Dahlgren 2005	37	56	45	53	5.4%	0.78 [0.62 , 0.97]
Dahlgren 2007	17	28	19	25	4.6%	0.80 [0.55 , 1.16]
El-Mekawy 2012	9	30	12	30	2.9%	0.75 [0.37 , 1.51]
Embu 2011	8	25	11	25	2.8%	0.73 [0.35 , 1.50]
French 1999	10	80	38	80	3.3%	0.26 [0.14 , 0.49]
Gunaydin 2009	24	30	25	30	5.3%	0.96 [0.76 , 1.22]
Hasan 2012	6	30	14	30	2.5%	0.43 [0.19 , 0.96]
Jabalameli 2011	32	50	27	50	4.8%	1.19 [0.85 , 1.65]
Karinen 1995	5	13	8	13	2.5%	0.63 [0.28 , 1.41]
Lin 1999	8	30	16	30	3.0%	0.50 [0.25 , 0.99]
Madi-Jebara 2008	39	61	48	59	5.4%	0.79 [0.63 , 0.98]
Mercier 2014	30	82	47	85	4.8%	0.66 [0.47 , 0.93]
Ozkan 2004	24	75	31	75	4.3%	0.77 [0.51 , 1.19]
Perumal 2004	13	20	14	20	4.3%	0.93 [0.60 , 1.43]
Romdhani 2014	33	48	46	53	5.4%	0.79 [0.64 , 0.98]
Selvan 2004	20	40	14	20	4.3%	0.71 [0.47 , 1.09]
Siddik 2000	8	20	16	20	3.5%	0.50 [0.28 , 0.89]
Singh 2009	0	30	0	30		Not estimable
Ueyama 1999	10	24	9	12	3.5%	0.56 [0.31 , 0.99]
Unlugenc 2015	6	30	13	30	2.4%	0.46 [0.20 , 1.05]
Upadya 2016	7	25	20	25	3.1%	0.35 [0.18 , 0.68]
Yorozu 2002	27	32	26	35	5.3%	1.14 [0.89 , 1.45]
Total (95% CI)		**1006**		**1003**	**100.0%**	**0.69 [0.58 , 0.81]**
Total events:	428		597			

Heterogeneity: Tau² = 0.12; Chi² = 140.36, df = 25 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable

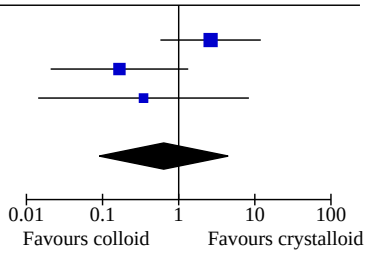


Footnotes
(1) coiloid preload arm only included here

Analysis 7.2. Comparison 7: Colloid vs crystalloid, Outcome 2: Women with hypertension requiring intervention

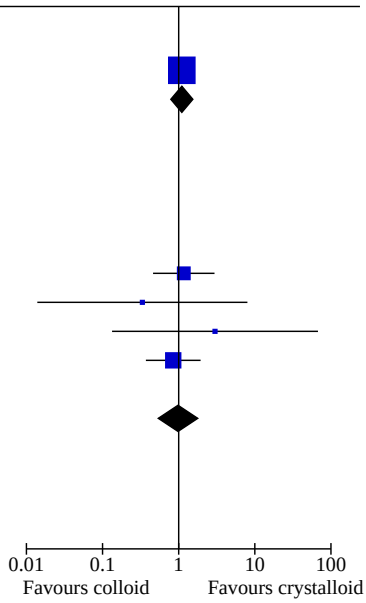
Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Bottiger 2010	6	32	2	28	42.6%	2.63 [0.58 , 11.98]
Jabalameli 2011	1	50	6	50	34.7%	0.17 [0.02 , 1.33]
Mercier 2014	0	82	1	85	22.7%	0.35 [0.01 , 8.36]
Total (95% CI)		**164**		**163**	**100.0%**	**0.64 [0.09 , 4.46]**
Total events:	7		9			

Heterogeneity: Tau² = 1.72; Chi² = 4.87, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



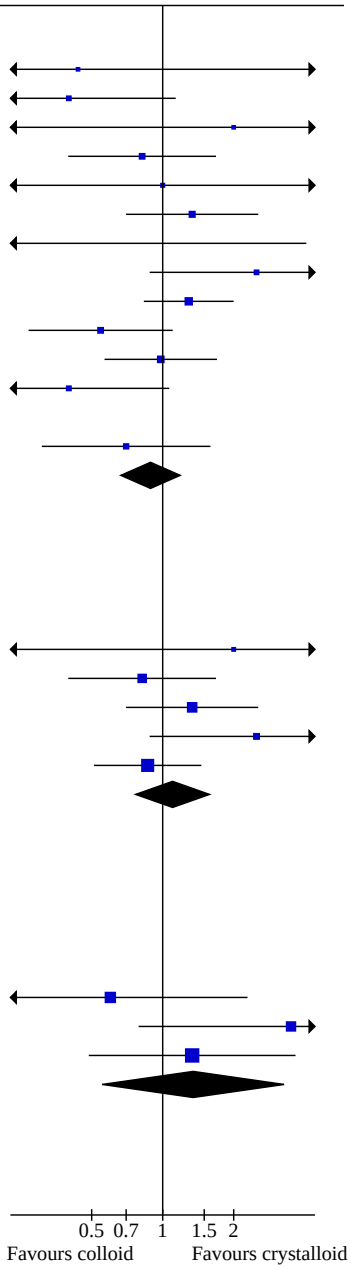
Analysis 7.3. Comparison 7: Colloid vs crystalloid, Outcome 3: Women with cardiac dysrhythmia

Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 Tachycardia						
Bouchnak 2012	22	30	20	30	100.0%	1.10 [0.79 , 1.53]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.10 [0.79 , 1.53]**
Total events:	22		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
7.3.2 Bradycardia						
Bottiger 2010	8	32	6	28	41.0%	1.17 [0.46 , 2.95]
Jabalameli 2011	0	50	1	50	3.5%	0.33 [0.01 , 7.99]
Karinen 1995	1	13	0	13	3.7%	3.00 [0.13 , 67.51]
Mercier 2014	9	82	11	85	51.8%	0.85 [0.37 , 1.94]
Singh 2009	0	30	0	30		Not estimable
Subtotal (95% CI)		**207**		**206**	**100.0%**	**0.98 [0.54 , 1.78]**
Total events:	18		18			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						



Analysis 7.4. Comparison 7: Colloid vs crystalloid, Outcome 4: Women with nausea and/or vomiting

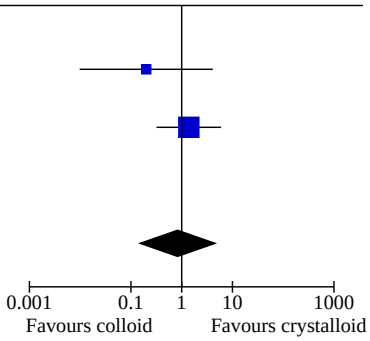
Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
7.4.1 Nausea and/or vomiting						
Bottiger 2010	1	32	2	28	1.4%	0.44 [0.04 , 4.57]
Bouchnak 2012	4	30	10	30	6.1%	0.40 [0.14 , 1.14]
Cardoso 2004a	2	25	1	25	1.5%	2.00 [0.19 , 20.67]
El-Mekawy 2012	9	30	11	30	10.4%	0.82 [0.40 , 1.68]
Embu 2011	3	25	3	25	3.3%	1.00 [0.22 , 4.49]
Gunaydin 2009	12	30	12	40	12.0%	1.33 [0.70 , 2.54]
Jabalameli 2011	0	50	2	50	0.9%	0.20 [0.01 , 4.06]
Lin 1999	10	30	4	30	6.1%	2.50 [0.88 , 7.10]
Madi-Jebara 2008	28	61	21	59	17.6%	1.29 [0.83 , 2.00]
Mercier 2014	10	82	19	85	10.8%	0.55 [0.27 , 1.10]
Romdhani 2014	16	48	18	53	14.3%	0.98 [0.57 , 1.70]
Siddik 2000	4	20	10	20	6.7%	0.40 [0.15 , 1.07]
Singh 2009	0	30	0	30		Not estimable
Unlugenc 2015	7	30	10	30	8.7%	0.70 [0.31 , 1.59]
Subtotal (95% CI)		**523**		**535**	**100.0%**	**0.89 [0.66 , 1.19]**
Total events:	106		123			
Heterogeneity: Tau² = 0.07; Chi² = 16.92, df = 12 (P = 0.15); I² = 29%						
Test for overall effect: Z = 0.80 (P = 0.42)						
7.4.2 Nausea						
Cardoso 2004a	2	25	1	25	2.4%	2.00 [0.19 , 20.67]
El-Mekawy 2012	9	30	11	30	22.0%	0.82 [0.40 , 1.68]
Gunaydin 2009	12	30	12	40	26.7%	1.33 [0.70 , 2.54]
Lin 1999	10	30	4	30	11.2%	2.50 [0.88 , 7.10]
Ozkan 2004	19	75	22	75	37.7%	0.86 [0.51 , 1.46]
Subtotal (95% CI)		**190**		**200**	**100.0%**	**1.10 [0.77 , 1.58]**
Total events:	52		50			
Heterogeneity: Tau² = 0.02; Chi² = 4.45, df = 4 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.52 (P = 0.60)						
7.4.3 Vomiting						
Cardoso 2004a	0	25	0	25		Not estimable
El-Mekawy 2012	3	30	5	30	30.4%	0.60 [0.16 , 2.29]
Gunaydin 2009	7	30	2	30	26.2%	3.50 [0.79 , 15.49]
Ozkan 2004	8	75	6	75	43.4%	1.33 [0.49 , 3.66]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**1.35 [0.55 , 3.27]**
Total events:	18		13			
Heterogeneity: Tau² = 0.21; Chi² = 3.00, df = 2 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.66 (P = 0.51)						



Analysis 7.5. Comparison 7: Colloid vs crystalloid, Outcome 5: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Alimian 2014	0	30	0	60		Not estimable
French 1999	0	80	2	80	26.4%	0.20 [0.01 , 4.10]
Jabalameli 2011	0	50	0	50		Not estimable
Mercier 2014	4	82	3	85	73.6%	1.38 [0.32 , 5.99]
Romdhani 2014	0	48	0	53		Not estimable
Unlugenc 2015	0	30	0	30		Not estimable
Total (95% CI)		**320**		**358**	**100.0%**	**0.83 [0.15 , 4.52]**
Total events:	4		5			

Heterogeneity: Tau² = 0.46; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



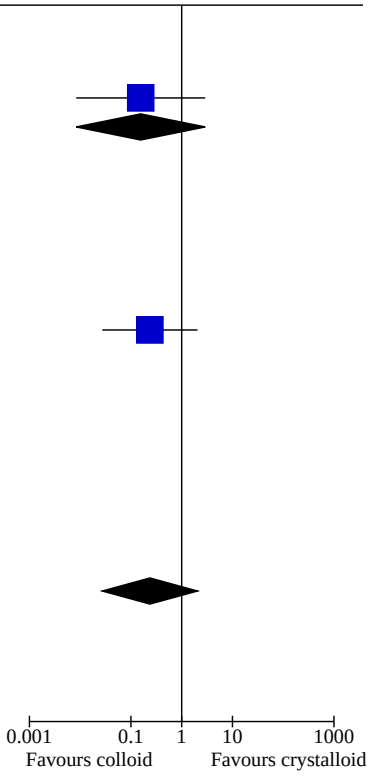
Analysis 7.6. Comparison 7: Colloid vs crystalloid, Outcome 6: Neonates: Apgar score

Study or Subgroup	Colloid Events	Colloid Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
7.6.1 Apgar < 7 at 5 min						
Singh 2009	0	30	0	30		Not estimable
Yorozu 2002	0	32	3	35	100.0%	0.16 [0.01 , 2.90]
Subtotal (95% CI)		**62**		**65**	**100.0%**	**0.16 [0.01 , 2.90]**
Total events:	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)

7.6.2 Apgar < 8 at 5 min						
Alimian 2014	0	30	0	60		Not estimable
Dahlgren 2005	1	56	4	53	100.0%	0.24 [0.03 , 2.05]
El-Mekawy 2012	0	30	0	30		Not estimable
Gunaydin 2009	0	30	0	30		Not estimable
Hasan 2012	0	30	0	30		Not estimable
Jabalameli 2011	0	50	0	50		Not estimable
Lin 1999	0	30	0	30		Not estimable
Romdhani 2014	0	48	0	53		Not estimable
Siddik 2000	0	20	0	20		Not estimable
Upadya 2016	0	25	0	25		Not estimable
Subtotal (95% CI)		**349**		**381**	**100.0%**	**0.24 [0.03 , 2.05]**
Total events:	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



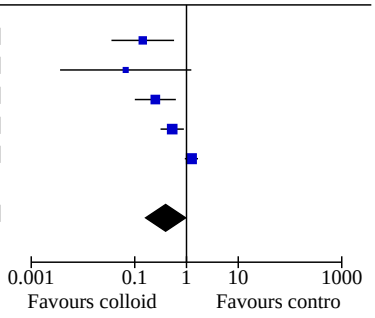
Comparison 8. Colloid vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Women with hypotension requiring intervention	5	426	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.16, 0.96]
8.2 Women with bradycardia	1	54	Risk Ratio (M-H, Random, 95% CI)	7.70 [0.46, 127.78]
8.3 Women with nausea and/or vomiting	2	245	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.75, 3.64]
8.4 Neonates with acidosis (pH < 7.2)	1	205	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.34, 4.48]
8.5 Neonates with Apgar score < 7 at 5 min	4	221	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.24]
8.6 Neonatal Apgar < 8 at 5 min	1	205	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 8.1. Comparison 8: Colloid vs control, Outcome 1: Women with hypotension requiring intervention

	Colloid		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Hasan 2012	2	30	14	30	16.8%	0.14 [0.04 , 0.57]	
Mathru 1980	0	46	3	21	7.0%	0.07 [0.00 , 1.24]	
Nishikawa 2007	5	36	10	18	22.1%	0.25 [0.10 , 0.62]	
Riley 1995	9	20	17	20	26.2%	0.53 [0.32 , 0.89]	
Tawfik 2014	54	103	43	102	27.9%	1.24 [0.93 , 1.67]	
Total (95% CI)		**235**		**191**	**100.0%**	**0.40 [0.16 , 0.96]**	
Total events:	70		87				

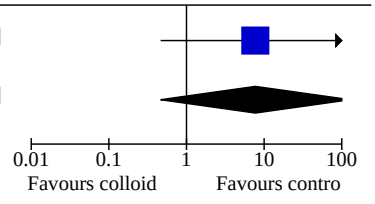
Heterogeneity: Tau² = 0.71; Chi² = 27.09, df = 4 (P < 0.0001); I² = 85%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Colloid vs control, Outcome 2: Women with bradycardia

	Colloid		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Nishikawa 2007	7	36	0	18	100.0%	7.70 [0.46 , 127.78]	
Total (95% CI)		**36**		**18**	**100.0%**	**7.70 [0.46 , 127.78]**	
Total events:	7		0				

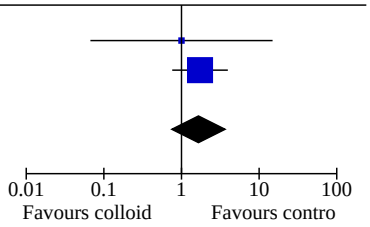
Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Colloid vs control, Outcome 3: Women with nausea and/or vomiting

Study or Subgroup	Colloid Events	Colloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Riley 1995	1	20	1	20	8.5%	1.00 [0.07 , 14.90]
Tawfik 2014	14	103	8	102	91.5%	1.73 [0.76 , 3.95]
Total (95% CI)		**123**		**122**	**100.0%**	**1.65 [0.75 , 3.64]**
Total events:	15		9			

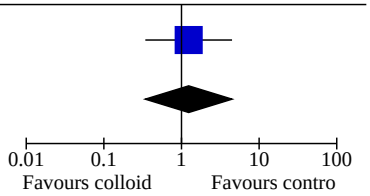
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Colloid vs control, Outcome 4: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Colloid Events	Colloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Tawfik 2014	5	103	4	102	100.0%	1.24 [0.34 , 4.48]
Total (95% CI)		**103**		**102**	**100.0%**	**1.24 [0.34 , 4.48]**
Total events:	5		4			

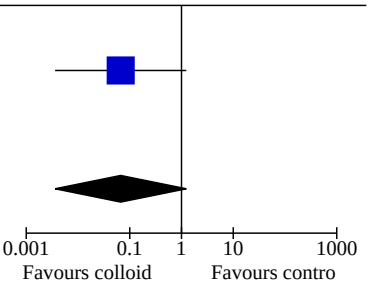
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8: Colloid vs control, Outcome 5: Neonates with Apgar score < 7 at 5 min

Study or Subgroup	Colloid Events	Colloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hasan 2012	0	30	0	30		Not estimable
Mathru 1980	0	46	3	21	100.0%	0.07 [0.00 , 1.24]
Nishikawa 2007	0	36	0	18		Not estimable
Riley 1995	0	20	0	20		Not estimable
Total (95% CI)		**132**		**89**	**100.0%**	**0.07 [0.00 , 1.24]**
Total events:	0		3			

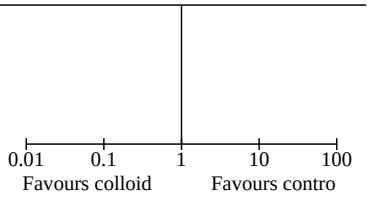
Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8: Colloid vs control, Outcome 6: Neonatal Apgar < 8 at 5 min

Study or Subgroup	Colloid Events	Colloid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Tawfik 2014	0	103	0	102		Not estimable
Total (95% CI)		**103**		**102**		**Not estimable**
Total events:	0		0			

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



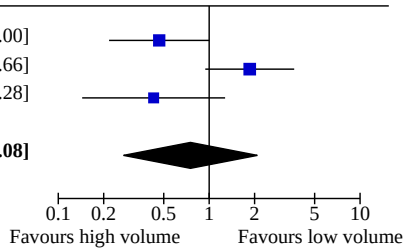
Comparison 9. Colloid: different volumes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Women with hypotension requiring intervention	3	134	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.27, 2.08]
9.2 Apgar < 9 at 5 min	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 9.1. Comparison 9: Colloid: different volumes, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	High volume Events	High volume Total	Low volume Events	Low volume Total	Weight	Risk Ratio M-H, Random, 95% CI
Davies 2006	7	35	15	35	34.8%	0.47 [0.22 , 1.00]
Selvan 2004	13	20	7	20	36.3%	1.86 [0.94 , 3.66]
Ueyama 1999	3	12	7	12	28.9%	0.43 [0.14 , 1.28]
Total (95% CI)		**67**		**67**	**100.0%**	**0.75 [0.27 , 2.08]**
Total events:	23		29			

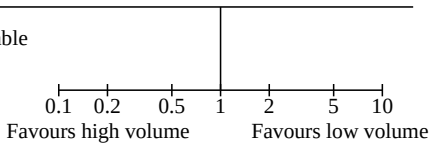
Heterogeneity: Tau² = 0.63; Chi² = 9.11, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Colloid: different volumes, Outcome 2: Apgar < 9 at 5 min

Study or Subgroup	High volume Events	High volume Total	Low volume Events	Low volume Total	Risk Ratio M-H, Random, 95% CI
Davies 2006	0	35	0	35	Not estimable

Test for subgroup differences: Not applicable



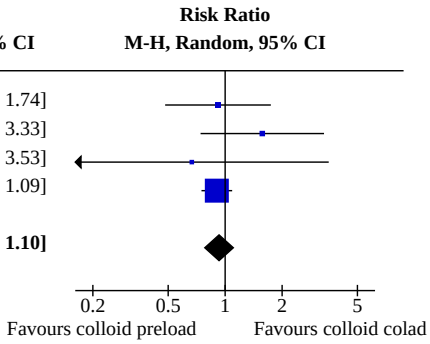
Comparison 10. Colloid preload vs colloid coload

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Women with hypotension requiring intervention	4	320	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.10]
10.2 Women with cardiac dysrhythmia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.2.1 Bradycardia	2	82	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.20, 2.88]
10.2.2 Tachycardia	1	46	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.3 Women with nausea and/or vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.3.1 Nausea and/or vomiting	1	178	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.63, 1.35]
10.3.2 Nausea	1	46	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.15, 6.51]
10.3.3 Vomiting	1	46	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.4 Women with anaphylaxis	1	178	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.5 Neonates with Apgar score < 7 at 5 min	1	36	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 10.1. Comparison 10: Colloid preload vs colloid coload, Outcome 1: Women with hypotension requiring intervention

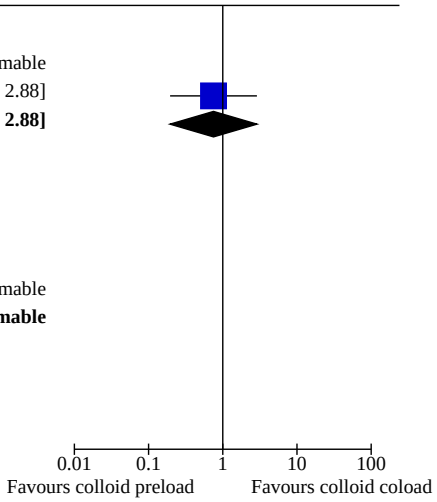
Study or Subgroup	colloid preload Events	Total	colloid coload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arora 2015	11	30	12	30	7.3%	0.92 [0.48 , 1.74]
Carvalho 2009	11	23	7	23	5.3%	1.57 [0.74 , 3.33]
Nishikawa 2007	2	18	3	18	1.1%	0.67 [0.13 , 3.53]
Siddik-Sayyid 2009	61	90	66	88	86.3%	0.90 [0.75 , 1.09]
Total (95% CI)		**161**		**159**	**100.0%**	**0.93 [0.78 , 1.10]**
Total events:	85		88			

Heterogeneity: Tau² = 0.00; Chi² = 2.19, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



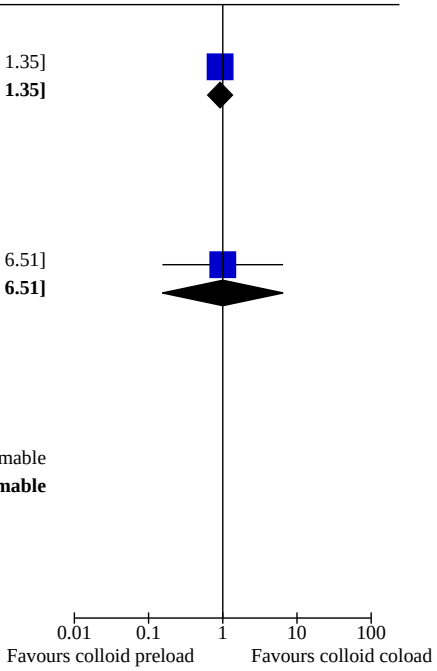
Analysis 10.2. Comparison 10: Colloid preload vs colloid coload, Outcome 2: Women with cardiac dysrhythmia

Study or Subgroup	Colloid preload Events	Total	Colloid coload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Bradycardia						
Carvalho 2009	0	23	0	23		Not estimable
Nishikawa 2007	3	18	4	18	100.0%	0.75 [0.20 , 2.88]
Subtotal (95% CI)		**41**		**41**	**100.0%**	**0.75 [0.20 , 2.88]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
10.2.2 Tachycardia						
Carvalho 2000	0	23	0	23		Not estimable
Subtotal (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 10.3. Comparison 10: Colloid preload vs colloid coload, Outcome 3: Women with nausea and/or vomiting

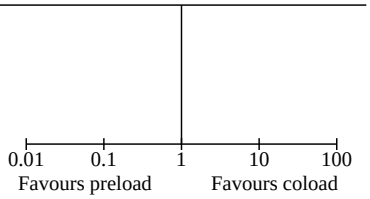
Study or Subgroup	colloid preload Events	Total	colloid coload Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Nausea and/or vomiting						
Siddik-Sayyid 2009	32	90	34	88	100.0%	0.92 [0.63 , 1.35]
Subtotal (95% CI)		**90**		**88**	**100.0%**	**0.92 [0.63 , 1.35]**
Total events:	32		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
10.3.2 Nausea						
Carvalho 2009	2	23	2	23	100.0%	1.00 [0.15 , 6.51]
Subtotal (95% CI)		**23**		**23**	**100.0%**	**1.00 [0.15 , 6.51]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
10.3.3 Vomiting						
Carvalho 2009	0	23	0	23		Not estimable
Subtotal (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 10.4. Comparison 10: Colloid preload vs colloid coload, Outcome 4: Women with anaphylaxis

Study or Subgroup	preload Events	preload Total	coload Events	coload Total	Weight	Risk Ratio M-H, Random, 95% CI
Siddik-Sayyid 2009	0	90	0	88		Not estimable
Total (95% CI)		**90**		**88**		**Not estimable**
Total events:	0		0			

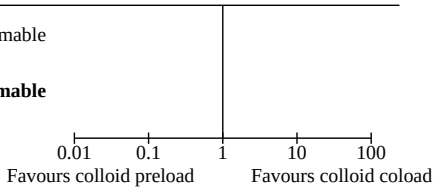
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10: Colloid preload vs colloid coload, Outcome 5: Neonates with Apgar score < 7 at 5 min

Study or Subgroup	colloid preload Events	colloid preload Total	colloid coload Events	colloid coload Total	Weight	Risk Ratio M-H, Random, 95% CI
Nishikawa 2007	0	18	0	18		Not estimable
Total (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			

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

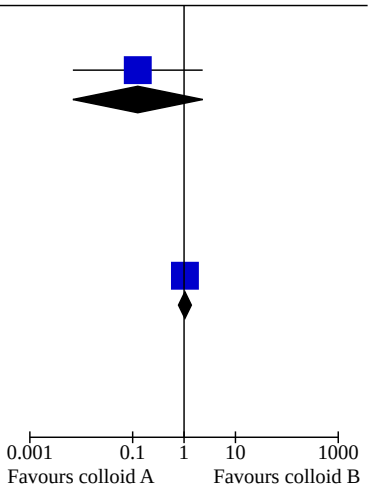


Comparison 11. Colloid + crystalloid vs another colloid + crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Women with hypotension requiring intervention	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1.1 Albumin or dextrose vs dextrose	1	45	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.30]
11.1.2 Unbalanced vs balanced hydroxyethyl starch	1	51	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.78, 1.39]
11.2 Neonates: Apgar score < 7	1	45	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.30]
11.2.1 Albumin or dextrose vs dextrose	1	45	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.30]
11.3 Neonates with Apgar score < 8 at 5 min	1	51	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.3.1 Unbalanced vs balanced hydroxyethyl starch	1	51	Risk Ratio (M-H, Random, 95% CI)	Not estimable

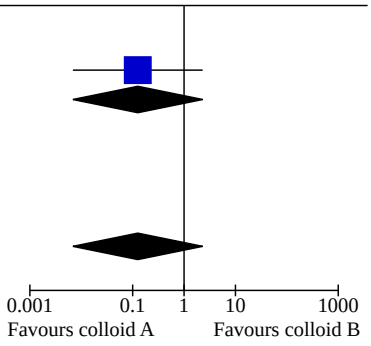
Analysis 11.1. Comparison 11: Colloid + crystalloid vs another colloid + crystalloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Colloid A Events	Colloid A Total	Colloid B Events	Colloid B Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Albumin or dextrose vs dextrose						
Mathru 1980	0	24	3	21	100.0%	0.13 [0.01 , 2.30]
Subtotal (95% CI)		**24**		**21**	**100.0%**	**0.13 [0.01 , 2.30]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
11.1.2 Unbalanced vs balanced hydroxyethyl starch						
Marciniak 2013	20	25	20	26	100.0%	1.04 [0.78 , 1.39]
Subtotal (95% CI)		**25**		**26**	**100.0%**	**1.04 [0.78 , 1.39]**
Total events:	20		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						



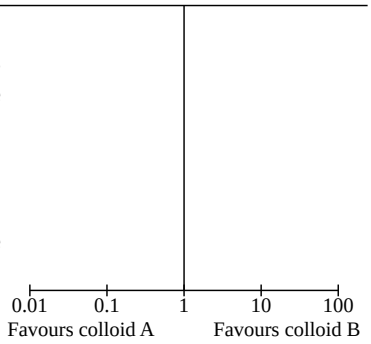
Analysis 11.2. Comparison 11: Colloid + crystalloid vs another colloid + crystalloid, Outcome 2: Neonates: Apgar score < 7

Study or Subgroup	Colloid A Events	Colloid A Total	Colloid B Events	Colloid B Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 Albumin or dextrose vs dextrose						
Mathru 1980	0	24	3	21	100.0%	0.13 [0.01 , 2.30]
Subtotal (95% CI)		**24**		**21**	**100.0%**	**0.13 [0.01 , 2.30]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**24**		**21**	**100.0%**	**0.13 [0.01 , 2.30]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Not applicable						



Analysis 11.3. Comparison 11: Colloid + crystalloid vs another colloid + crystalloid, Outcome 3: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Colloid A Events	Colloid A Total	Colloid B Events	Colloid B Total	Weight	Risk Ratio M-H, Random, 95% CI
11.3.1 Unbalanced vs balanced hydroxyethyl starch						
Marciniak 2013	0	25	0	26		Not estimable
Subtotal (95% CI)		**25**		**26**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**25**		**26**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



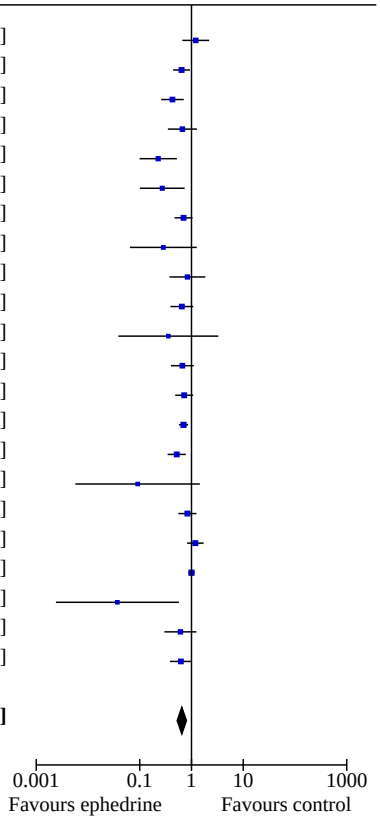
Comparison 12. Ephedrine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Women with hypotension requiring intervention	22	1401	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.80]
12.2 Women with hypertension requiring intervention	7	520	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.00, 2.61]
12.3 Women with cardiac arrhythmia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.3.1 Tachycardia	2	93	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.74, 1.70]
12.3.2 Bradycardia	2	103	Risk Ratio (M-H, Random, 95% CI)	14.46 [0.87, 241.09]
12.4 Women with nausea and/or vomiting	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.4.1 Nausea and/or vomiting	5	219	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.22, 2.34]
12.4.2 Nausea	8	620	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.96]
12.4.3 Vomiting	6	516	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.44, 1.07]
12.5 Neonates with acidosis (pH < 7.2)	9	576	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.67, 2.49]
12.6 Neonates: Apgar score	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.6.1 Apgar < 8 at 5 min	10	579	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.6.2 Apgar < 7 at 5 min	4	263	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.34, 3.81]

Analysis 12.1. Comparison 12: Ephedrine vs control, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 1999a	29	60	8	20	4.8%	1.21 [0.67 , 2.20]
Carvalho 1999b	36	80	14	20	6.3%	0.64 [0.44 , 0.94]
Carvalho 2000	18	80	21	40	5.4%	0.43 [0.26 , 0.71]
Damevski 2011	8	20	12	20	4.5%	0.67 [0.35 , 1.27]
Gomaa 2003	5	30	22	30	3.5%	0.23 [0.10 , 0.52]
Grubb 2004	3	12	11	12	2.8%	0.27 [0.10 , 0.74]
Hall 1994	12	19	9	10	6.1%	0.70 [0.47 , 1.05]
Imam 2012	2	30	7	30	1.5%	0.29 [0.06 , 1.26]
King 1998	5	10	6	10	3.6%	0.83 [0.37 , 1.85]
Loughrey 2002	18	46	12	20	5.3%	0.65 [0.39 , 1.08]
Mathru 1980	1	42	3	45	0.8%	0.36 [0.04 , 3.30]
Morgan 2000	26	78	12	24	5.3%	0.67 [0.40 , 1.11]
Moslemi 2015	15	27	20	26	6.1%	0.72 [0.49 , 1.07]
Ngan Kee 2000	40	60	19	20	7.4%	0.70 [0.57 , 0.86]
Ozkan 2004	28	100	27	50	6.1%	0.52 [0.35 , 0.78]
Ramin 1994	0	10	5	10	0.5%	0.09 [0.01 , 1.45]
Singh 2016	15	25	18	25	6.1%	0.83 [0.56 , 1.25]
Torres unpub	19	25	16	25	6.3%	1.19 [0.82 , 1.71]
Tsen 2000	19	20	19	20	7.7%	1.00 [0.87 , 1.15]
Turkoz 2002	0	15	13	15	0.5%	0.04 [0.00 , 0.57]
Ueyama 1992	11	60	12	40	4.1%	0.61 [0.30 , 1.25]
Webb 1998	10	20	16	20	5.5%	0.63 [0.38 , 1.02]
Total (95% CI)		**869**		**532**	**100.0%**	**0.65 [0.53 , 0.80]**
Total events:	320		302			

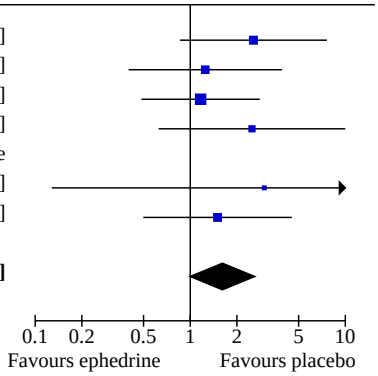
Heterogeneity: Tau² = 0.14; Chi² = 82.62, df = 21 (P < 0.00001); I² = 75%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Ephedrine vs control, Outcome 2: Women with hypertension requiring intervention

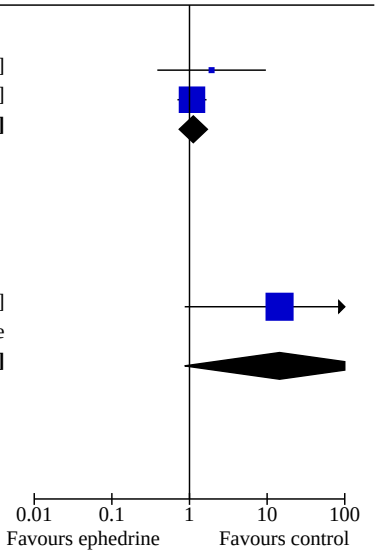
Study or Subgroup	Ephedrine Events	Ephedrine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 1999a	23	60	3	20	19.3%	2.56 [0.86 , 7.61]
Carvalho 1999b	15	80	3	20	17.7%	1.25 [0.40 , 3.90]
Carvalho 2000	14	80	6	40	29.8%	1.17 [0.48 , 2.81]
Ngan Kee 2000	15	60	2	20	12.0%	2.50 [0.63 , 10.00]
Singh 2016	0	25	0	25		Not estimable
Torres unpub	1	25	0	25	2.3%	3.00 [0.13 , 70.30]
Webb 1998	6	20	4	20	18.9%	1.50 [0.50 , 4.52]
Total (95% CI)		**350**		**170**	**100.0%**	**1.61 [1.00 , 2.61]**
Total events:	74		18			

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable



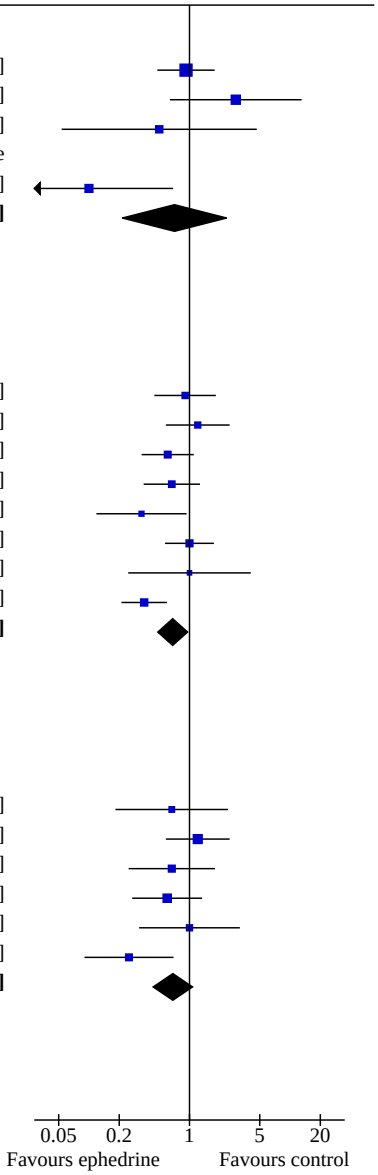
Analysis 12.3. Comparison 12: Ephedrine vs control, Outcome 3: Women with cardiac arrhythmia

Study or Subgroup	Ephedrine Events	Ephedrine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Tachycardia						
Moslemi 2015	4	27	2	26	6.7%	1.93 [0.39 , 9.63]
Webb 1998	14	20	13	20	93.3%	1.08 [0.70 , 1.66]
Subtotal (95% CI)		**47**		**46**	**100.0%**	**1.12 [0.74 , 1.70]**
Total events:	18		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
12.3.2 Bradycardia						
Moslemi 2015	7	27	0	26	100.0%	14.46 [0.87 , 241.09]
Singh 2016	0	25	0	25		Not estimable
Subtotal (95% CI)		**52**		**51**	**100.0%**	**14.46 [0.87 , 241.09]**
Total events:	7		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: Chi² = 3.11, df = 1 (P = 0.08), I² = 67.8%						



Analysis 12.4. Comparison 12: Ephedrine vs control, Outcome 4: Women with nausea and/or vomiting

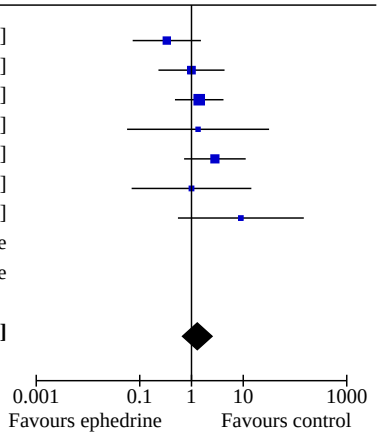
Study or Subgroup	Ephedrine Events	Ephedrine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.4.1 Nausea and/or vomiting						
Loughrey 2002	17	46	8	20	37.5%	0.92 [0.48 , 1.78]
Moslemi 2015	6	27	2	26	25.3%	2.89 [0.64 , 13.04]
Ramin 1994	1	10	2	10	17.0%	0.50 [0.05 , 4.67]
Singh 2016	0	25	0	25		Not estimable
Turkoz 2002	1	15	10	15	20.1%	0.10 [0.01 , 0.69]
Subtotal (95% CI)		**123**		**96**	**100.0%**	**0.71 [0.22 , 2.34]**
Total events:	25		22			
Heterogeneity: Tau² = 0.88; Chi² = 7.94, df = 3 (P = 0.05); I² = 62%						
Test for overall effect: Z = 0.56 (P = 0.57)						
12.4.2 Nausea						
Carvalho 1999a	19	60	7	20	12.8%	0.90 [0.45 , 1.83]
Carvalho 1999b	29	80	6	20	12.3%	1.21 [0.58 , 2.51]
Carvalho 2000	17	80	14	40	15.1%	0.61 [0.33 , 1.10]
Damevski 2011	8	20	12	20	14.0%	0.67 [0.35 , 1.27]
Grubb 2004	3	12	9	12	7.9%	0.33 [0.12 , 0.94]
Ngan Kee 2000	27	60	9	20	16.0%	1.00 [0.57 , 1.75]
Olsen 1994	3	13	3	13	4.9%	1.00 [0.25 , 4.07]
Ozkan 2004	17	100	24	50	17.0%	0.35 [0.21 , 0.60]
Subtotal (95% CI)		**425**		**195**	**100.0%**	**0.68 [0.48 , 0.96]**
Total events:	123		84			
Heterogeneity: Tau² = 0.11; Chi² = 13.12, df = 7 (P = 0.07); I² = 47%						
Test for overall effect: Z = 2.21 (P = 0.03)						
12.4.3 Vomiting						
Carvalho 1999a	6	60	3	20	10.3%	0.67 [0.18 , 2.42]
Carvalho 1999b	29	80	6	20	24.4%	1.21 [0.58 , 2.51]
Carvalho 2000	8	80	6	40	15.9%	0.67 [0.25 , 1.79]
Damevski 2011	6	20	10	20	21.6%	0.60 [0.27 , 1.34]
Olsen 1994	4	13	4	13	12.5%	1.00 [0.32 , 3.17]
Ozkan 2004	5	100	10	50	15.2%	0.25 [0.09 , 0.69]
Subtotal (95% CI)		**353**		**163**	**100.0%**	**0.68 [0.44 , 1.07]**
Total events:	58		39			
Heterogeneity: Tau² = 0.08; Chi² = 6.64, df = 5 (P = 0.25); I² = 25%						
Test for overall effect: Z = 1.66 (P = 0.10)						



Analysis 12.5. Comparison 12: Ephedrine vs control, Outcome 5: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Ephedrine Events	Ephedrine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 1999a	3	60	3	20	16.7%	0.33 [0.07 , 1.52]
Carvalho 1999b	8	80	2	20	17.7%	1.00 [0.23 , 4.35]
Carvalho 2000	11	78	4	40	30.1%	1.41 [0.48 , 4.15]
Loughrey 2002	1	46	0	20	4.2%	1.34 [0.06 , 31.56]
Ngan Kee 2000	17	57	2	19	20.1%	2.83 [0.72 , 11.15]
Olsen 1994	1	13	1	13	5.8%	1.00 [0.07 , 14.34]
Ramin 1994	4	10	0	10	5.3%	9.00 [0.55 , 147.95]
Singh 2016	0	25	0	25		Not estimable
Webb 1998	0	20	0	20		Not estimable
Total (95% CI)		**389**		**187**	**100.0%**	**1.29 [0.67 , 2.49]**
Total events:	45		12			

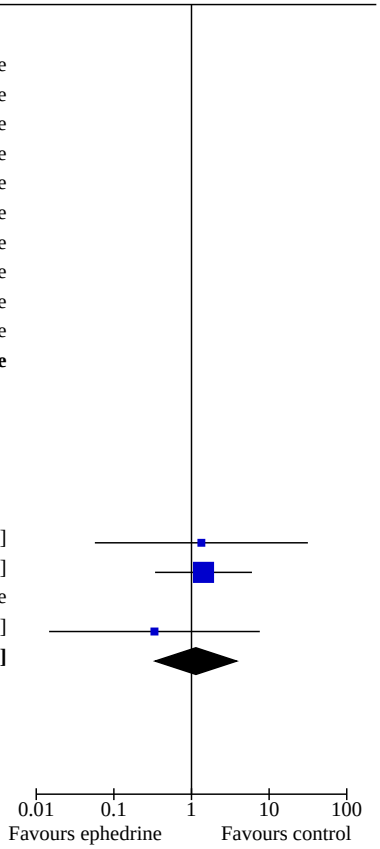
Heterogeneity: Tau² = 0.07; Chi² = 6.55, df = 6 (P = 0.36); I² = 8%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 12.6. Comparison 12: Ephedrine vs control, Outcome 6: Neonates: Apgar score

Study or Subgroup	Ephedrine Events	Ephedrine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.6.1 Apgar < 8 at 5 min						
Carvalho 1999a	0	60	0	20		Not estimable
Carvalho 1999b	0	80	0	20		Not estimable
Carvalho 2000	0	80	0	40		Not estimable
King 1998	0	10	0	10		Not estimable
Moslemi 2015	0	27	0	26		Not estimable
Olsen 1994	0	13	0	13		Not estimable
Singh 2016	0	25	0	25		Not estimable
Torres unpub	0	25	0	25		Not estimable
Tsen 2000	0	20	0	20		Not estimable
Webb 1998	0	20	0	20		Not estimable
Subtotal (95% CI)		**360**		**219**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.6.2 Apgar < 7 at 5 min						
Loughrey 2002	1	46	0	20	14.6%	1.34 [0.06 , 31.56]
Mathru 1980	4	42	3	45	70.5%	1.43 [0.34 , 6.01]
Ngan Kee 2000	0	60	0	20		Not estimable
Turkoz 2002	0	15	1	15	14.9%	0.33 [0.01 , 7.58]
Subtotal (95% CI)		**163**		**100**	**100.0%**	**1.14 [0.34 , 3.81]**
Total events:	5		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)



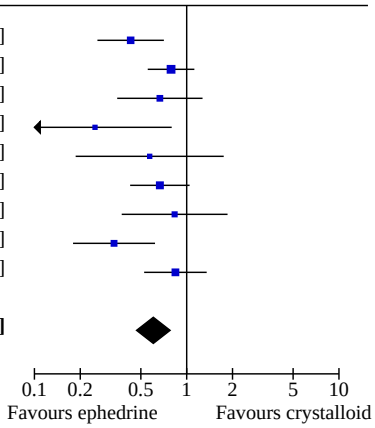
Comparison 13. Ephedrine vs crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Women with hypotension requiring intervention	9	613	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.47, 0.78]
13.2 Women with hypertension requiring intervention	3	280	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.37, 3.28]
13.3 Women with bradycardia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]
13.4 Women with nausea and/or vomiting	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.4.1 Nausea and/or vomiting	2	146	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.48, 2.08]
13.4.2 Nausea	3	220	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.31, 0.93]
13.4.3 Vomiting	3	220	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.31, 1.05]
13.5 Women with impaired consciousness	1	46	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.09, 1.86]
13.6 Neonates with acidosis (pH < 7.2)	2	218	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.48, 4.15]
13.7 Neonatal Apgar score	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.7.1 Apgar < 8 at 5 min	4	226	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.92]
13.7.2 Apgar < 7 at 5 min	1	120	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 13.1. Comparison 13: Ephedrine vs crystalloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 2000	18	80	21	40	13.8%	0.43 [0.26 , 0.71]
Chan 1997	15	23	19	23	19.1%	0.79 [0.55 , 1.12]
Damevski 2011	8	20	12	20	10.2%	0.67 [0.35 , 1.27]
El-Mekawy 2012	3	30	12	30	4.1%	0.25 [0.08 , 0.80]
Imam 2012	4	30	7	30	4.4%	0.57 [0.19 , 1.75]
Jabalameli 2011	18	50	27	50	15.5%	0.67 [0.43 , 1.04]
King 1998	5	10	6	10	7.5%	0.83 [0.37 , 1.85]
Kundra 2008	8	30	24	30	10.7%	0.33 [0.18 , 0.62]
Morgan 2000	35	83	12	24	14.7%	0.84 [0.53 , 1.35]
Total (95% CI)		**356**		**257**	**100.0%**	**0.60 [0.47 , 0.78]**
Total events:	114		140			

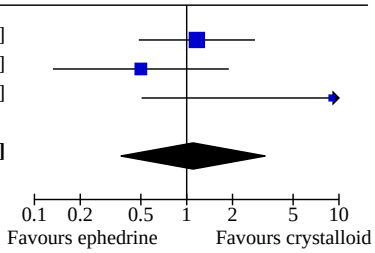
Heterogeneity: Tau² = 0.06; Chi² = 13.26, df = 8 (P = 0.10); I² = 40%
Test for overall effect: Z = 3.91 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Ephedrine vs crystalloid, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 2000	14	80	6	40	51.7%	1.17 [0.48 , 2.81]
Jabalameli 2011	3	50	6	50	36.1%	0.50 [0.13 , 1.89]
Kundra 2008	4	30	0	30	12.1%	9.00 [0.51 , 160.17]
Total (95% CI)		**160**		**120**	**100.0%**	**1.10 [0.37 , 3.28]**
Total events:	21		12			

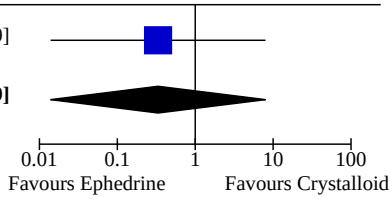
Heterogeneity: Tau² = 0.40; Chi² = 3.49, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13: Ephedrine vs crystalloid, Outcome 3: Women with bradycardia

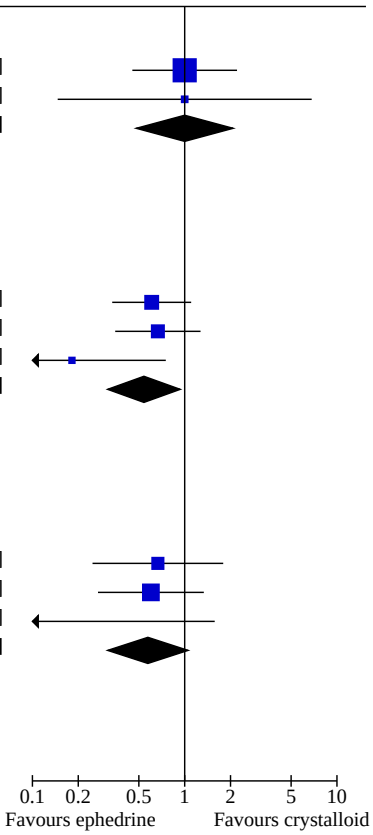
Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jabalameli 2011	0	50	1	50	100.0%	0.33 [0.01 , 7.99]
Total (95% CI)		**50**		**50**	**100.0%**	**0.33 [0.01 , 7.99]**
Total events:	0		1			

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



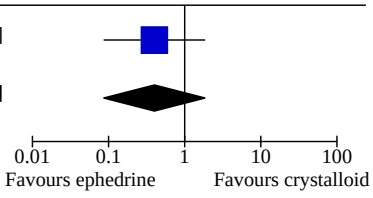
Analysis 13.4. Comparison 13: Ephedrine vs crystalloid, Outcome 4: Women with nausea and/or vomiting

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
13.4.1 Nausea and/or vomiting						
Chan 1997	8	23	8	23	85.5%	1.00 [0.45 , 2.21]
Jabalameli 2011	2	50	2	50	14.5%	1.00 [0.15 , 6.82]
Subtotal (95% CI)		**73**		**73**	**100.0%**	**1.00 [0.48 , 2.08]**
Total events:	10		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
13.4.2 Nausea						
Carvalho 2000	17	80	14	40	45.4%	0.61 [0.33 , 1.10]
Damevski 2011	8	20	12	20	41.6%	0.67 [0.35 , 1.27]
El-Mekawy 2012	2	30	11	30	13.0%	0.18 [0.04 , 0.75]
Subtotal (95% CI)		**130**		**90**	**100.0%**	**0.54 [0.31 , 0.93]**
Total events:	27		37			
Heterogeneity: Tau² = 0.08; Chi² = 3.00, df = 2 (P = 0.22); I² = 33%						
Test for overall effect: Z = 2.20 (P = 0.03)						
13.4.3 Vomiting						
Carvalho 2000	8	80	6	40	37.8%	0.67 [0.25 , 1.79]
Damevski 2011	6	20	10	20	57.7%	0.60 [0.27 , 1.34]
El-Mekawy 2012	0	30	5	30	4.5%	0.09 [0.01 , 1.57]
Subtotal (95% CI)		**130**		**90**	**100.0%**	**0.57 [0.31 , 1.05]**
Total events:	14		21			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						



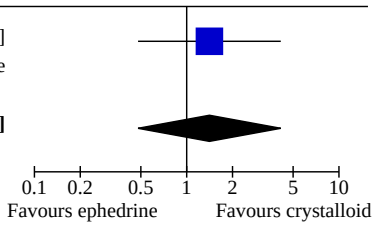
Analysis 13.5. Comparison 13: Ephedrine vs crystalloid, Outcome 5: Women with impaired consciousness

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 1997	2	23	5	23	100.0%	0.40 [0.09 , 1.86]
Total (95% CI)		**23**		**23**	**100.0%**	**0.40 [0.09 , 1.86]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						



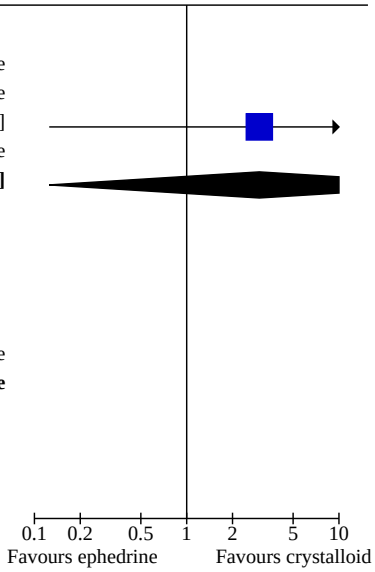
Analysis 13.6. Comparison 13: Ephedrine vs crystalloid, Outcome 6: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Carvalho 2000	11	78	4	40	100.0%	1.41 [0.48 , 4.15]
Jabalameli 2011	0	50	0	50		Not estimable
Total (95% CI)		**128**		**90**	**100.0%**	**1.41 [0.48 , 4.15]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Test for subgroup differences: Not applicable						



Analysis 13.7. Comparison 13: Ephedrine vs crystalloid, Outcome 7: Neonatal Apgar score

Study or Subgroup	Ephedrine Events	Ephedrine Total	Crystalloid Events	Crystalloid Total	Weight	Risk Ratio M-H, Random, 95% CI
13.7.1 Apgar < 8 at 5 min						
Chan 1997	0	23	0	23		Not estimable
El-Mekawy 2012	0	30	0	30		Not estimable
Jabalameli 2011	1	50	0	50	100.0%	3.00 [0.13 , 71.92]
King 1998	0	10	0	10		Not estimable
Subtotal (95% CI)		**113**		**113**	**100.0%**	**3.00 [0.13 , 71.92]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
13.7.2 Apgar < 7 at 5 min						
Carvalho 2000	0	80	0	40		Not estimable
Subtotal (95% CI)		**80**		**40**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

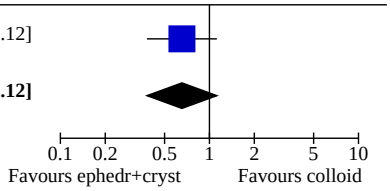


Comparison 14. Ephedrine + crystalloid vs colloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Women with hypotension requiring intervention	1	75	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.38, 1.12]
14.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.2.1 Nausea	1	75	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.81]
14.2.2 Vomiting	1	75	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.77]

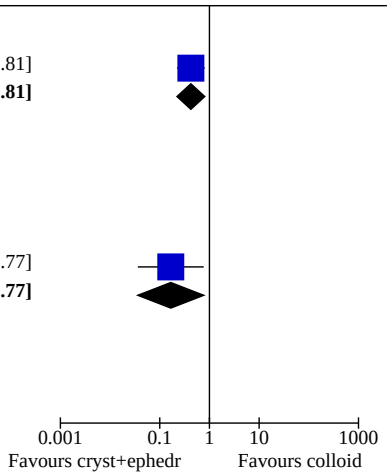
Analysis 14.1. Comparison 14: Ephedrine + crystalloid vs colloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Crystalloid+ephedrin Events	Total	Colloid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ozkan 2004	17	50	13	25	100.0%	0.65 [0.38 , 1.12]
Total (95% CI)		**50**		**25**	**100.0%**	**0.65 [0.38 , 1.12]**
Total events:	17		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: Not applicable						



Analysis 14.2. Comparison 14: Ephedrine + crystalloid vs colloid, Outcome 2: Women with nausea and/or vomiting

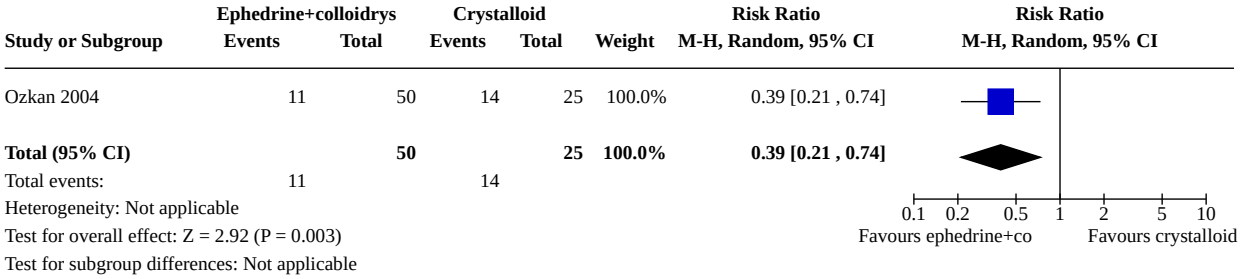
Study or Subgroup	Crystalloid+ephedrin Events	Total	Colloid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.2.1 Nausea						
Ozkan 2004	11	50	13	25	100.0%	0.42 [0.22 , 0.81]
Subtotal (95% CI)		**50**		**25**	**100.0%**	**0.42 [0.22 , 0.81]**
Total events:	11		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
14.2.2 Vomiting						
Ozkan 2004	2	50	6	25	100.0%	0.17 [0.04 , 0.77]
Subtotal (95% CI)		**50**		**25**	**100.0%**	**0.17 [0.04 , 0.77]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						



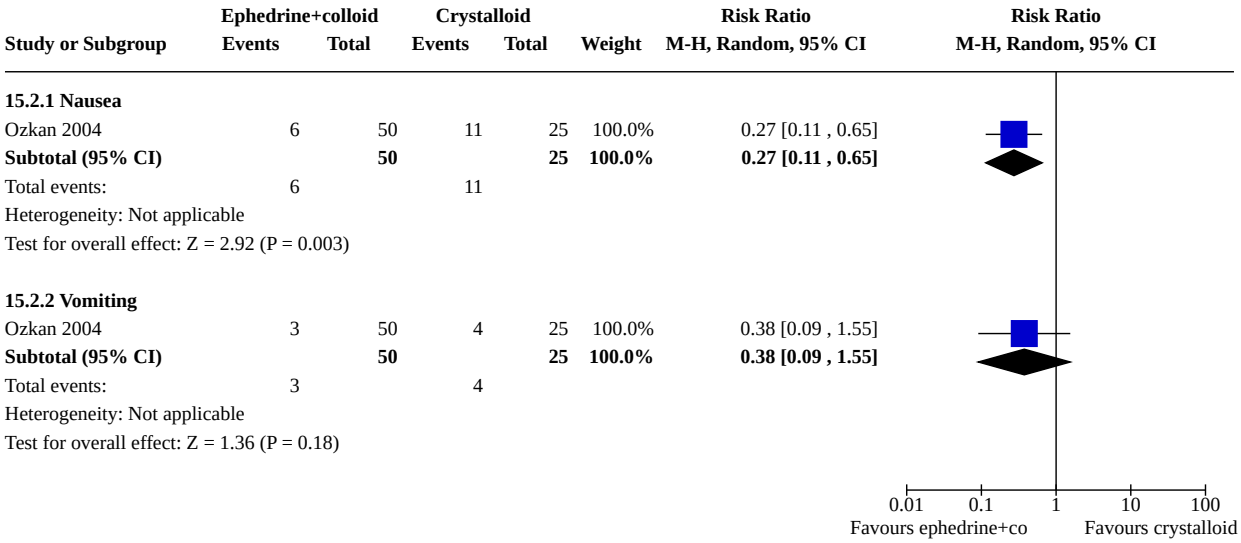
Comparison 15. Ephedrine + colloid vs crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Women with hypotension requiring intervention	1	75	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.21, 0.74]
15.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.2.1 Nausea	1	75	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.65]
15.2.2 Vomiting	1	75	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.09, 1.55]

Analysis 15.1. Comparison 15: Ephedrine + colloid vs crystalloid, Outcome 1: Women with hypotension requiring intervention



Analysis 15.2. Comparison 15: Ephedrine + colloid vs crystalloid, Outcome 2: Women with nausea and/or vomiting



Comparison 16. Ephedrine vs phenylephrine

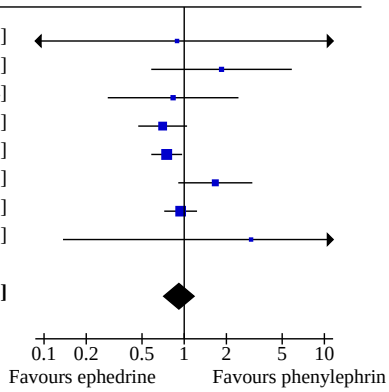
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Women with hypotension requiring intervention	8	401	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.18]
16.2 Women with hypertension requiring intervention	2	118	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.71, 4.16]
16.3 Cardiac dysrhythmia	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.3.1 Bradycardia	5	304	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.21, 0.64]
16.3.2 Tachycardia	1	57	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.44, 11.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.4 Women with nausea and/or vomiting	4	204	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.39, 1.49]
16.5 Neonates with acidosis (pH < 7.2)	3	175	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.07, 12.00]
16.6 Neonates with Apgar score < 8 at 5 min	6	321	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 16.1. Comparison 16: Ephedrine vs phenylephrine, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
Alahuhta 1992	1	9	1	8	0.9%	0.89 [0.07 , 12.00]
Bhardwaj 2013	6	26	4	32	4.2%	1.85 [0.58 , 5.86]
Gomaa 2003	5	30	6	30	4.8%	0.83 [0.28 , 2.44]
Hall 1994	12	19	9	10	20.1%	0.70 [0.47 , 1.05]
Magalhaes 2009	21	30	28	30	29.3%	0.75 [0.58 , 0.97]
Moslemi 2015	15	27	10	30	12.0%	1.67 [0.91 , 3.06]
Nazir 2012	33	50	35	50	28.1%	0.94 [0.72 , 1.23]
Ueyama 2002	1	10	0	10	0.6%	3.00 [0.14 , 65.90]
Total (95% CI)		**201**		**200**	**100.0%**	**0.92 [0.71 , 1.18]**
Total events:	94		93			

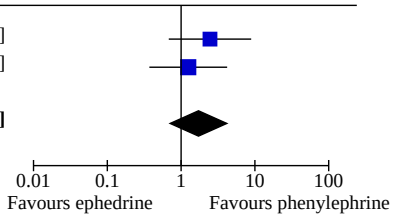
Heterogeneity: Tau² = 0.04; Chi² = 11.19, df = 7 (P = 0.13); I² = 37%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16: Ephedrine vs phenylephrine, Outcome 2: Women with hypertension requiring intervention

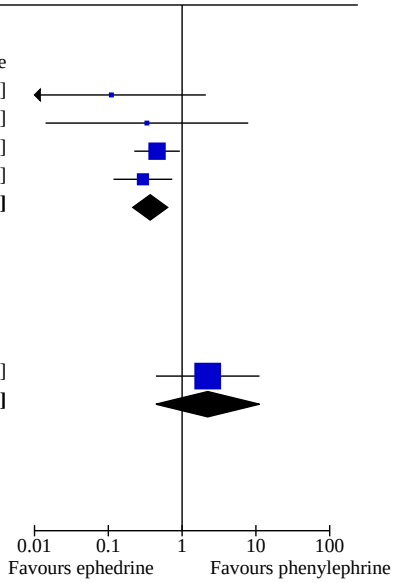
Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	6	26	3	32	47.1%	2.46 [0.68 , 8.90]
Magalhaes 2009	5	30	4	30	52.9%	1.25 [0.37 , 4.21]
Total (95% CI)		**56**		**62**	**100.0%**	**1.72 [0.71 , 4.16]**
Total events:	11		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable



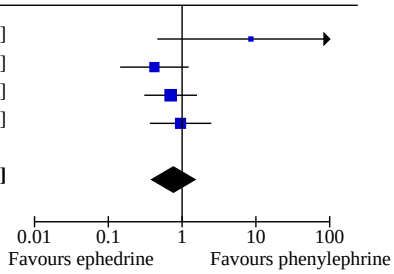
Analysis 16.3. Comparison 16: Ephedrine vs phenylephrine, Outcome 3: Cardiac dysrhythmia

Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
16.3.1 Bradycardia						
Bhardwaj 2013	0	26	0	32		Not estimable
Hall 1994	0	19	2	10	3.4%	0.11 [0.01 , 2.09]
Magalhaes 2009	0	30	1	30	3.0%	0.33 [0.01 , 7.87]
Moslemi 2015	7	27	17	30	58.5%	0.46 [0.22 , 0.93]
Nazir 2012	5	50	17	50	35.1%	0.29 [0.12 , 0.74]
Subtotal (95% CI)		**152**		**152**	**100.0%**	**0.37 [0.21 , 0.64]**
Total events:	12		37			
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.59 (P = 0.0003)						
16.3.2 Tachycardia						
Moslemi 2015	4	27	2	30	100.0%	2.22 [0.44 , 11.18]
Subtotal (95% CI)		**27**		**30**	**100.0%**	**2.22 [0.44 , 11.18]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 4.25, df = 1 (P = 0.04), I² = 76.5%						



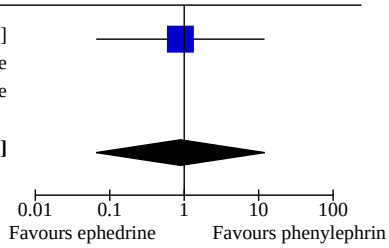
Analysis 16.4. Comparison 16: Ephedrine vs phenylephrine, Outcome 4: Women with nausea and/or vomiting

Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	3	26	0	32	5.0%	8.56 [0.46 , 158.51]
Hall 1994	4	19	5	10	26.9%	0.42 [0.14 , 1.23]
Magalhaes 2009	7	30	10	30	37.1%	0.70 [0.31 , 1.59]
Moslemi 2015	6	27	7	30	31.0%	0.95 [0.37 , 2.48]
Total (95% CI)		**102**		**102**	**100.0%**	**0.76 [0.39 , 1.49]**
Total events:	20		22			
Heterogeneity: Tau² = 0.14; Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Not applicable						



Analysis 16.5. Comparison 16: Ephedrine vs phenylephrine, Outcome 5: Neonates with acidosis (pH < 7.2)

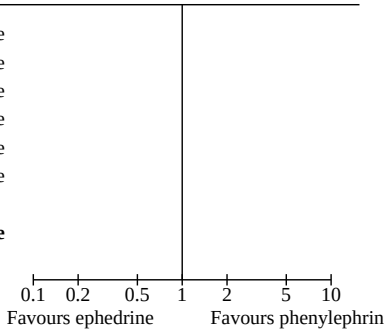
Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
Alahuhta 1992	1	9	1	8	100.0%	0.89 [0.07 , 12.00]
Bhardwaj 2013	0	26	0	32		Not estimable
Nazir 2012	0	50	0	50		Not estimable
Total (95% CI)		**85**		**90**	**100.0%**	**0.89 [0.07 , 12.00]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Not applicable						



Analysis 16.6. Comparison 16: Ephedrine vs phenylephrine, Outcome 6: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Ephedrine Events	Ephedrine Total	Phenylephrine Events	Phenylephrine Total	Weight	Risk Ratio M-H, Random, 95% CI
Alahuhta 1992	0	9	0	8		Not estimable
Bhardwaj 2013	0	26	0	32		Not estimable
Hall 1994	0	19	0	10		Not estimable
Magalhaes 2009	0	30	0	30		Not estimable
Moslemi 2015	0	27	0	30		Not estimable
Nazir 2012	0	50	0	50		Not estimable
Total (95% CI)		**161**		**160**		**Not estimable**
Total events:	0		0			

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



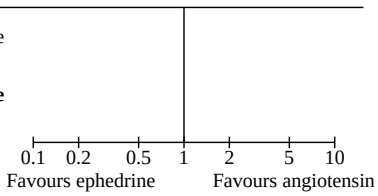
Comparison 17. Ephedrine vs angiotensin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Women with hypotension requiring intervention	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable
17.2 Women with nausea and/or vomiting	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
17.3 Neonates with acidosis (pH < 7.2)	1	20	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.55, 147.95]

Analysis 17.1. Comparison 17: Ephedrine vs angiotensin, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Angiotensin Events	Angiotensin Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramin 1994	0	10	0	10		Not estimable
Total (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			

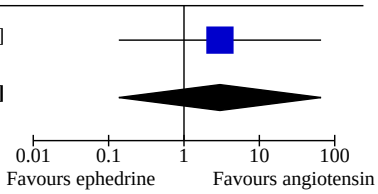
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 17.2. Comparison 17: Ephedrine vs angiotensin, Outcome 2: Women with nausea and/or vomiting

Study or Subgroup	Ephedrine Events	Ephedrine Total	Angiotensin Events	Angiotensin Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramin 1994	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Total (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			

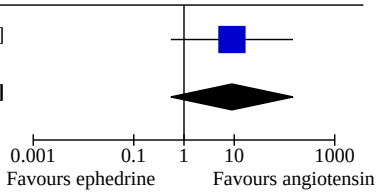
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 17.3. Comparison 17: Ephedrine vs angiotensin, Outcome 3: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Ephedrine Events	Ephedrine Total	Angiotensin Events	Angiotensin Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramin 1994	4	10	0	10	100.0%	9.00 [0.55 , 147.95]
Total (95% CI)		**10**		**10**	**100.0%**	**9.00 [0.55 , 147.95]**
Total events:	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable



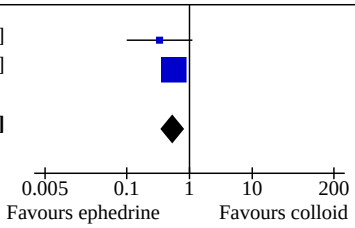
Comparison 18. Ephedrine vs colloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Women with hypotension requiring intervention	2	160	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.79]
18.2 Women with hypertension requiring intervention	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.87]
18.3 Women with bradycardia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.4 Women with nausea and vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.4.1 Women with nausea and/or vomiting	1	100	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 101.58]
18.4.2 Women with nausea	1	60	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.94]
18.4.3 Women with vomiting	1	60	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.65]
18.5 5 Neonates with acidosis (pH < 7.2)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.6 Apgar score < 8 at 5 min	2	160	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.92]

Analysis 18.1. Comparison 18: Ephedrine vs colloid, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
El-Mekawy 2012	3	30	9	30	11.0%	0.33 [0.10 , 1.11]
Jabalameli 2011	18	50	32	50	89.0%	0.56 [0.37 , 0.86]
Total (95% CI)		**80**		**80**	**100.0%**	**0.53 [0.36 , 0.79]**
Total events:	21		41			

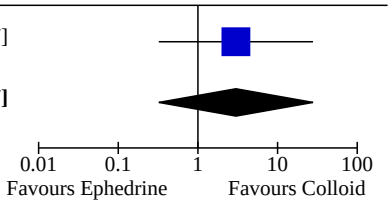
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 3.10 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 18.2. Comparison 18: Ephedrine vs colloid, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jabalameli 2011	3	50	1	50	100.0%	3.00 [0.32 , 27.87]
Total (95% CI)		**50**		**50**	**100.0%**	**3.00 [0.32 , 27.87]**
Total events:	3		1			

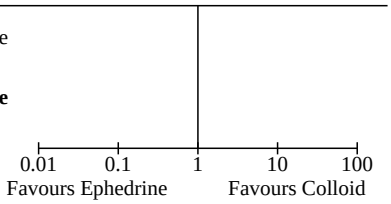
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 18.3. Comparison 18: Ephedrine vs colloid, Outcome 3: Women with bradycardia

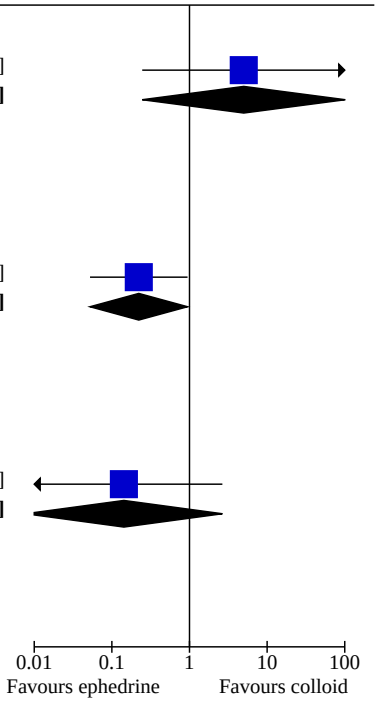
Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jabalameli 2011	0	50	0	50		Not estimable
Total (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			

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



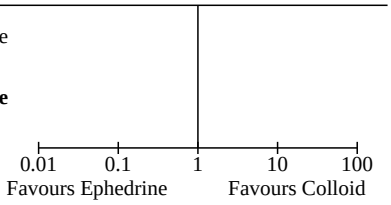
Analysis 18.4. Comparison 18: Ephedrine vs colloid, Outcome 4: Women with nausea and vomiting

Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
18.4.1 Women with nausea and/or vomiting						
Jabalameli 2011	2	50	0	50	100.0%	5.00 [0.25 , 101.58]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**5.00 [0.25 , 101.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
18.4.2 Women with nausea						
El-Mekawy 2012	2	30	9	30	100.0%	0.22 [0.05 , 0.94]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.22 [0.05 , 0.94]**
Total events:	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
18.4.3 Women with vomiting						
El-Mekawy 2012	0	30	3	30	100.0%	0.14 [0.01 , 2.65]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.14 [0.01 , 2.65]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 3.73, df = 2 (P = 0.15), I² = 46.4%						



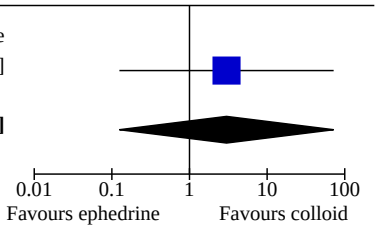
Analysis 18.5. Comparison 18: Ephedrine vs colloid, Outcome 5: 5 Neonates with acidosis (pH < 7.2)

Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jabalameli 2011	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						



Analysis 18.6. Comparison 18: Ephedrine vs colloid, Outcome 6: Apgar score < 8 at 5 min

Study or Subgroup	Ephedrine Events	Ephedrine Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
El-Mekawy 2012	0	30	0	30		Not estimable
Jabalameli 2011	1	50	0	50	100.0%	3.00 [0.13 , 71.92]
Total (95% CI)		**80**		**80**	**100.0%**	**3.00 [0.13 , 71.92]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



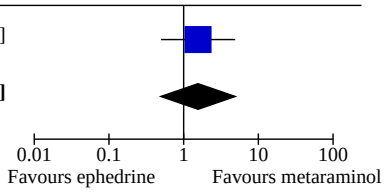
Comparison 19. Ephedrine vs metaraminol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Women with hypotension requiring intervention	1	53	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.50, 4.89]
19.2 Women with hypertension requiring intervention	1	53	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.47]
19.3 Women with bradycardia	1	53	Risk Ratio (M-H, Random, 95% CI)	Not estimable
19.4 Women with nausea and/or vomiting	1	53	Risk Ratio (M-H, Random, 95% CI)	7.26 [0.39, 134.01]
19.5 5 Neonates with acidosis (pH < 7.2)	1	53	Risk Ratio (M-H, Random, 95% CI)	Not estimable
19.6 Neonatal Apgar score < 8 at 5 min	1	53	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 19.1. Comparison 19: Ephedrine vs metaraminol, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	6	26	4	27	100.0%	1.56 [0.50 , 4.89]
Total (95% CI)		**26**		**27**	**100.0%**	**1.56 [0.50 , 4.89]**
Total events:	6		4			

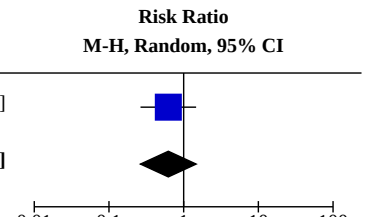
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 19.2. Comparison 19: Ephedrine vs metaraminol, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	6	26	10	27	100.0%	0.62 [0.26 , 1.47]
Total (95% CI)		**26**		**27**	**100.0%**	**0.62 [0.26 , 1.47]**
Total events:	6		10			

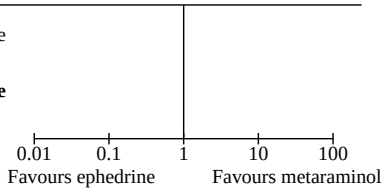
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 19.3. Comparison 19: Ephedrine vs metaraminol, Outcome 3: Women with bradycardia

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	26	0	27		Not estimable
Total (95% CI)		**26**		**27**		**Not estimable**
Total events:	0		0			

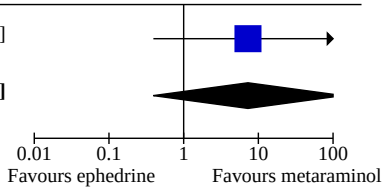
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 19.4. Comparison 19: Ephedrine vs metaraminol, Outcome 4: Women with nausea and/or vomiting

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	3	26	0	27	100.0%	7.26 [0.39 , 134.01]
Total (95% CI)		**26**		**27**	**100.0%**	**7.26 [0.39 , 134.01]**
Total events:	3		0			

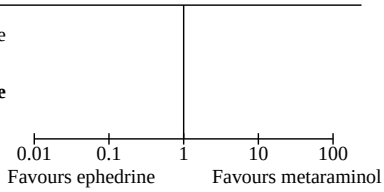
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 19.5. Comparison 19: Ephedrine vs metaraminol, Outcome 5: 5 Neonates with acidosis (pH < 7.2)

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	26	0	27		Not estimable
Total (95% CI)		**26**		**27**		**Not estimable**
Total events:	0		0			

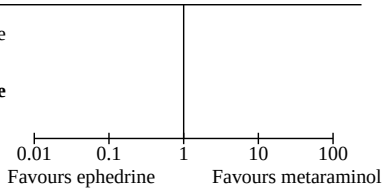
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 19.6. Comparison 19: Ephedrine vs metaraminol, Outcome 6: Neonatal Apgar score < 8 at 5 min

Study or Subgroup	Ephedrine Events	Ephedrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	26	0	27		Not estimable
Total (95% CI)		**26**		**27**		**Not estimable**
Total events:	0		0			

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



Comparison 20. Ephedrine: different doses

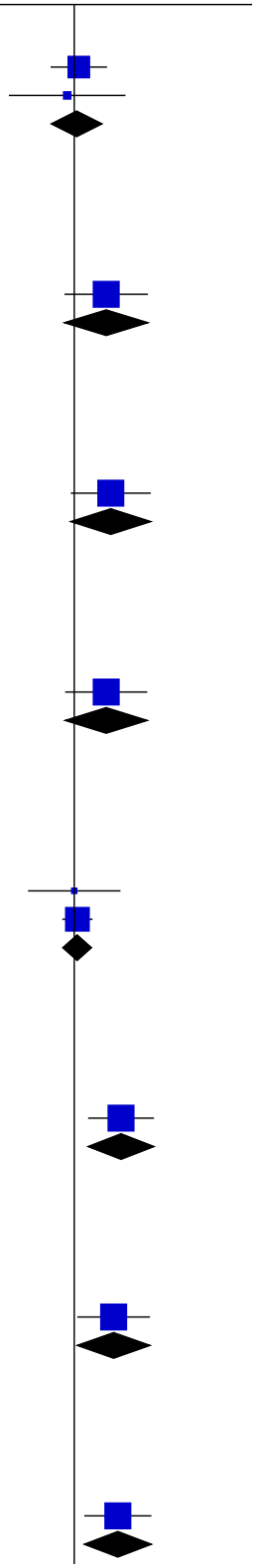
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Women with hypotension requiring intervention	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1.1 5 mg vs 10 mg	2	100	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.65, 1.69]
20.1.2 6 mg vs 12 mg	1	46	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.83, 4.04]
20.1.3 5 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.94, 4.27]
20.1.4 10 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.84, 3.99]
20.1.5 10 mg vs 20 mg	2	60	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.80, 1.39]
20.1.6 10 mg vs 30 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	2.43 [1.30, 4.54]
20.1.7 15 mg vs 30 mg	1	100	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.06, 4.21]
20.1.8 20 mg vs 30 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.21, 4.32]
20.2 Women with hypertension requiring intervention	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.2.1 5 mg vs 10 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.44, 3.30]
20.2.2 5 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.23, 1.07]
20.2.3 10 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.18, 0.96]
20.2.4 10 mg vs 20 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.56]
20.2.5 10 mg vs 30 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.02, 0.80]
20.2.6 20 mg vs 30 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.23, 1.37]
20.3 Women with nausea and/or vomiting	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.3.1 6 mg vs 12 mg (nausea and/or vomiting)	1	46	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.38, 1.74]
20.3.2 5 mg vs 10 mg (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.45]
20.3.3 5 mg vs 15 mg (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.28, 8.04]
20.3.4 10 mg vs 15 mg (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.08]
20.3.5 5 mg vs 10 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.83, 4.81]
20.3.6 5 mg vs 15 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.94, 6.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3.7 10 mg vs 15 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.39, 3.99]
20.3.8 10 mg vs 20 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.39, 1.24]
20.3.9 10 mg vs 30 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.73, 4.43]
20.3.10 15 mg vs 30 mg (nausea)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.59, 3.45]
20.3.11 20 mg vs 30 mg (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.14, 5.93]
20.3.12 15 mg vs 30 mg (vomiting)	1	100	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.82]
20.4 Neonates with acidosis (pH < 7.2)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.4.1 5 mg vs 10 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.92]
20.4.2 5 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.72]
20.4.3 6 mg vs 12 mg	1	46	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.16]
20.4.4 10 mg vs 15 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.20, 20.33]
20.4.5 10 mg vs 20 mg	1	39	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.24, 1.50]
20.4.6 10 mg vs 30 mg	1	38	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.36, 3.55]
20.4.7 20 mg vs 30 mg	1	37	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.69, 5.21]
20.5 Neonatal Apgar score at 5 min	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.5.1 6 mg vs 12 mg (Apgar < 7)	1	46	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.16]
20.5.2 5 mg vs 10 mg (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.5.3 5 mg vs 15 mg (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.5.4 10 mg vs 15 mg (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.5.5 10 mg vs 20 mg (Apgar < 7)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.5.6 10 mg vs 30 mg (Apgar < 7)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.5.7 20 mg vs 30 mg (Apgar < 7)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.5.8 10 mg vs 20 mg (Apgar < 8)	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 20.1. Comparison 20: Ephedrine: different doses, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 5 mg vs 10 mg						
Carvalho 1999a	12	20	11	20	81.1%	1.09 [0.64 , 1.86]
Ueyama 1992	7	40	4	20	18.9%	0.88 [0.29 , 2.64]
Subtotal (95% CI)		**60**		**40**	**100.0%**	**1.05 [0.65 , 1.69]**
Total events:	19		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.85)						
20.1.2 6 mg vs 12 mg						
Loughrey 2002	12	24	6	22	100.0%	1.83 [0.83 , 4.04]
Subtotal (95% CI)		**24**		**22**	**100.0%**	**1.83 [0.83 , 4.04]**
Total events:	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
20.1.3 5 mg vs 15 mg						
Carvalho 1999a	12	20	6	20	100.0%	2.00 [0.94 , 4.27]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.00 [0.94 , 4.27]**
Total events:	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
20.1.4 10 mg vs 15 mg						
Carvalho 1999a	11	20	6	20	100.0%	1.83 [0.84 , 3.99]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.83 [0.84 , 3.99]**
Total events:	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
20.1.5 10 mg vs 20 mg						
King 1998	5	10	5	10	9.6%	1.00 [0.42 , 2.40]
Ngan Kee 2000	17	20	16	20	90.4%	1.06 [0.80 , 1.41]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.06 [0.80 , 1.39]**
Total events:	22		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
20.1.6 10 mg vs 30 mg						
Ngan Kee 2000	17	20	7	20	100.0%	2.43 [1.30 , 4.54]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.43 [1.30 , 4.54]**
Total events:	17		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
20.1.7 15 mg vs 30 mg						
Ozkan 2004	19	50	9	50	100.0%	2.11 [1.06 , 4.21]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**2.11 [1.06 , 4.21]**
Total events:	19		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
20.1.8 20 mg vs 30 mg						
Ngan Kee 2000	16	20	7	20	100.0%	2.29 [1.21 , 4.32]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.29 [1.21 , 4.32]**

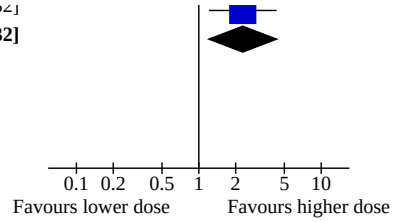


Analysis 20.1. (Continued)

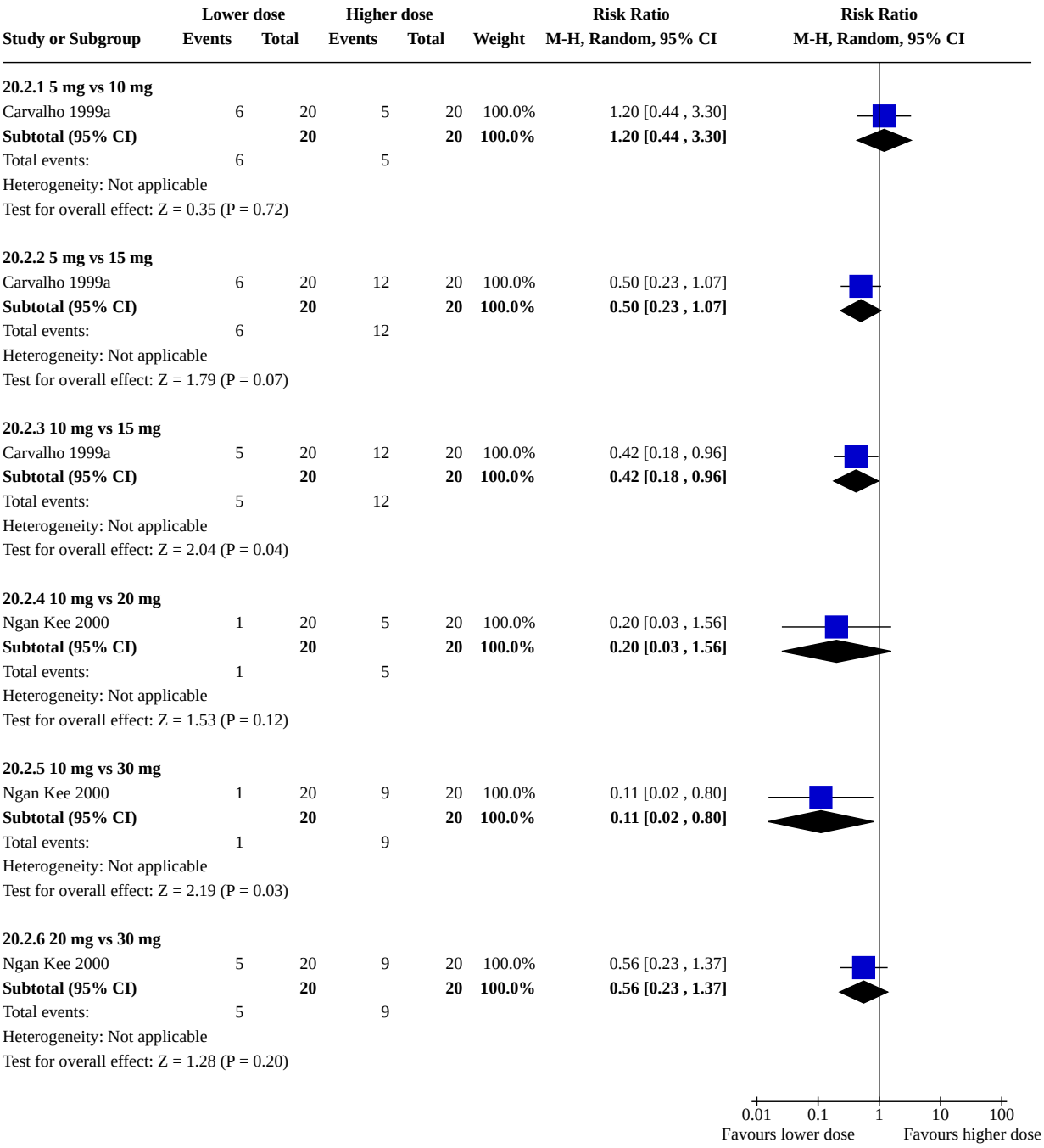
Ngan Kee 2000	16	20	7	20	100.0%	2.29 [1.21 , 4.32]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.29 [1.21 , 4.32]**
Total events:	16		7			

Heterogeneity: Not applicable

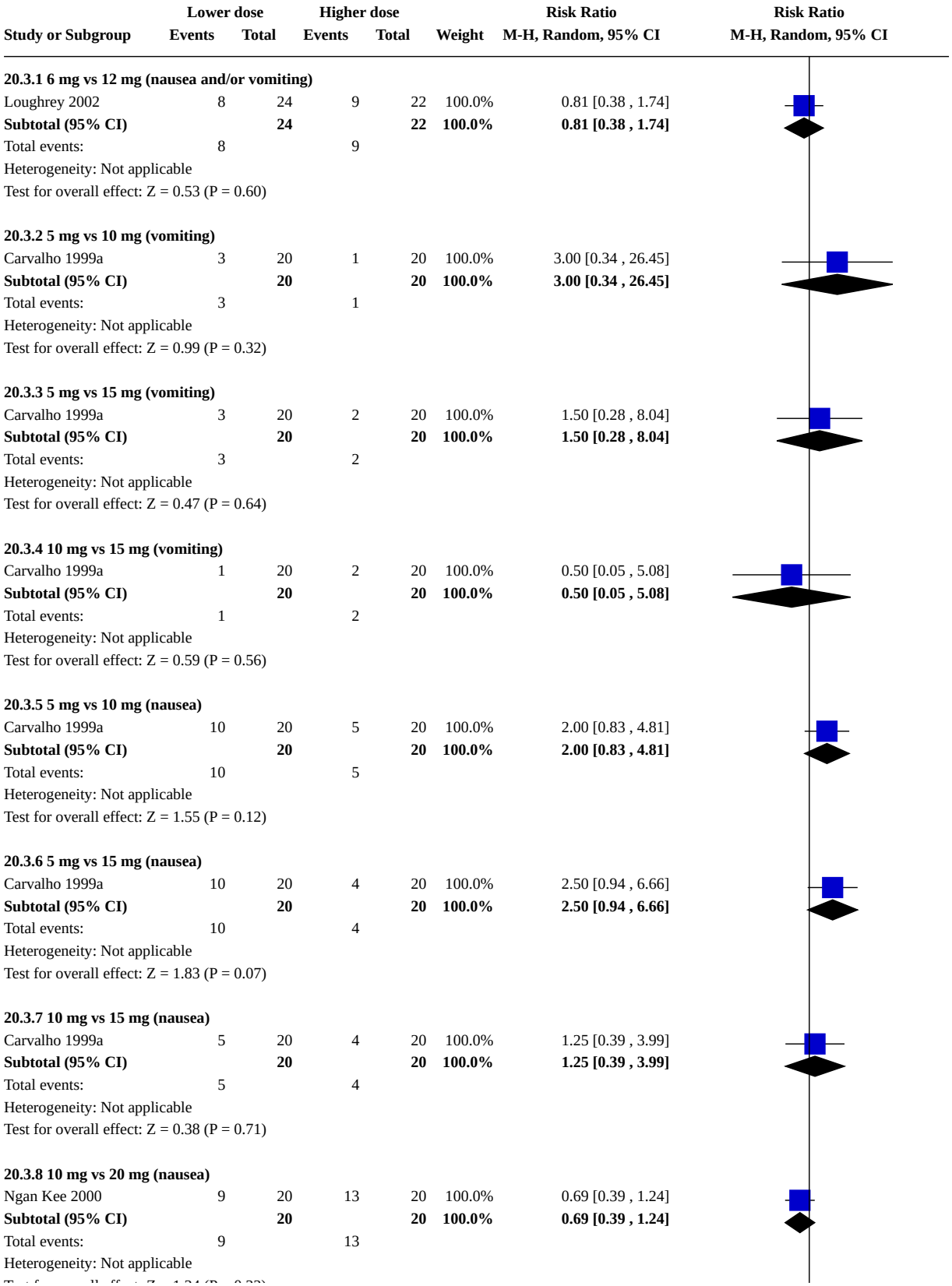
Test for overall effect: Z = 2.55 (P = 0.01)



Analysis 20.2. Comparison 20: Ephedrine: different doses, Outcome 2: Women with hypertension requiring intervention

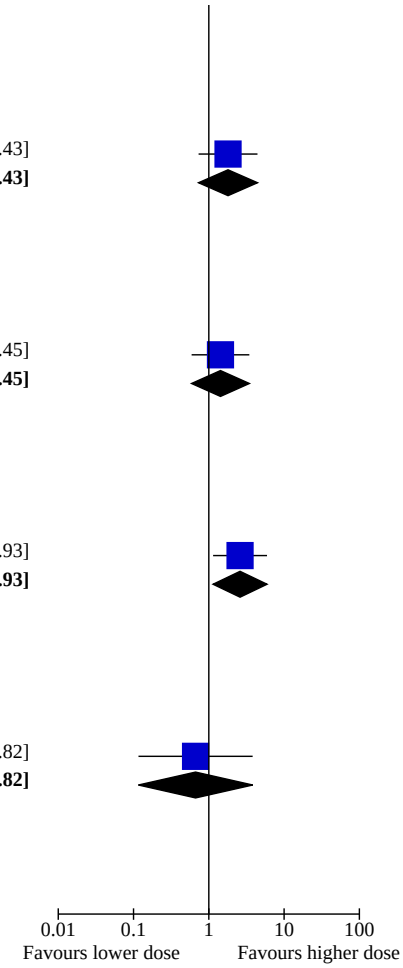


Analysis 20.3. Comparison 20: Ephedrine: different doses, Outcome 3: Women with nausea and/or vomiting

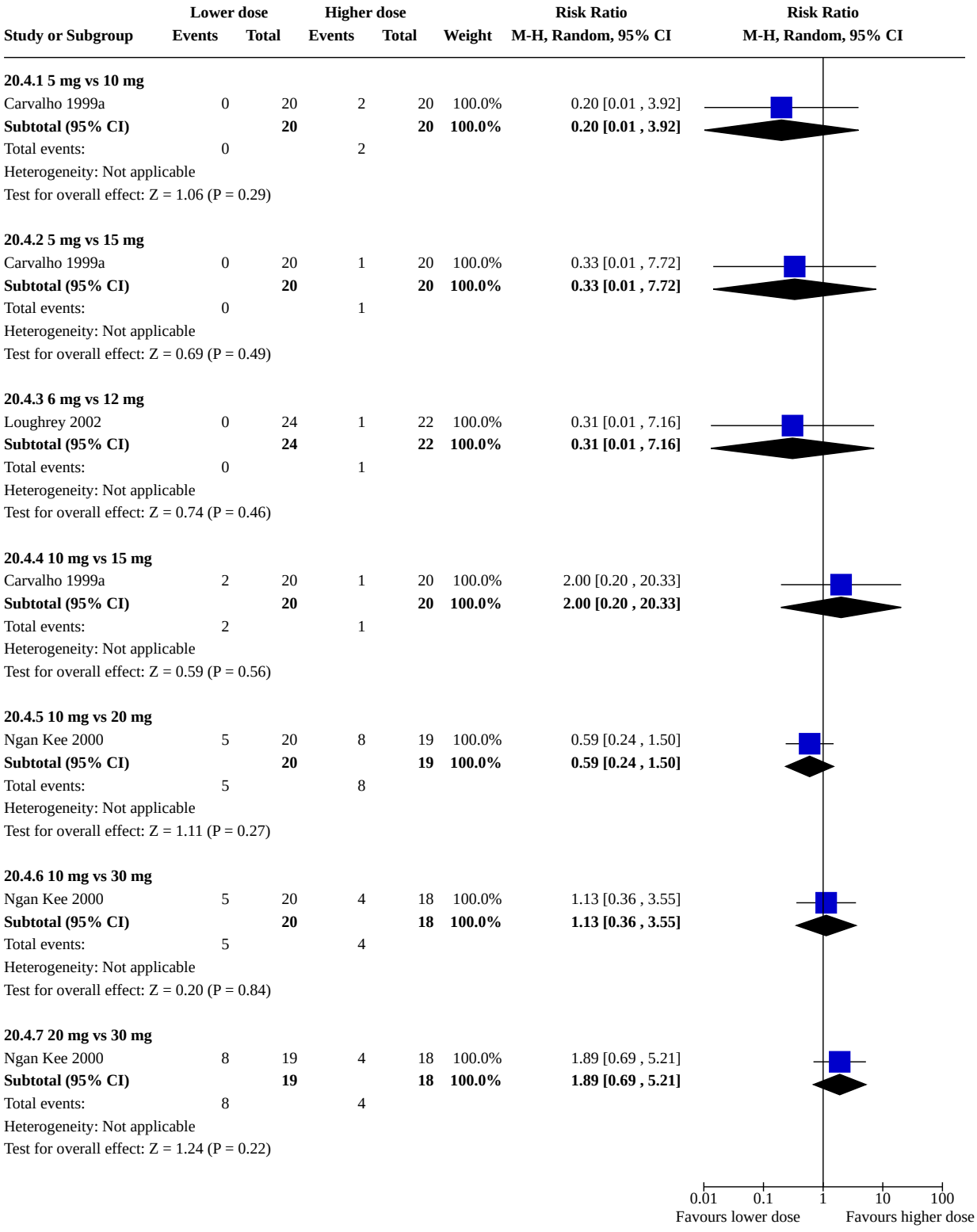


Analysis 20.3. (Continued)

Total events:	9		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
20.3.9 10 mg vs 30 mg (nausea)						
Ngan Kee 2000	9	20	5	20	100.0%	1.80 [0.73 , 4.43]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.80 [0.73 , 4.43]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
20.3.10 15 mg vs 30 mg (nausea)						
Ozkan 2004	10	50	7	50	100.0%	1.43 [0.59 , 3.45]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**1.43 [0.59 , 3.45]**
Total events:	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
20.3.11 20 mg vs 30 mg (nausea)						
Ngan Kee 2000	13	20	5	20	100.0%	2.60 [1.14 , 5.93]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.60 [1.14 , 5.93]**
Total events:	13		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
20.3.12 15 mg vs 30 mg (vomiting)						
Ozkan 2004	2	50	3	50	100.0%	0.67 [0.12 , 3.82]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.67 [0.12 , 3.82]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						



Analysis 20.4. Comparison 20: Ephedrine: different doses, Outcome 4: Neonates with acidosis (pH < 7.2)



Analysis 20.5. Comparison 20: Ephedrine: different doses, Outcome 5: Neonatal Apgar score at 5 min

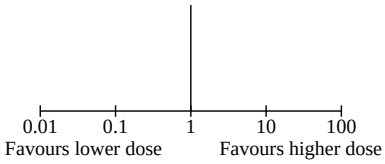
Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
20.5.1 6 mg vs 12 mg (Apgar < 7)						
Loughrey 2002	0	24	1	22	100.0%	0.31 [0.01 , 7.16]
Subtotal (95% CI)		**24**		**22**	**100.0%**	**0.31 [0.01 , 7.16]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
20.5.2 5 mg vs 10 mg (Apgar < 8)						
Carvalho 1999a	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						
20.5.3 5 mg vs 15 mg (Apgar < 8)						
Carvalho 1999a	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						
20.5.4 10 mg vs 15 mg (Apgar < 8)						
Carvalho 1999a	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						
20.5.5 10 mg vs 20 mg (Apgar < 7)						
Ngan Kee 2000	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						
20.5.6 10 mg vs 30 mg (Apgar < 7)						
Ngan Kee 2000	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						
20.5.7 20 mg vs 30 mg (Apgar < 7)						
Ngan Kee 2000	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						
20.5.8 10 mg vs 20 mg (Apgar < 8)						
King 1998	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						

Analysis 20.5. (Continued)

Total events: 0 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable



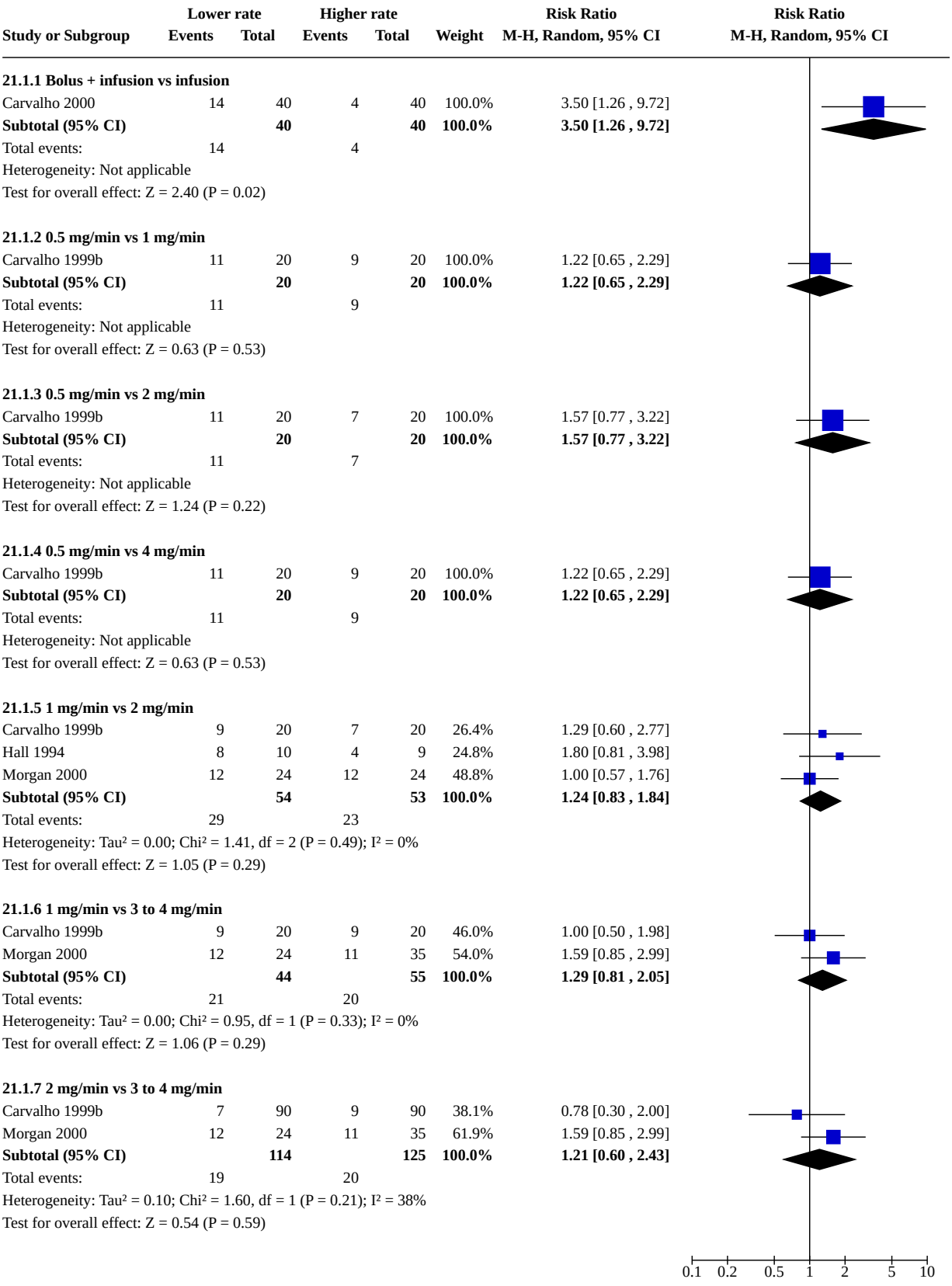
Comparison 21. Ephedrine: different rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Women with hypotension requiring intervention	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1.1 Bolus + infusion vs infusion	1	80	Risk Ratio (M-H, Random, 95% CI)	3.50 [1.26, 9.72]
21.1.2 0.5 mg/min vs 1 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.65, 2.29]
21.1.3 0.5 mg/min vs 2 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.77, 3.22]
21.1.4 0.5 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.65, 2.29]
21.1.5 1 mg/min vs 2 mg/min	3	107	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.83, 1.84]
21.1.6 1 mg/min vs 3 to 4 mg/min	2	99	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.81, 2.05]
21.1.7 2 mg/min vs 3 to 4 mg/min	2	239	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.60, 2.43]
21.2 Women with hypertension requiring intervention	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.2.1 Bolus + infusion vs infusion	1	80	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.39, 2.59]
21.2.2 0.5 mg/min vs 1 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.26, 98.00]
21.2.3 0.5 mg/min vs 2 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.57]
21.2.4 0.5 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.80]
21.2.5 1 mg/min vs 2 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.60]
21.2.6 1 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2.7 2 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.10, 0.93]
21.3 Women with bradycardia	1	19	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.3.1 1 mg/min vs 2 mg/min	1	19	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.4 Women with nausea and/or vomiting	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.4.1 Bolus + infusion vs infusion (nausea)	1	80	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.75, 4.48]
21.4.2 0.5 mg/min vs 1 mg/min (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.60, 2.77]
21.4.3 0.5 mg/min vs 2 mg/min (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.66, 3.43]
21.4.4 0.5 mg/min vs 4 mg/min (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.60, 2.77]
21.4.5 1 mg/min vs 2 mg/min (nausea)	2	60	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.30, 15.85]
21.4.6 1 mg/min vs 4 mg/min (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.43, 2.33]
21.4.7 2 mg/min vs 4 mg/min (nausea)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.35, 2.10]
21.4.8 Bolus + infusion vs infusion (vomiting)	1	80	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.43, 6.51]
21.4.9 0.5 mg/min vs 1 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.57]
21.4.10 0.5 mg/min vs 2 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.20, 20.33]
21.4.11 0.5 mg/min vs 4 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.20, 20.33]
21.4.12 1 mg/min vs 2 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.45]
21.4.13 1 mg/min vs 4 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.45]
21.4.14 2 mg/min vs 4 mg/min (vomiting)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 14.90]

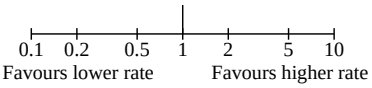
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.4.15 1 mg/min vs 2 mg/min (nausea or vomiting)	1	19	Risk Ratio (M-H, Random, 95% CI)	8.18 [0.50, 133.66]
21.5 Neonates with acidosis (pH < 7.2)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.5.1 Bolus + infusion vs infusion	1	78	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.53, 5.23]
21.5.2 0.5 mg/min vs 1 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.94]
21.5.3 0.5 mg/min vs 2 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 69.52]
21.5.4 0.5 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.05]
21.5.5 1 mg/min vs 2 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	7.00 [0.38, 127.32]
21.5.6 1 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.19, 2.93]
21.5.7 2 mg/min vs 4 mg/min	1	40	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.94]
21.6 Neonatal Apgar score at 5 min	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.6.1 Bolus + infusion vs infusion (Apgar < 7)	1	80	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.2 0.5 mg/min vs 1 mg/min (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.3 0.5 mg/min vs 2 mg/min (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.4 0.5 mg/min vs 4 mg/min (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.5 1 mg/min vs 2 mg/min (Apgar < 8)	2	59	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.6 1 mg/min vs 4 mg/min (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
21.6.7 2 mg/min vs 4 mg/min (Apgar < 8)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 21.1. Comparison 21: Ephedrine: different rates, Outcome 1: Women with hypotension requiring intervention

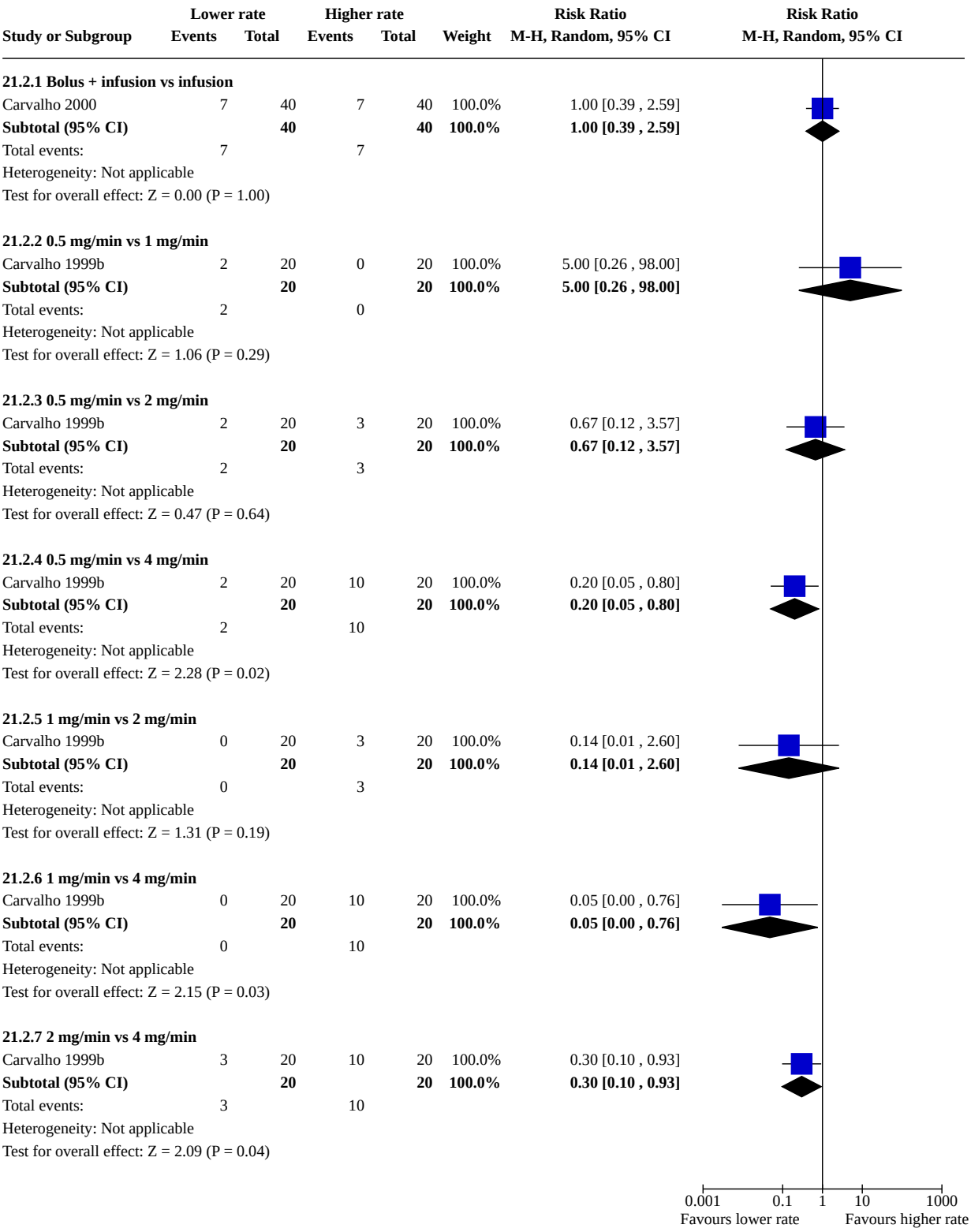


Study or Subgroup	Lower rate Events	Lower rate Total	Higher rate Events	Higher rate Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Bolus + infusion vs infusion						
Carvalho 2000	14	40	4	40	100.0%	3.50 [1.26 , 9.72]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**3.50 [1.26 , 9.72]**
Total events:	14		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
21.1.2 0.5 mg/min vs 1 mg/min						
Carvalho 1999b	11	20	9	20	100.0%	1.22 [0.65 , 2.29]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.22 [0.65 , 2.29]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
21.1.3 0.5 mg/min vs 2 mg/min						
Carvalho 1999b	11	20	7	20	100.0%	1.57 [0.77 , 3.22]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.57 [0.77 , 3.22]**
Total events:	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
21.1.4 0.5 mg/min vs 4 mg/min						
Carvalho 1999b	11	20	9	20	100.0%	1.22 [0.65 , 2.29]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.22 [0.65 , 2.29]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
21.1.5 1 mg/min vs 2 mg/min						
Carvalho 1999b	9	20	7	20	26.4%	1.29 [0.60 , 2.77]
Hall 1994	8	10	4	9	24.8%	1.80 [0.81 , 3.98]
Morgan 2000	12	24	12	24	48.8%	1.00 [0.57 , 1.76]
Subtotal (95% CI)		**54**		**53**	**100.0%**	**1.24 [0.83 , 1.84]**
Total events:	29		23			
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
21.1.6 1 mg/min vs 3 to 4 mg/min						
Carvalho 1999b	9	20	9	20	46.0%	1.00 [0.50 , 1.98]
Morgan 2000	12	24	11	35	54.0%	1.59 [0.85 , 2.99]
Subtotal (95% CI)		**44**		**55**	**100.0%**	**1.29 [0.81 , 2.05]**
Total events:	21		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
21.1.7 2 mg/min vs 3 to 4 mg/min						
Carvalho 1999b	7	90	9	90	38.1%	0.78 [0.30 , 2.00]
Morgan 2000	12	24	11	35	61.9%	1.59 [0.85 , 2.99]
Subtotal (95% CI)		**114**		**125**	**100.0%**	**1.21 [0.60 , 2.43]**
Total events:	19		20			
Heterogeneity: Tau² = 0.10; Chi² = 1.60, df = 1 (P = 0.21); I² = 38%						
Test for overall effect: Z = 0.54 (P = 0.59)						

Analysis 21.1. (Continued)

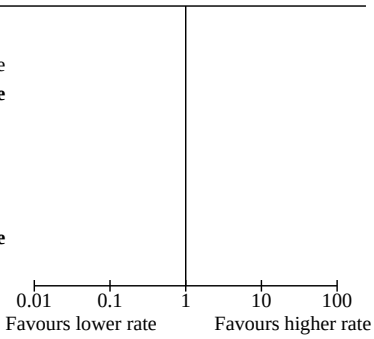


Analysis 21.2. Comparison 21: Ephedrine: different rates, Outcome 2: Women with hypertension requiring intervention

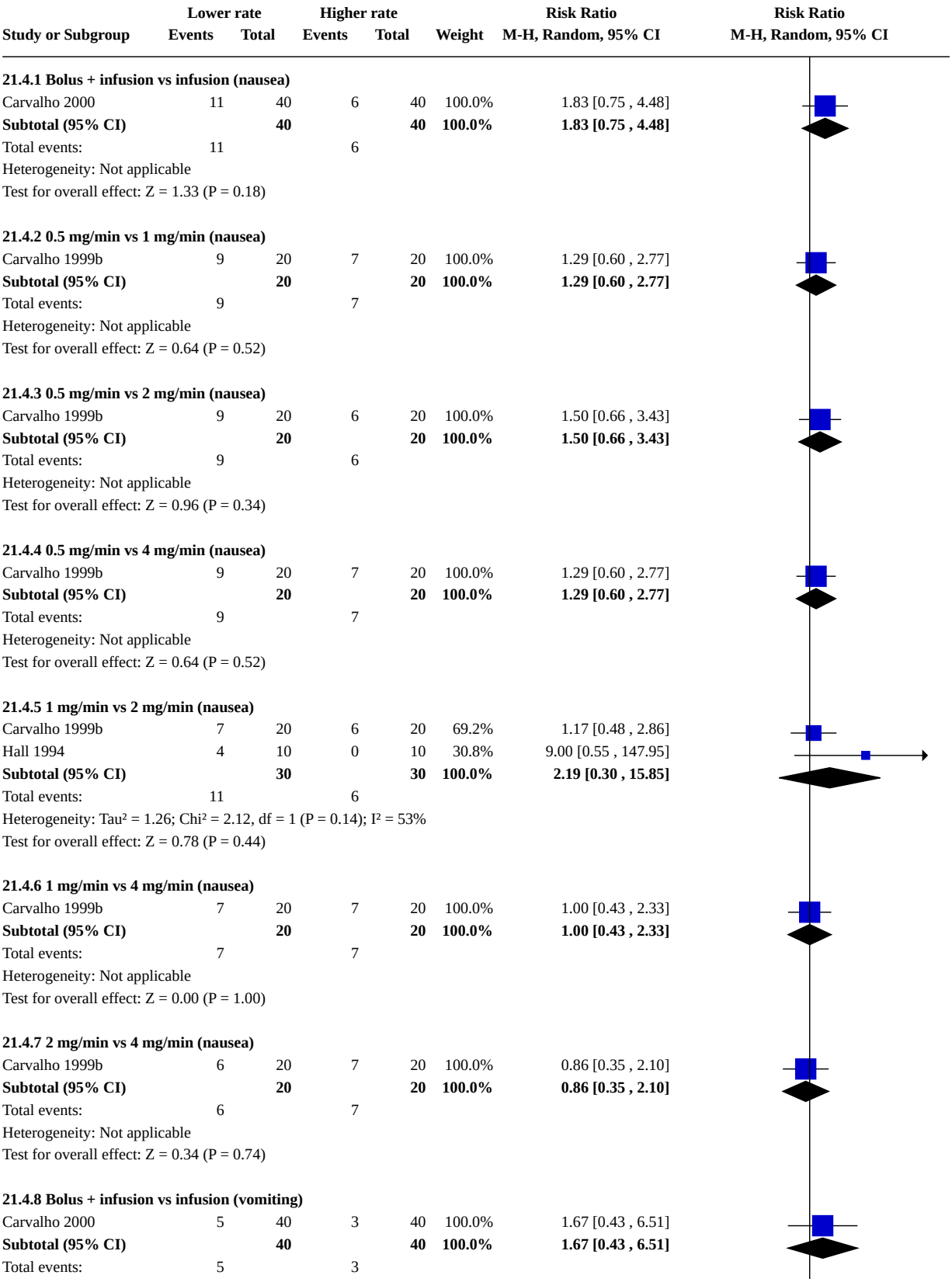


Analysis 21.3. Comparison 21: Ephedrine: different rates, Outcome 3: Women with bradycardia

Study or Subgroup	Lower rate Events	Lower rate Total	Higher rate Events	Higher rate Total	Weight	Risk Ratio M-H, Random, 95% CI
21.3.1 1 mg/min vs 2 mg/min						
Hall 1994	0	10	0	9		Not estimable
Subtotal (95% CI)		**10**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**10**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

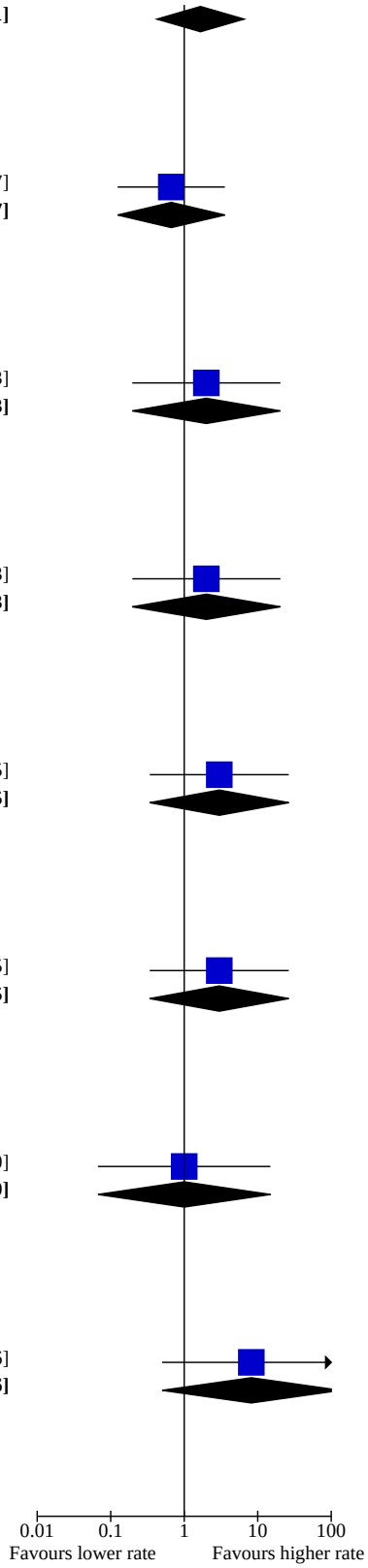


Analysis 21.4. Comparison 21: Ephedrine: different rates, Outcome 4: Women with nausea and/or vomiting



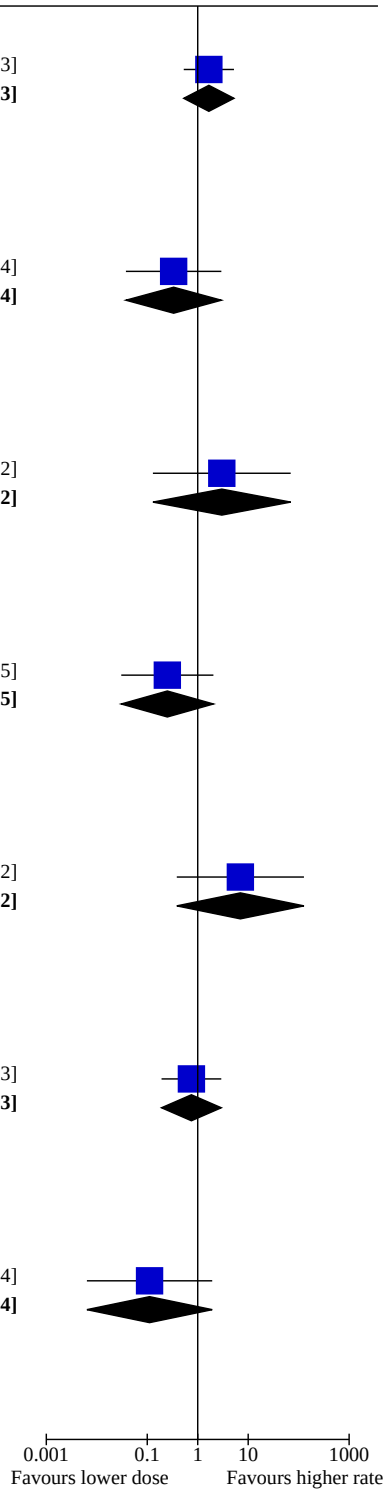
Analysis 21.4. (Continued)

Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.67 [0.43 , 6.51]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
21.4.9 0.5 mg/min vs 1 mg/min (vomiting)						
Carvalho 1999b	2	20	3	20	100.0%	0.67 [0.12 , 3.57]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.67 [0.12 , 3.57]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
21.4.10 0.5 mg/min vs 2 mg/min (vomiting)						
Carvalho 1999b	2	20	1	20	100.0%	2.00 [0.20 , 20.33]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.00 [0.20 , 20.33]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
21.4.11 0.5 mg/min vs 4 mg/min (vomiting)						
Carvalho 1999b	2	20	1	20	100.0%	2.00 [0.20 , 20.33]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.00 [0.20 , 20.33]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
21.4.12 1 mg/min vs 2 mg/min (vomiting)						
Carvalho 1999b	3	20	1	20	100.0%	3.00 [0.34 , 26.45]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.34 , 26.45]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
21.4.13 1 mg/min vs 4 mg/min (vomiting)						
Carvalho 1999b	3	20	1	20	100.0%	3.00 [0.34 , 26.45]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.34 , 26.45]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
21.4.14 2 mg/min vs 4 mg/min (vomiting)						
Carvalho 1999b	1	20	1	20	100.0%	1.00 [0.07 , 14.90]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.07 , 14.90]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
21.4.15 1 mg/min vs 2 mg/min (nausea or vomiting)						
Hall 1994	4	10	0	9	100.0%	8.18 [0.50 , 133.66]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**8.18 [0.50 , 133.66]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						



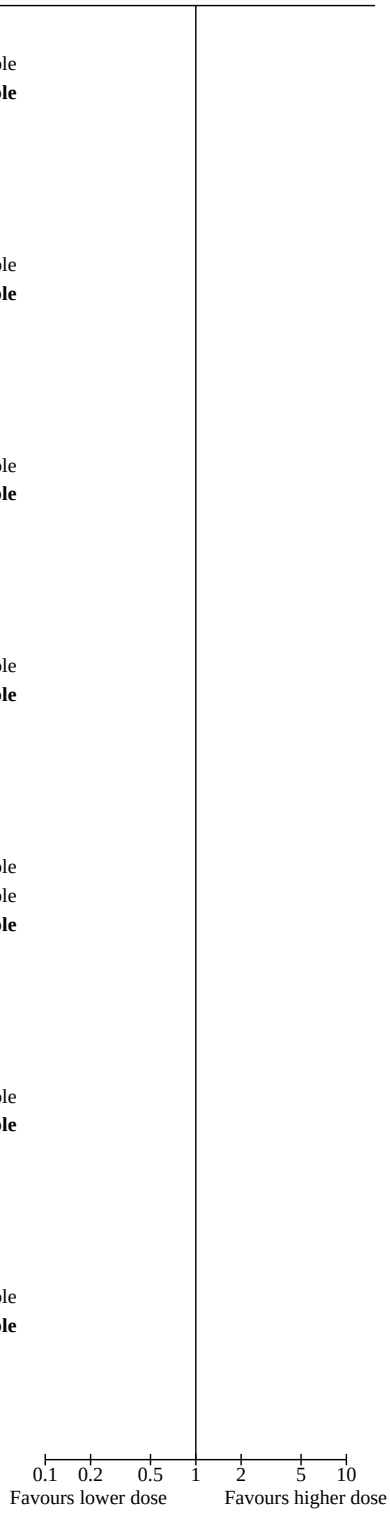
Analysis 21.5. Comparison 21: Ephedrine: different rates, Outcome 5: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Lower rate Events	Lower rate Total	Higher rate Events	Higher rate Total	Weight	Risk Ratio M-H, Random, 95% CI
21.5.1 Bolus + infusion vs infusion						
Carvalho 2000	7	40	4	38	100.0%	1.66 [0.53 , 5.23]
Subtotal (95% CI)		**40**		**38**	**100.0%**	**1.66 [0.53 , 5.23]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						
21.5.2 0.5 mg/min vs 1 mg/min						
Carvalho 1999b	1	20	3	20	100.0%	0.33 [0.04 , 2.94]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.04 , 2.94]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
21.5.3 0.5 mg/min vs 2 mg/min						
Carvalho 1999b	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)						
21.5.4 0.5 mg/min vs 4 mg/min						
Carvalho 1999b	1	20	4	20	100.0%	0.25 [0.03 , 2.05]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.25 [0.03 , 2.05]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
21.5.5 1 mg/min vs 2 mg/min						
Carvalho 1999b	3	20	0	20	100.0%	7.00 [0.38 , 127.32]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**7.00 [0.38 , 127.32]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
21.5.6 1 mg/min vs 4 mg/min						
Carvalho 1999b	3	20	4	20	100.0%	0.75 [0.19 , 2.93]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.75 [0.19 , 2.93]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
21.5.7 2 mg/min vs 4 mg/min						
Carvalho 1999b	0	20	4	20	100.0%	0.11 [0.01 , 1.94]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.11 [0.01 , 1.94]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						



Analysis 21.6. Comparison 21: Ephedrine: different rates, Outcome 6: Neonatal Apgar score at 5 min

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
21.6.1 Bolus + infusion vs infusion (Apgar < 7)						
Carvalho 2000	0	40	0	40		Not estimable
Subtotal (95% CI)		**40**		**40**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
21.6.2 0.5 mg/min vs 1 mg/min (Apgar < 8)						
Carvalho 1999b	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						
21.6.3 0.5 mg/min vs 2 mg/min (Apgar < 8)						
Carvalho 1999b	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						
21.6.4 0.5 mg/min vs 4 mg/min (Apgar < 8)						
Carvalho 1999b	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						
21.6.5 1 mg/min vs 2 mg/min (Apgar < 8)						
Carvalho 1999b	0	20	0	20		Not estimable
Hall 1994	0	10	0	9		Not estimable
Subtotal (95% CI)		**30**		**29**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
21.6.6 1 mg/min vs 4 mg/min (Apgar < 8)						
Carvalho 1999b	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						
21.6.7 2 mg/min vs 4 mg/min (Apgar < 8)						
Carvalho 1999b	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						

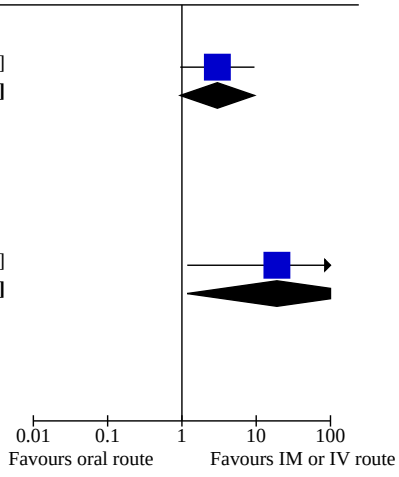


Comparison 22. Ephedrine: oral vs IM or IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Women with hypotension requiring intervention	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1.1 Oral vs IM	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.95, 9.48]
22.1.2 Oral vs IV	1	40	Risk Ratio (M-H, Random, 95% CI)	19.00 [1.18, 305.88]
22.2 Women with hypertension requiring intervention	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.2.1 Oral vs IM	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
22.2.2 Oral vs IV	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
22.3 Women with nausea and vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.3.1 Oral vs IM	1	40	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.34, 5.21]
22.3.2 Oral vs IV	1	40	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]

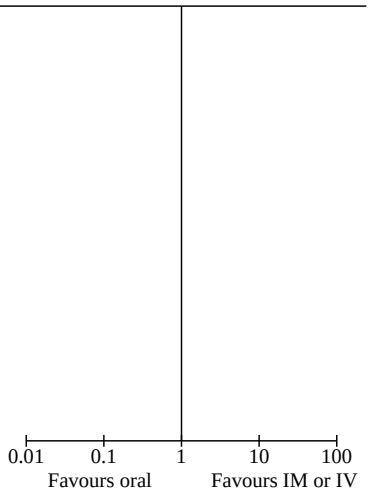
Analysis 22.1. Comparison 22: Ephedrine: oral vs IM or IV, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	oral Events	oral Total	IM or IV Events	IM or IV Total	Weight	Risk Ratio M-H, Random, 95% CI
22.1.1 Oral vs IM						
Chohedri 2007	9	20	3	20	100.0%	3.00 [0.95 , 9.48]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.95 , 9.48]**
Total events:	9		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
22.1.2 Oral vs IV						
Chohedri 2007	9	20	0	20	100.0%	19.00 [1.18 , 305.88]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**19.00 [1.18 , 305.88]**
Total events:	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 30.9%						



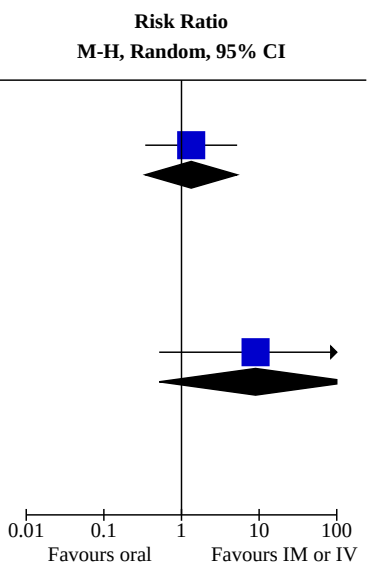
Analysis 22.2. Comparison 22: Ephedrine: oral vs IM or IV, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	oral Events	oral Total	IM or IV Events	IM or IV Total	Weight	Risk Ratio M-H, Random, 95% CI
22.2.1 Oral vs IM						
Chohedri 2007	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						
22.2.2 Oral vs IV						
Chohedri 2007	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						
Test for subgroup differences: Not applicable						



Analysis 22.3. Comparison 22: Ephedrine: oral vs IM or IV, Outcome 3: Women with nausea and vomiting

Study or Subgroup	oral Events	oral Total	IM or IV Events	IM or IV Total	Weight	Risk Ratio M-H, Random, 95% CI
22.3.1 Oral vs IM						
Chohedri 2007	4	20	3	20	100.0%	1.33 [0.34 , 5.21]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.33 [0.34 , 5.21]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
22.3.2 Oral vs IV						
Chohedri 2007	4	20	0	20	100.0%	9.00 [0.52 , 156.91]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**9.00 [0.52 , 156.91]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: $Chi^2 = 1.40$, df = 1 (P = 0.24), $I^2 = 28.4\%$						



Comparison 23. Ephedrine: IM vs IV

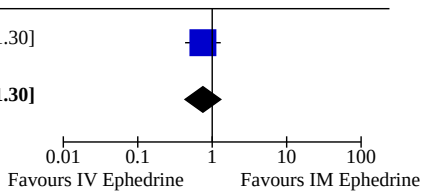
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Women with hypotension requiring intervention	1	60	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.43, 1.30]
23.2 Women with hypertension requiring intervention	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.3 Apgar < 8 at 5 min	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 23.1. Comparison 23: Ephedrine: IM vs IV, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	IM Events	IM Total	IV Events	IV Total	Weight	Risk Ratio M-H, Random, 95% CI
Pouliou 2006	12	30	16	30	100.0%	0.75 [0.43 , 1.30]
Total (95% CI)		**30**		**30**	**100.0%**	**0.75 [0.43 , 1.30]**
Total events:	12		16			

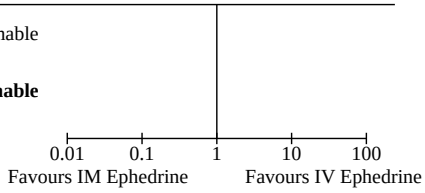
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 23.2. Comparison 23: Ephedrine: IM vs IV, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	IM Events	IM Total	IV Events	IV Total	Weight	Risk Ratio M-H, Random, 95% CI
Pouliou 2006	0	30	0	30		Not estimable
Total (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			

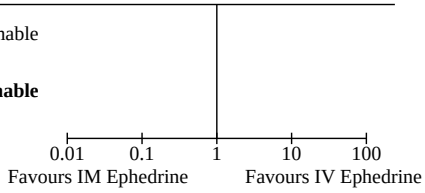
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 23.3. Comparison 23: Ephedrine: IM vs IV, Outcome 3: Apgar < 8 at 5 min

Study or Subgroup	IM Events	IM Total	IV Events	IV Total	Weight	Risk Ratio M-H, Random, 95% CI
Pouliou 2006	0	30	0	30		Not estimable
Total (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			

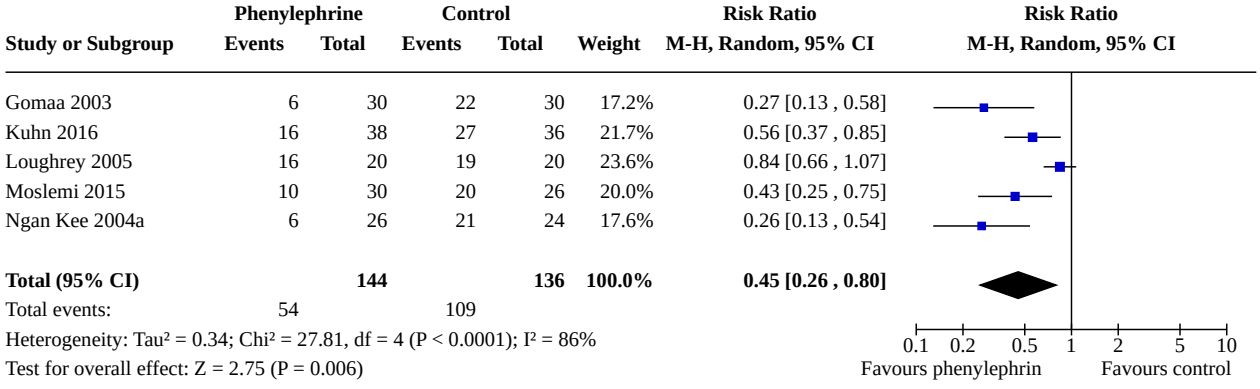
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Comparison 24. Phenylephrine vs control

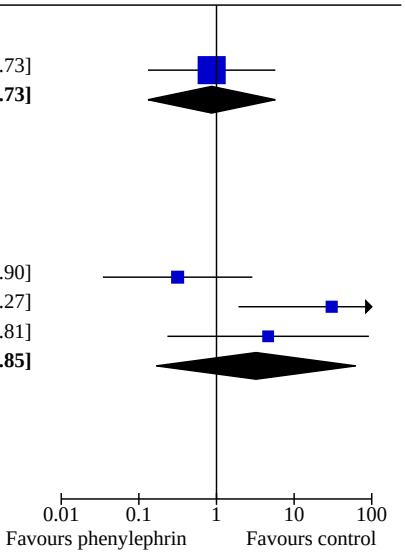
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Women with hypotension requiring intervention	5	280	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.26, 0.80]
24.2 Women with cardiac dysrhythmia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.2.1 Tachycardia	1	56	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.13, 5.73]
24.2.2 Bradycardia	3	180	Risk Ratio (M-H, Random, 95% CI)	3.23 [0.17, 61.85]
24.3 Women with nausea and/or vomiting	3	180	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.16, 2.98]
24.4 Neonates with acidosis (pH < 7.2)	1	49	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.50]
24.5 Neonates with Apgar < 7 at 5 min	1	50	Risk Ratio (M-H, Random, 95% CI)	Not estimable
24.6 Neonates with Apgar < 8 at 5 min	2	96	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 24.1. Comparison 24: Phenylephrine vs control, Outcome 1: Women with hypotension requiring intervention



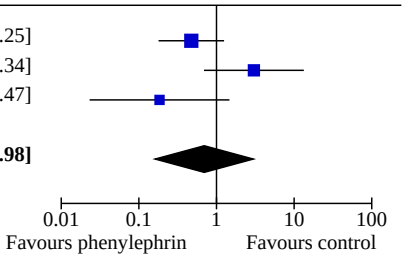
Analysis 24.2. Comparison 24: Phenylephrine vs control, Outcome 2: Women with cardiac dysrhythmia

Study or Subgroup	Phenylephrine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
24.2.1 Tachycardia						
Moslemi 2015	2	30	2	26	100.0%	0.87 [0.13 , 5.73]
Subtotal (95% CI)		**30**		**26**	**100.0%**	**0.87 [0.13 , 5.73]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
24.2.2 Bradycardia						
Kuhn 2016	1	38	3	36	36.3%	0.32 [0.03 , 2.90]
Moslemi 2015	17	30	0	26	32.6%	30.48 [1.92 , 483.27]
Ngan Kee 2004a	2	26	0	24	31.1%	4.63 [0.23 , 91.81]
Subtotal (95% CI)		**94**		**86**	**100.0%**	**3.23 [0.17 , 61.85]**
Total events:	20		3			
Heterogeneity: Tau² = 4.97; Chi² = 7.49, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%						



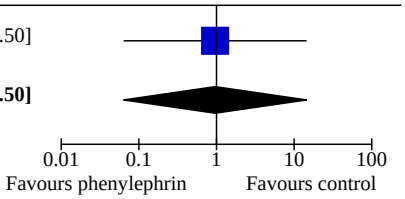
Analysis 24.3. Comparison 24: Phenylephrine vs control, Outcome 3: Women with nausea and/or vomiting

Study or Subgroup	Phenylephrine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kuhn 2016	5	38	10	36	41.6%	0.47 [0.18 , 1.25]
Moslemi 2015	7	30	2	26	33.4%	3.03 [0.69 , 13.34]
Ngan Kee 2004a	1	26	5	24	25.1%	0.18 [0.02 , 1.47]
Total (95% CI)		**94**		**86**	**100.0%**	**0.70 [0.16 , 2.98]**
Total events:	13		17			
Heterogeneity: Tau² = 1.08; Chi² = 5.97, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Not applicable						



Analysis 24.4. Comparison 24: Phenylephrine vs control, Outcome 4: Neonates with acidosis (pH < 7.2)

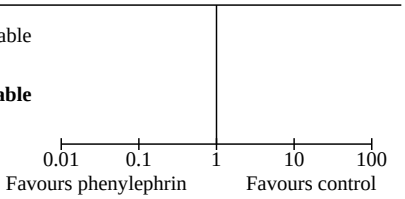
Study or Subgroup	Phenylephrine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2004a	1	25	1	24	100.0%	0.96 [0.06 , 14.50]
Total (95% CI)		**25**		**24**	**100.0%**	**0.96 [0.06 , 14.50]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Not applicable						



Analysis 24.5. Comparison 24: Phenylephrine vs control, Outcome 5: Neonates with Apgar < 7 at 5 min

Study or Subgroup	Phenylephrine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2004a	0	26	0	24		Not estimable
Total (95% CI)		**26**		**24**		**Not estimable**
Total events:	0		0			

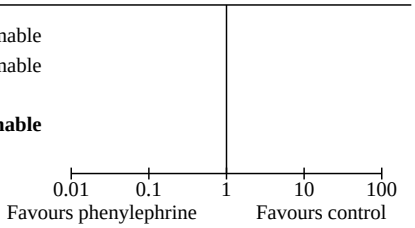
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 24.6. Comparison 24: Phenylephrine vs control, Outcome 6: Neonates with Apgar < 8 at 5 min

Study or Subgroup	Phenylephrine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Loughrey 2005	0	20	0	20		Not estimable
Moslemi 2015	0	30	0	26		Not estimable
Total (95% CI)		**50**		**46**		**Not estimable**
Total events:	0		0			

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



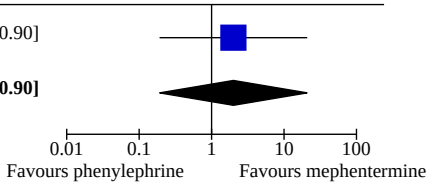
Comparison 25. Phenylephrine vs mephentermine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Women with hypotension requiring intervention	1	60	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.90]
25.2 Women with hypertension requiring intervention	1	60	Risk Ratio (M-H, Random, 95% CI)	17.00 [1.03, 281.91]
25.3 Cardiac dysrhythmia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.3.1 Bradycardia	1	60	Risk Ratio (M-H, Random, 95% CI)	15.00 [0.89, 251.42]
25.4 Nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.4.1 Nausea	1	60	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.00]
25.4.2 Vomiting	1	60	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.26]

Analysis 25.1. Comparison 25: Phenylephrine vs mephentermine, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	phenylephrine Events	phenylephrine Total	mephentermine Events	mephentermine Total	Weight	Risk Ratio M-H, Random, 95% CI
Mohta 2010	2	30	1	30	100.0%	2.00 [0.19 , 20.90]
Total (95% CI)		**30**		**30**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			

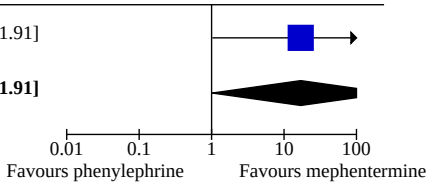
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 25.2. Comparison 25: Phenylephrine vs mephentermine, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	phenylephrine Events	phenylephrine Total	mephentermine Events	mephentermine Total	Weight	Risk Ratio M-H, Random, 95% CI
Mohta 2010	8	30	0	30	100.0%	17.00 [1.03 , 281.91]
Total (95% CI)		**30**		**30**	**100.0%**	**17.00 [1.03 , 281.91]**
Total events:	8		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

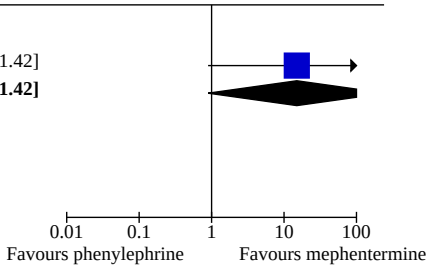


Analysis 25.3. Comparison 25: Phenylephrine vs mephentermine, Outcome 3: Cardiac dysrhythmia

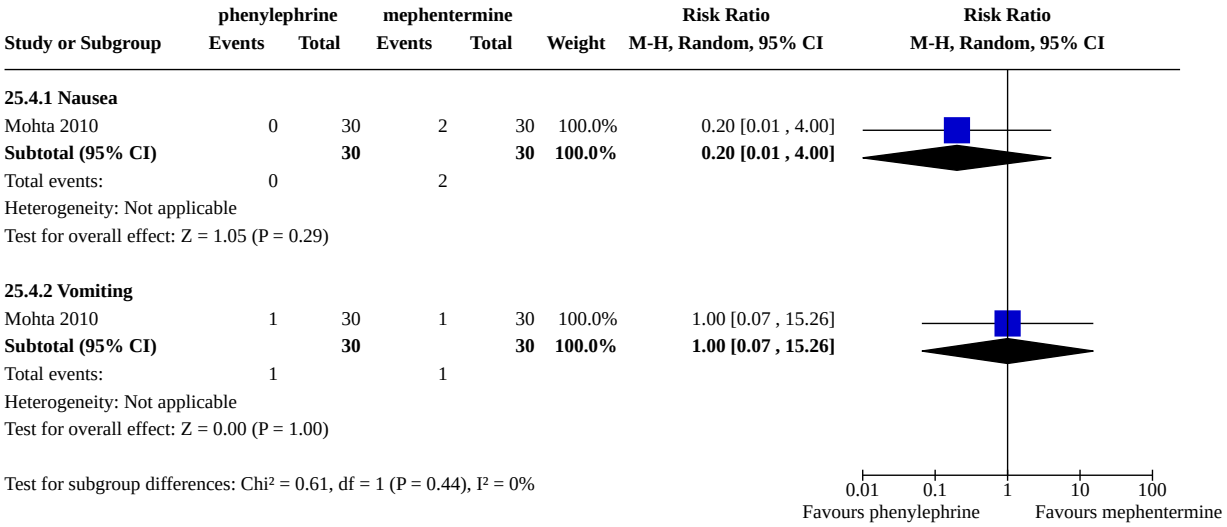
Study or Subgroup	phenylephrine Events	phenylephrine Total	mephentermine Events	mephentermine Total	Weight	Risk Ratio M-H, Random, 95% CI
25.3.1 Bradycardia						
Mohta 2010	7	30	0	30	100.0%	15.00 [0.89 , 251.42]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**15.00 [0.89 , 251.42]**
Total events:	7		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)

Test for subgroup differences: Not applicable



Analysis 25.4. Comparison 25: Phenylephrine vs mephentermine, Outcome 4: Nausea and/or vomiting



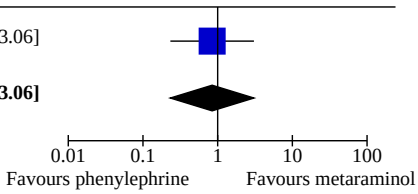
Comparison 26. Phenylephrine vs metaraminol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Women with hypotension requiring intervention	1	59	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.23, 3.06]
26.2 Women with hypertension requiring intervention	1	59	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.83]
26.3 Women with bradycardia	1	59	Risk Ratio (M-H, Random, 95% CI)	Not estimable
26.4 Women with nausea and/or vomiting	1	59	Risk Ratio (M-H, Random, 95% CI)	Not estimable
26.5 Neonatal pH < 7.2	1	59	Risk Ratio (M-H, Random, 95% CI)	Not estimable
26.6 Neonatal Apgar score < 8 at 5 min	1	59	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 26.1. Comparison 26: Phenylephrine vs metaraminol, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	4	32	4	27	100.0%	0.84 [0.23 , 3.06]
Total (95% CI)		**32**		**27**	**100.0%**	**0.84 [0.23 , 3.06]**
Total events:	4		4			

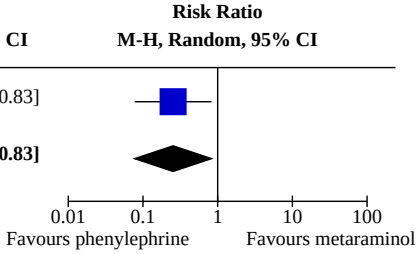
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 26.2. Comparison 26: Phenylephrine vs metaraminol, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	3	32	10	27	100.0%	0.25 [0.08 , 0.83]
Total (95% CI)		**32**		**27**	**100.0%**	**0.25 [0.08 , 0.83]**
Total events:	3		10			

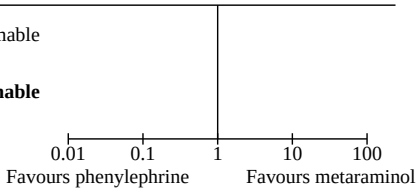
Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 26.3. Comparison 26: Phenylephrine vs metaraminol, Outcome 3: Women with bradycardia

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	32	0	27		Not estimable
Total (95% CI)		**32**		**27**		**Not estimable**
Total events:	0		0			

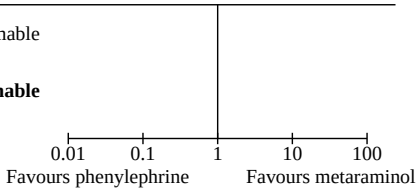
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 26.4. Comparison 26: Phenylephrine vs metaraminol, Outcome 4: Women with nausea and/or vomiting

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	32	0	27		Not estimable
Total (95% CI)		**32**		**27**		**Not estimable**
Total events:	0		0			

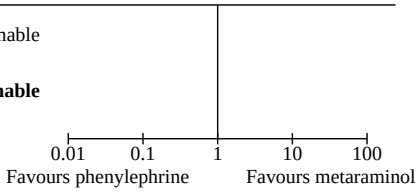
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 26.5. Comparison 26: Phenylephrine vs metaraminol, Outcome 5: Neonatal pH < 7.2

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	32	0	27		Not estimable
Total (95% CI)		**32**		**27**		**Not estimable**
Total events:	0		0			

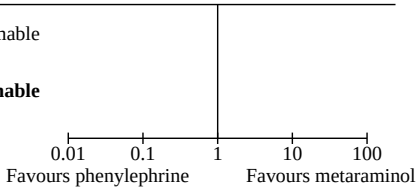
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 26.6. Comparison 26: Phenylephrine vs metaraminol, Outcome 6: Neonatal Apgar score < 8 at 5 min

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Metaraminol Events	Metaraminol Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhardwaj 2013	0	32	0	27		Not estimable
Total (95% CI)		**32**		**27**		**Not estimable**
Total events:	0		0			

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



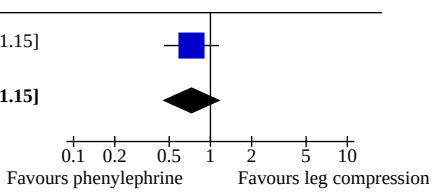
Comparison 27. Phenylephrine vs leg compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Women with hypotension requiring intervention	1	76	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.15]
27.2 Women with bradycardia	1	76	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.28]
27.3 Women with nausea and/or vomiting	1	76	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.32, 3.17]

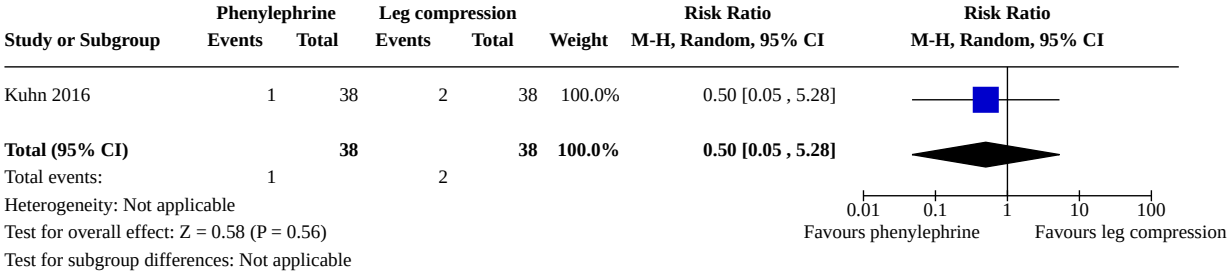
Analysis 27.1. Comparison 27: Phenylephrine vs leg compression, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Phenylephrine Events	Phenylephrine Total	Leg compression Events	Leg compression Total	Weight	Risk Ratio M-H, Random, 95% CI
Kuhn 2016	16	38	22	38	100.0%	0.73 [0.46 , 1.15]
Total (95% CI)		**38**		**38**	**100.0%**	**0.73 [0.46 , 1.15]**
Total events:	16		22			

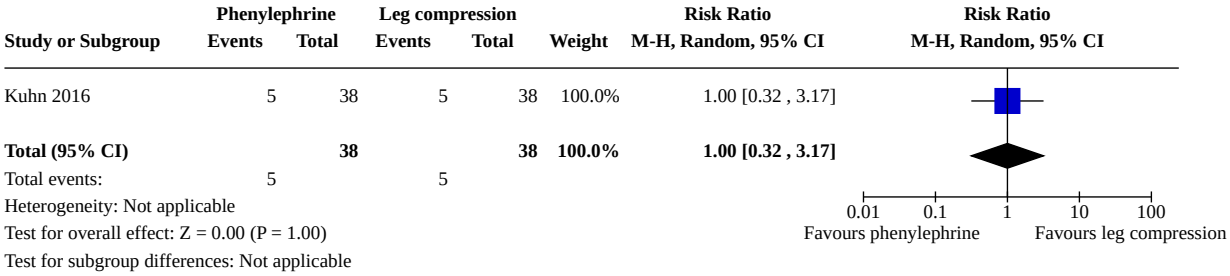
Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 27.2. Comparison 27: Phenylephrine vs leg compression, Outcome 2: Women with bradycardia



Analysis 27.3. Comparison 27: Phenylephrine vs leg compression, Outcome 3: Women with nausea and/or vomiting

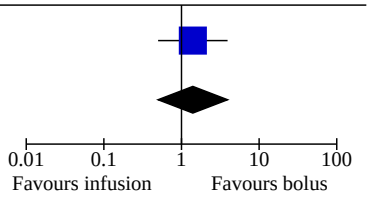


Comparison 28. Phenylephrine: infusion vs bolus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Women with hypotension requiring intervention	1	60	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.50, 3.92]
28.2 Women with cardiac dysrhythmia	1	60	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.59, 2.51]
28.2.1 Bradycardia	1	60	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.59, 2.51]
28.3 Women with nausea/vomiting	1	60	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.18, 1.15]
28.4 Neonatal Apgar score < 8 at 5 min	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable

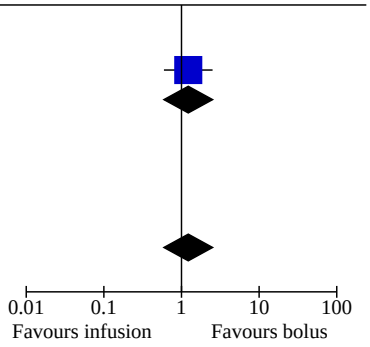
Analysis 28.1. Comparison 28: Phenylephrine: infusion vs bolus, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	infusion Events	infusion Total	bolus Events	bolus Total	Weight	Risk Ratio M-H, Random, 95% CI
Doherty 2012	7	30	5	30	100.0%	1.40 [0.50 , 3.92]
Total (95% CI)		**30**		**30**	**100.0%**	**1.40 [0.50 , 3.92]**
Total events:	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						



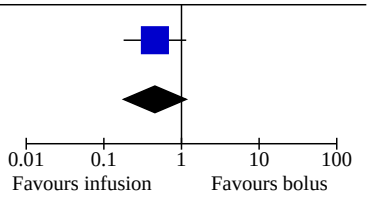
Analysis 28.2. Comparison 28: Phenylephrine: infusion vs bolus, Outcome 2: Women with cardiac dysrhythmia

Study or Subgroup	infusion Events	infusion Total	bolus Events	bolus Total	Weight	Risk Ratio M-H, Random, 95% CI
28.2.1 Bradycardia						
Doherty 2012	11	30	9	30	100.0%	1.22 [0.59 , 2.51]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.22 [0.59 , 2.51]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.59)						
Total (95% CI)		**30**		**30**	**100.0%**	**1.22 [0.59 , 2.51]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.59)						
Test for subgroup differences: Not applicable						

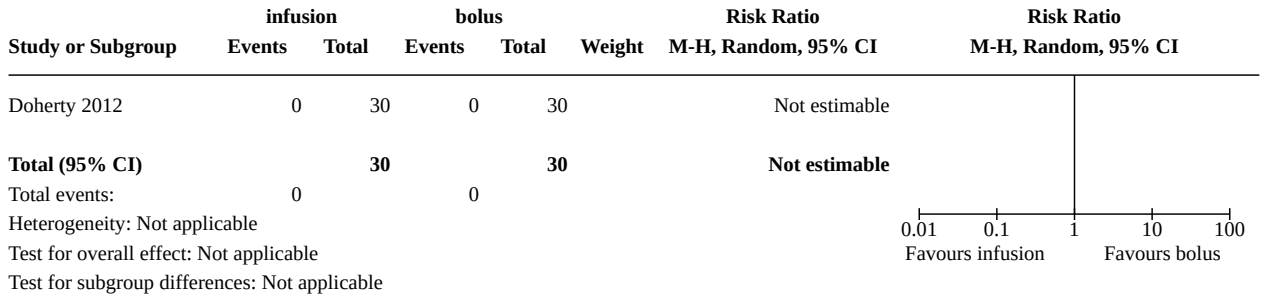


Analysis 28.3. Comparison 28: Phenylephrine: infusion vs bolus, Outcome 3: Women with nausea/vomiting

Study or Subgroup	infusion Events	infusion Total	bolus Events	bolus Total	Weight	Risk Ratio M-H, Random, 95% CI
Doherty 2012	5	30	11	30	100.0%	0.45 [0.18 , 1.15]
Total (95% CI)		**30**		**30**	**100.0%**	**0.45 [0.18 , 1.15]**
Total events:	5		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Not applicable						



Analysis 28.4. Comparison 28: Phenylephrine: infusion vs bolus, Outcome 4: Neonatal Apgar score < 8 at 5 min

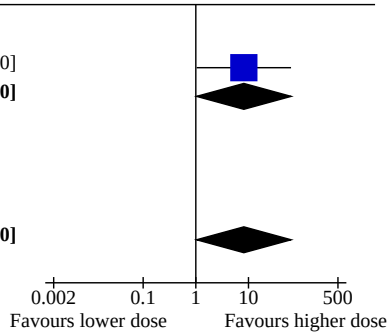


Comparison 29. Phenylephrine: different doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Women with hypotension requiring intervention	1	117	Risk Ratio (M-H, Random, 95% CI)	8.17 [1.04, 64.30]
29.1.1 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	8.17 [1.04, 64.30]
29.2 Women with hypertension requiring intervention	1	117	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.02]
29.2.1 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.02]
29.3 Women with cardiac dysrhythmia	1	117	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.80]
29.3.1 Bradycardia: 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.80]
29.4 Women with nausea and/or vomiting	1	117	Risk Ratio (M-H, Random, 95% CI)	3.50 [0.37, 32.67]
29.4.1 Nausea and vomiting: 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	3.50 [0.37, 32.67]
29.5 Neonatal cord blood pH < 7.2	1	117	Risk Ratio (M-H, Random, 95% CI)	Not estimable
29.5.1 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	Not estimable
29.6 Neonatal Apgar score < 8 at 5 min	1	117	Risk Ratio (M-H, Random, 95% CI)	Not estimable
29.6.1 50 µg/mL vs 100 µg/mL	1	117	Risk Ratio (M-H, Random, 95% CI)	Not estimable

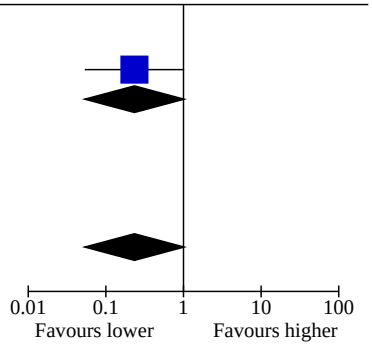
Analysis 29.1. Comparison 29: Phenylephrine: different doses, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.1.1 50 µg/mL vs 100 µg/mL						
Ansari 2011	7	54	1	63	100.0%	8.17 [1.04 , 64.30]
Subtotal (95% CI)		**54**		**63**	**100.0%**	**8.17 [1.04 , 64.30]**
Total events:	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Total (95% CI)		**54**		**63**	**100.0%**	**8.17 [1.04 , 64.30]**
Total events:	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Test for subgroup differences: Not applicable						



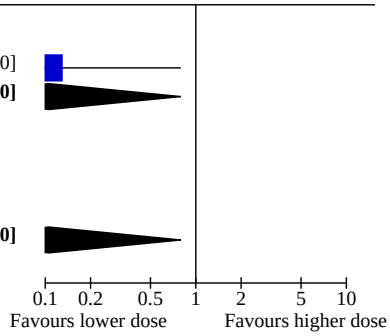
Analysis 29.2. Comparison 29: Phenylephrine: different doses, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.2.1 50 µg/mL vs 100 µg/mL						
Ansari 2011	2	54	10	63	100.0%	0.23 [0.05 , 1.02]
Subtotal (95% CI)		**54**		**63**	**100.0%**	**0.23 [0.05 , 1.02]**
Total events:	2		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
Total (95% CI)		**54**		**63**	**100.0%**	**0.23 [0.05 , 1.02]**
Total events:	2		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
Test for subgroup differences: Not applicable						



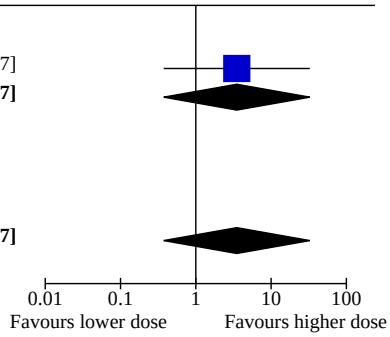
Analysis 29.3. Comparison 29: Phenylephrine: different doses, Outcome 3: Women with cardiac dysrhythmia

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.3.1 Bradycardia: 50 µg/mL vs 100 µg/mL						
Ansari 2011	1	54	11	63	100.0%	0.11 [0.01 , 0.80]
Subtotal (95% CI)		**54**		**63**	**100.0%**	**0.11 [0.01 , 0.80]**
Total events:	1		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						
Total (95% CI)		**54**		**63**	**100.0%**	**0.11 [0.01 , 0.80]**
Total events:	1		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: Not applicable						



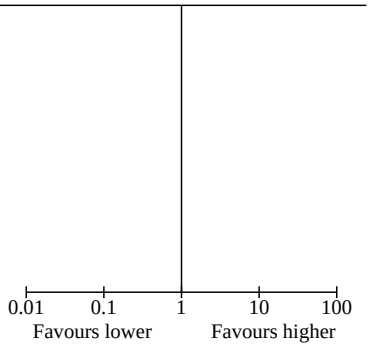
Analysis 29.4. Comparison 29: Phenylephrine: different doses, Outcome 4: Women with nausea and/or vomiting

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.4.1 Nausea and vomiting: 50 µg/mL vs 100 µg/mL						
Ansari 2011	3	54	1	63	100.0%	3.50 [0.37 , 32.67]
Subtotal (95% CI)		**54**		**63**	**100.0%**	**3.50 [0.37 , 32.67]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)		**54**		**63**	**100.0%**	**3.50 [0.37 , 32.67]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						



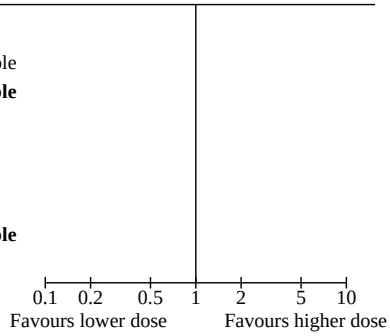
Analysis 29.5. Comparison 29: Phenylephrine: different doses, Outcome 5: Neonatal cord blood pH < 7.2

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.5.1 50 µg/mL vs 100 µg/mL						
Ansari 2011	0	54	0	63		Not estimable
Subtotal (95% CI)		**54**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**54**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 29.6. Comparison 29: Phenylephrine: different doses, Outcome 6: Neonatal Apgar score < 8 at 5 min

Study or Subgroup	Lower dose Events	Lower dose Total	Higher dose Events	Higher dose Total	Weight	Risk Ratio M-H, Random, 95% CI
29.6.1 50 µg/mL vs 100 µg/mL						
Ansari 2011	0	54	0	63		Not estimable
Subtotal (95% CI)		**54**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**54**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



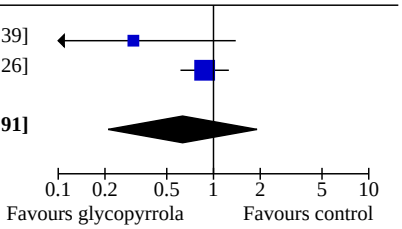
Comparison 30. Glycopyrrolate vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 Women with hypotension requiring intervention	2	142	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.21, 1.91]
30.2 Women with hypertension requiring intervention	1	93	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.31, 5.43]
30.3 Women with bradycardia	1	93	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 4.32]
30.4 Women with nausea and/or vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.4.1 Nausea or vomiting	1	93	Risk Ratio (M-H, Random, 95% CI)	2.49 [0.69, 9.04]
30.4.2 Nausea	1	49	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.36, 1.06]
30.4.3 Vomiting	1	49	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.59]
30.5 Neonates with Apgar score < 8 at 5 min	2	142	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 30.1. Comparison 30: Glycopyrrolate vs control, Outcome 1: Women with hypotension requiring intervention

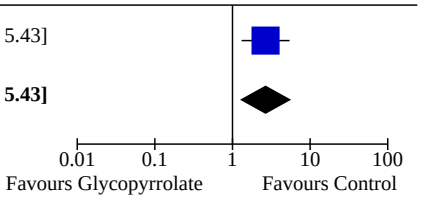
Study or Subgroup	Glycopyrrolate Events	Glycopyrrolate Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2013a	2	45	7	48	30.9%	0.30 [0.07 , 1.39]
Ure 1999	16	24	19	25	69.1%	0.88 [0.61 , 1.26]
Total (95% CI)		**69**		**73**	**100.0%**	**0.63 [0.21 , 1.91]**
Total events:	18		26			

Heterogeneity: Tau² = 0.43; Chi² = 2.34, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



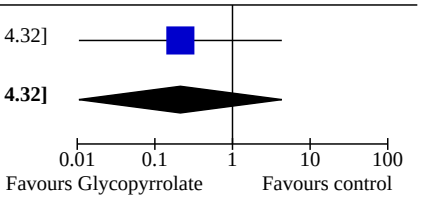
Analysis 30.2. Comparison 30: Glycopyrrolate vs control, Outcome 2: Women with hypertension requiring intervention

Study or Subgroup	Glycopyrrolate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2013a	20	45	8	48	100.0%	2.67 [1.31 , 5.43]
Total (95% CI)		**45**		**48**	**100.0%**	**2.67 [1.31 , 5.43]**
Total events:	20		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.70 (P = 0.007)						
Test for subgroup differences: Not applicable						



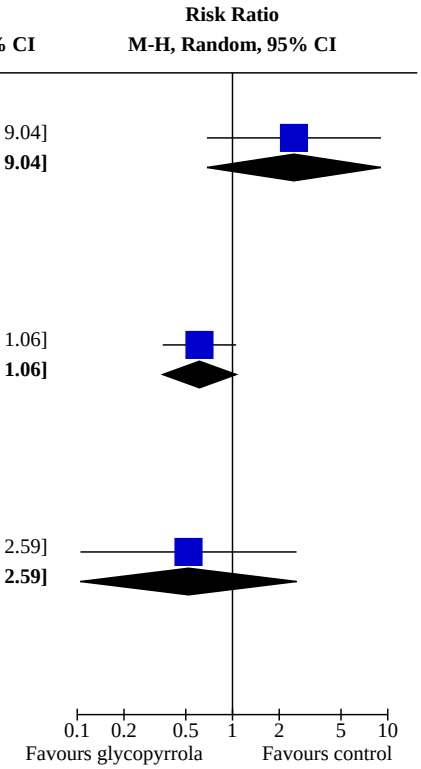
Analysis 30.3. Comparison 30: Glycopyrrolate vs control, Outcome 3: Women with bradycardia

Study or Subgroup	Glycopyrrolate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2013a	0	45	2	48	100.0%	0.21 [0.01 , 4.32]
Total (95% CI)		**45**		**48**	**100.0%**	**0.21 [0.01 , 4.32]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Not applicable						



Analysis 30.4. Comparison 30: Glycopyrrolate vs control, Outcome 4: Women with nausea and/or vomiting

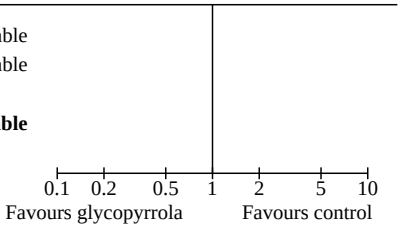
Study or Subgroup	Glycopyrrolate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
30.4.1 Nausea or vomiting						
Ngan Kee 2013a	7	45	3	48	100.0%	2.49 [0.69 , 9.04]
Subtotal (95% CI)		**45**		**48**	**100.0%**	**2.49 [0.69 , 9.04]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.17)						
30.4.2 Nausea						
Ure 1999	10	24	17	25	100.0%	0.61 [0.36 , 1.06]
Subtotal (95% CI)		**24**		**25**	**100.0%**	**0.61 [0.36 , 1.06]**
Total events:	10		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
30.4.3 Vomiting						
Ure 1999	2	24	4	25	100.0%	0.52 [0.10 , 2.59]
Subtotal (95% CI)		**24**		**25**	**100.0%**	**0.52 [0.10 , 2.59]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						



Analysis 30.5. Comparison 30: Glycopyrrolate vs control, Outcome 5: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Glycopyrrolate Events	Glycopyrrolate Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ngan Kee 2013a	0	45	0	48		Not estimable
Ure 1999	0	24	0	25		Not estimable
Total (95% CI)		**69**		**73**		**Not estimable**
Total events:	0		0			

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

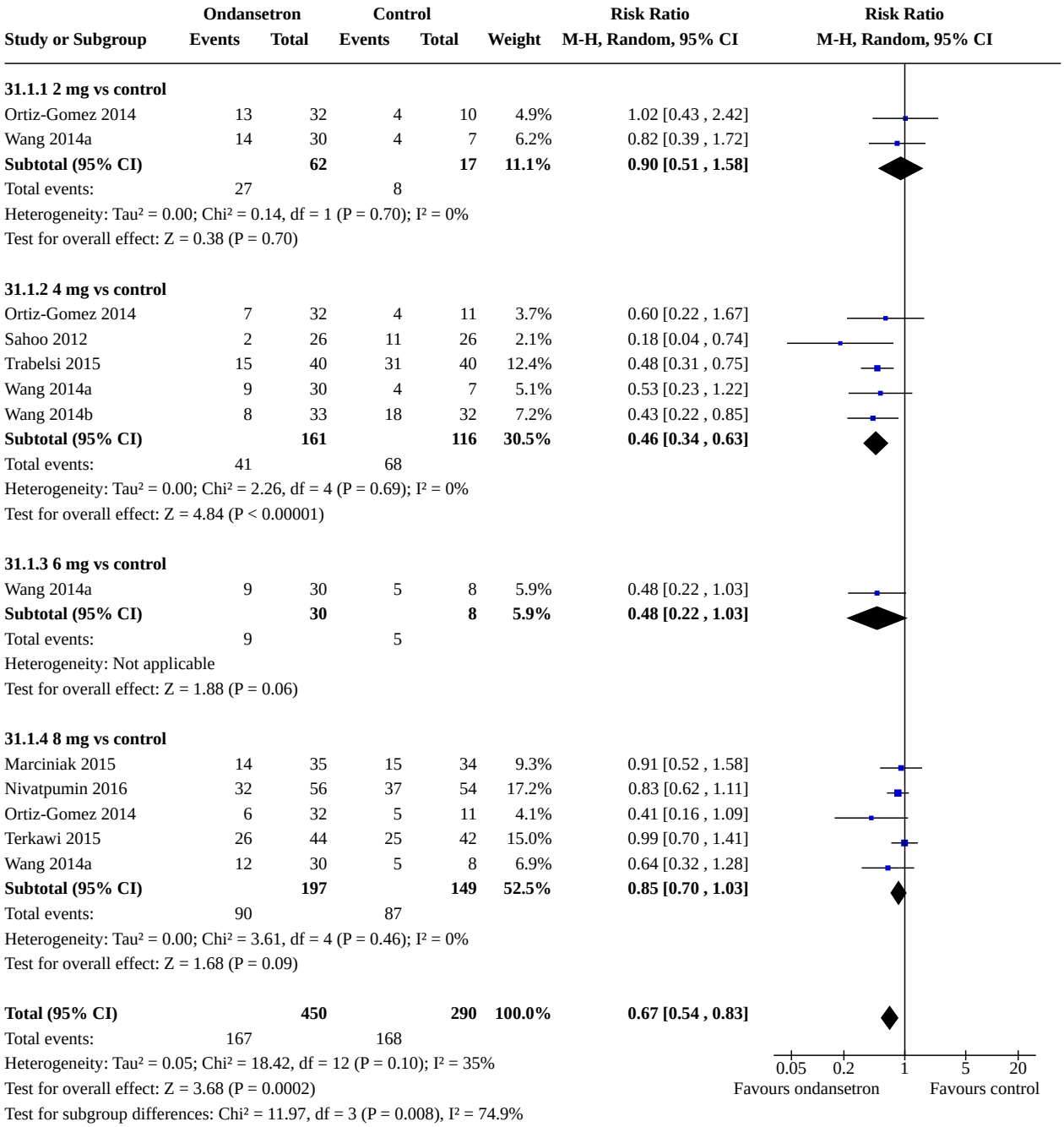


Comparison 31. Ondansetron vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Women with hypotension requiring intervention	8	740	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.54, 0.83]
31.1.1 2 mg vs control	2	79	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.51, 1.58]
31.1.2 4 mg vs control	5	277	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.63]
31.1.3 6 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.22, 1.03]
31.1.4 8 mg vs control	5	346	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]
31.2 Women with bradycardia	8	740	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.87]
31.2.1 2 mg vs control	2	79	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.02, 3.29]
31.2.2 4 mg vs control	5	277	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.16, 0.71]
31.2.3 6 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.2.4 8 mg vs control	5	346	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.38, 2.37]
31.3 Women with nausea or vomiting	7	653	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]
31.3.1 2 mg vs control	2	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.18, 1.59]
31.3.2 4 mg vs control	5	277	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]
31.3.3 6 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.74]
31.3.4 8 mg vs control	4	259	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.19, 0.76]
31.4 Women with anaphylaxis	1	150	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
31.4.1 2 mg vs control	1	37	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.4.2 4 mg vs control	1	37	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.4.3 6 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.4.4 8 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.5 Neonatal Apgar score < 8 at 5 min	3	284	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.5.1 2 mg vs control	1	37	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.5.2 4 mg vs control	2	102	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.5.3 6 mg vs control	1	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.5.4 8 mg vs control	2	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable
31.6 Neonatal pH < 7.2	2	134	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.05, 5.09]
31.6.1 4 mg vs control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.05, 5.09]
31.6.2 8 mg vs control	1	69	Risk Ratio (M-H, Random, 95% CI)	Not estimable

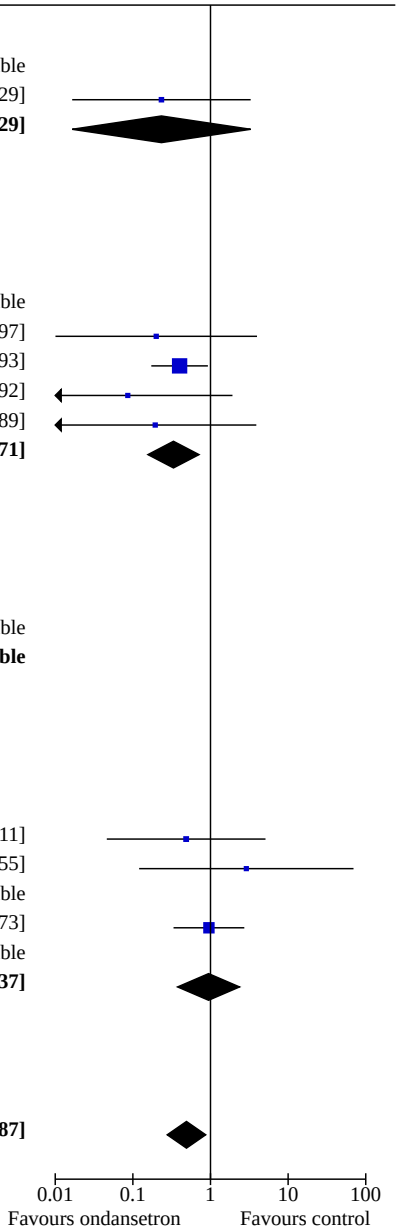
Analysis 31.1. Comparison 31: Ondansetron vs control, Outcome 1: Women with hypotension requiring intervention



Study or Subgroup	Ondansetron Events	Ondansetron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.1.1 2 mg vs control						
Ortiz-Gomez 2014	13	32	4	10	4.9%	1.02 [0.43 , 2.42]
Wang 2014a	14	30	4	7	6.2%	0.82 [0.39 , 1.72]
Subtotal (95% CI)		**62**		**17**	**11.1%**	**0.90 [0.51 , 1.58]**
Total events:	27		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
31.1.2 4 mg vs control						
Ortiz-Gomez 2014	7	32	4	11	3.7%	0.60 [0.22 , 1.67]
Sahoo 2012	2	26	11	26	2.1%	0.18 [0.04 , 0.74]
Trabelsi 2015	15	40	31	40	12.4%	0.48 [0.31 , 0.75]
Wang 2014a	9	30	4	7	5.1%	0.53 [0.23 , 1.22]
Wang 2014b	8	33	18	32	7.2%	0.43 [0.22 , 0.85]
Subtotal (95% CI)		**161**		**116**	**30.5%**	**0.46 [0.34 , 0.63]**
Total events:	41		68			
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 4 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.84 (P < 0.00001)						
31.1.3 6 mg vs control						
Wang 2014a	9	30	5	8	5.9%	0.48 [0.22 , 1.03]
Subtotal (95% CI)		**30**		**8**	**5.9%**	**0.48 [0.22 , 1.03]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
31.1.4 8 mg vs control						
Marciniak 2015	14	35	15	34	9.3%	0.91 [0.52 , 1.58]
Nivatpumin 2016	32	56	37	54	17.2%	0.83 [0.62 , 1.11]
Ortiz-Gomez 2014	6	32	5	11	4.1%	0.41 [0.16 , 1.09]
Terkawi 2015	26	44	25	42	15.0%	0.99 [0.70 , 1.41]
Wang 2014a	12	30	5	8	6.9%	0.64 [0.32 , 1.28]
Subtotal (95% CI)		**197**		**149**	**52.5%**	**0.85 [0.70 , 1.03]**
Total events:	90		87			
Heterogeneity: Tau² = 0.00; Chi² = 3.61, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**450**		**290**	**100.0%**	**0.67 [0.54 , 0.83]**
Total events:	167		168			
Heterogeneity: Tau² = 0.05; Chi² = 18.42, df = 12 (P = 0.10); I² = 35%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Test for subgroup differences: Chi² = 11.97, df = 3 (P = 0.008), I² = 74.9%						

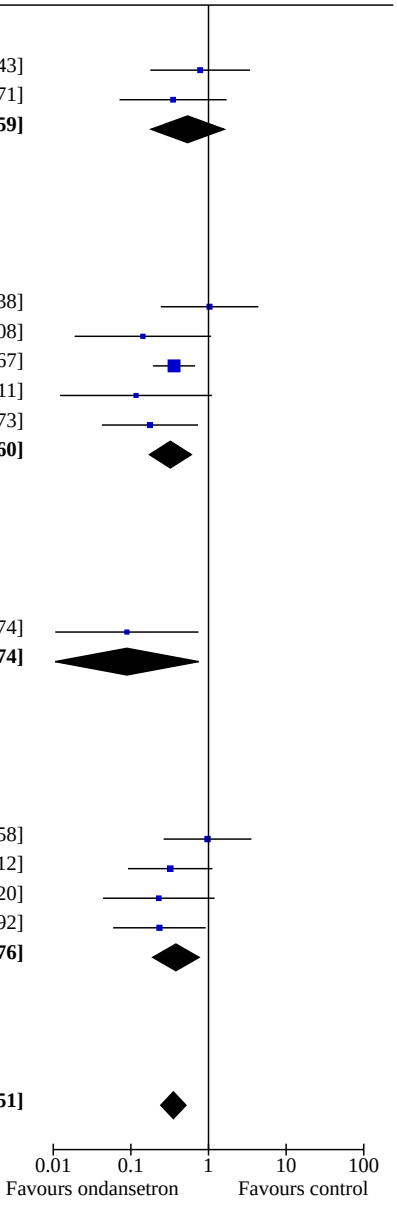
Analysis 31.2. Comparison 31: Ondansetron vs control, Outcome 2: Women with bradycardia

Study or Subgroup	Ondansetron Events	Ondansetron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.2.1 2 mg vs control						
Ortiz-Gomez 2014	0	32	0	10		Not estimable
Wang 2014a	1	30	1	7	4.6%	0.23 [0.02 , 3.29]
Subtotal (95% CI)		**62**		**17**	**4.6%**	**0.23 [0.02 , 3.29]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
31.2.2 4 mg vs control						
Ortiz-Gomez 2014	0	32	0	11		Not estimable
Sahoo 2012	0	26	2	26	3.6%	0.20 [0.01 , 3.97]
Trabelsi 2015	6	40	15	40	46.2%	0.40 [0.17 , 0.93]
Wang 2014a	0	30	1	7	3.4%	0.09 [0.00 , 1.92]
Wang 2014b	0	33	2	32	3.6%	0.19 [0.01 , 3.89]
Subtotal (95% CI)		**161**		**116**	**56.8%**	**0.33 [0.16 , 0.71]**
Total events:	6		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 2.84 (P = 0.004)						
31.2.3 6 mg vs control						
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.2.4 8 mg vs control						
Marciniak 2015	1	35	2	34	5.9%	0.49 [0.05 , 5.11]
Nivatpumin 2016	1	56	0	54	3.2%	2.89 [0.12 , 69.55]
Ortiz-Gomez 2014	0	32	0	11		Not estimable
Terkawi 2015	6	44	6	42	29.5%	0.95 [0.33 , 2.73]
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**197**		**149**	**38.6%**	**0.94 [0.38 , 2.37]**
Total events:	8		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**450**		**290**	**100.0%**	**0.49 [0.28 , 0.87]**
Total events:	15		29			
Heterogeneity: Tau² = 0.00; Chi² = 5.19, df = 7 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
Test for subgroup differences: Chi² = 3.26, df = 2 (P = 0.20), I² = 38.7%						



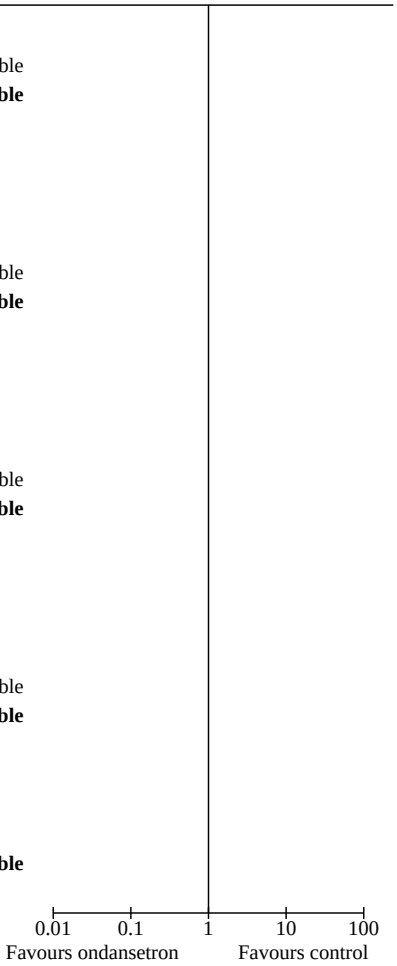
Analysis 31.3. Comparison 31: Ondansetron vs control, Outcome 3: Women with nausea or vomiting

Study or Subgroup	Ondansetron Events	Ondansetron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.3.1 2 mg vs control						
Ortiz-Gomez 2014	5	32	2	10	6.4%	0.78 [0.18 , 3.43]
Wang 2014a	3	30	2	7	5.5%	0.35 [0.07 , 1.71]
Subtotal (95% CI)		**62**		**17**	**11.9%**	**0.54 [0.18 , 1.59]**
Total events:	8		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
31.3.2 4 mg vs control						
Ortiz-Gomez 2014	6	32	2	11	6.7%	1.03 [0.24 , 4.38]
Sahoo 2012	1	26	7	26	3.4%	0.14 [0.02 , 1.08]
Trabelsi 2015	9	40	25	40	35.8%	0.36 [0.19 , 0.67]
Wang 2014a	1	30	2	7	2.7%	0.12 [0.01 , 1.11]
Wang 2014b	2	33	11	32	6.8%	0.18 [0.04 , 0.73]
Subtotal (95% CI)		**161**		**116**	**55.5%**	**0.32 [0.17 , 0.60]**
Total events:	19		47			
Heterogeneity: Tau² = 0.09; Chi² = 4.75, df = 4 (P = 0.31); I² = 16%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
31.3.3 6 mg vs control						
Wang 2014a	1	30	3	8	3.1%	0.09 [0.01 , 0.74]
Subtotal (95% CI)		**30**		**8**	**3.1%**	**0.09 [0.01 , 0.74]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.23 (P = 0.03)						
31.3.4 8 mg vs control						
Marciniak 2015	4	35	4	34	8.2%	0.97 [0.26 , 3.58]
Nivatpumin 2016	3	56	9	54	8.9%	0.32 [0.09 , 1.12]
Ortiz-Gomez 2014	2	32	3	11	5.1%	0.23 [0.04 , 1.20]
Wang 2014a	3	30	3	7	7.4%	0.23 [0.06 , 0.92]
Subtotal (95% CI)		**153**		**106**	**29.6%**	**0.38 [0.19 , 0.76]**
Total events:	12		19			
Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.76 (P = 0.006)						
Total (95% CI)		**406**		**247**	**100.0%**	**0.35 [0.24 , 0.51]**
Total events:	40		73			
Heterogeneity: Tau² = 0.00; Chi² = 10.42, df = 11 (P = 0.49); I² = 0%						
Test for overall effect: Z = 5.47 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.33, df = 3 (P = 0.51), I² = 0%						



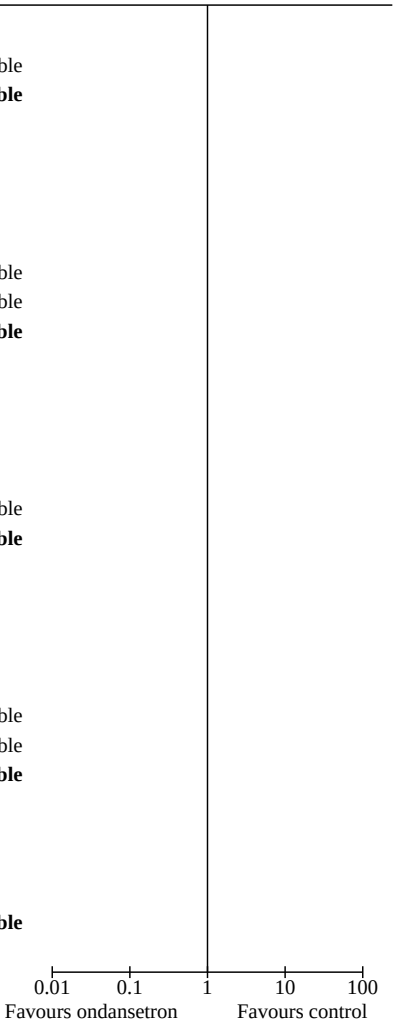
Analysis 31.4. Comparison 31: Ondansetron vs control, Outcome 4: Women with anaphylaxis

Study or Subgroup	Ondansetron Events	Ondansetron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.4.1 2 mg vs control						
Wang 2014a	0	30	0	7		Not estimable
Subtotal (95% CI)		**30**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.4.2 4 mg vs control						
Wang 2014a	0	30	0	7		Not estimable
Subtotal (95% CI)		**30**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.4.3 6 mg vs control						
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.4.4 8 mg vs control						
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**120**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

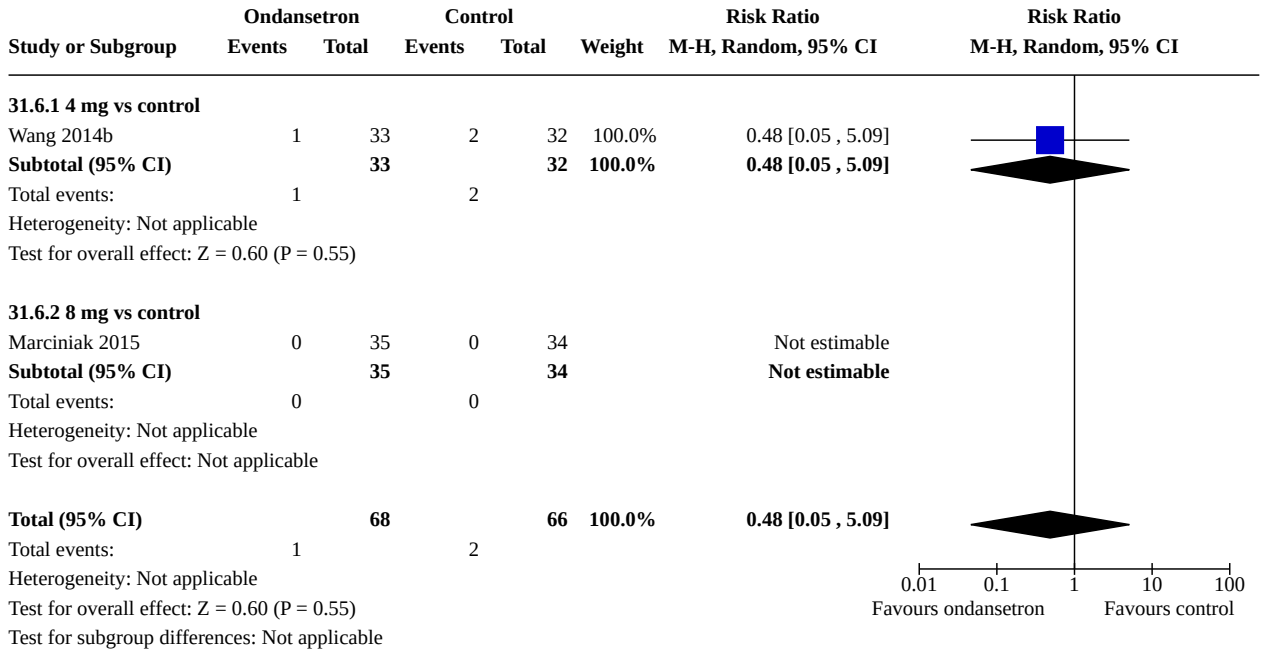


Analysis 31.5. Comparison 31: Ondansetron vs control, Outcome 5: Neonatal Apgar score < 8 at 5 min

Study or Subgroup	Ondansetron Events	Ondansetron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.5.1 2 mg vs control						
Wang 2014a	0	30	0	7		Not estimable
Subtotal (95% CI)		**30**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.5.2 4 mg vs control						
Wang 2014a	0	30	0	7		Not estimable
Wang 2014b	0	33	0	32		Not estimable
Subtotal (95% CI)		**63**		**39**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.5.3 6 mg vs control						
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
31.5.4 8 mg vs control						
Marciniak 2015	0	35	0	34		Not estimable
Wang 2014a	0	30	0	8		Not estimable
Subtotal (95% CI)		**65**		**42**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**188**		**96**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



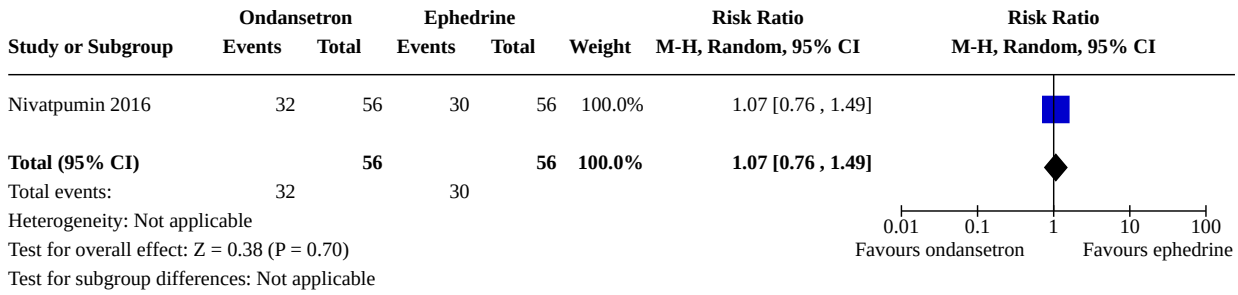
Analysis 31.6. Comparison 31: Ondansetron vs control, Outcome 6: Neonatal pH < 7.2



Comparison 32. Ondansetron vs ephedrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.1 Women with hypotension requiring intervention	1	112	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.49]
32.2 Women with bradycardia	1	112	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.10]
32.3 Women with nausea and/or vomiting	1	112	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.34]

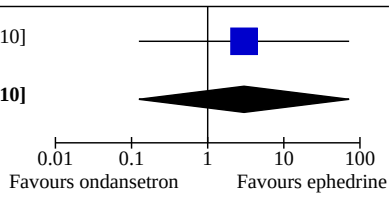
Analysis 32.1. Comparison 32: Ondansetron vs ephedrine, Outcome 1: Women with hypotension requiring intervention



Analysis 32.2. Comparison 32: Ondansetron vs ephedrine, Outcome 2: Women with bradycardia

Study or Subgroup	Ondansetron Events	Total	Ephedrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Nivatpumin 2016	1	56	0	56	100.0%	3.00 [0.12 , 72.10]
Total (95% CI)		**56**		**56**	**100.0%**	**3.00 [0.12 , 72.10]**
Total events:	1		0			

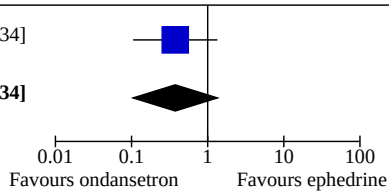
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 32.3. Comparison 32: Ondansetron vs ephedrine, Outcome 3: Women with nausea and/or vomiting

Study or Subgroup	Ondansetron Events	Total	Ephedrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Nivatpumin 2016	3	56	8	56	100.0%	0.38 [0.10 , 1.34]
Total (95% CI)		**56**		**56**	**100.0%**	**0.38 [0.10 , 1.34]**
Total events:	3		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



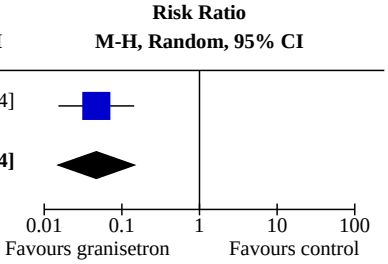
Comparison 33. Granisetron vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Women with hypotension requiring intervention	1	200	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.02, 0.14]

Analysis 33.1. Comparison 33: Granisetron vs control, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Granisetron Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Eldaba 2015	3	100	64	100	100.0%	0.05 [0.02 , 0.14]
Total (95% CI)		**100**		**100**	**100.0%**	**0.05 [0.02 , 0.14]**
Total events:	3		64			

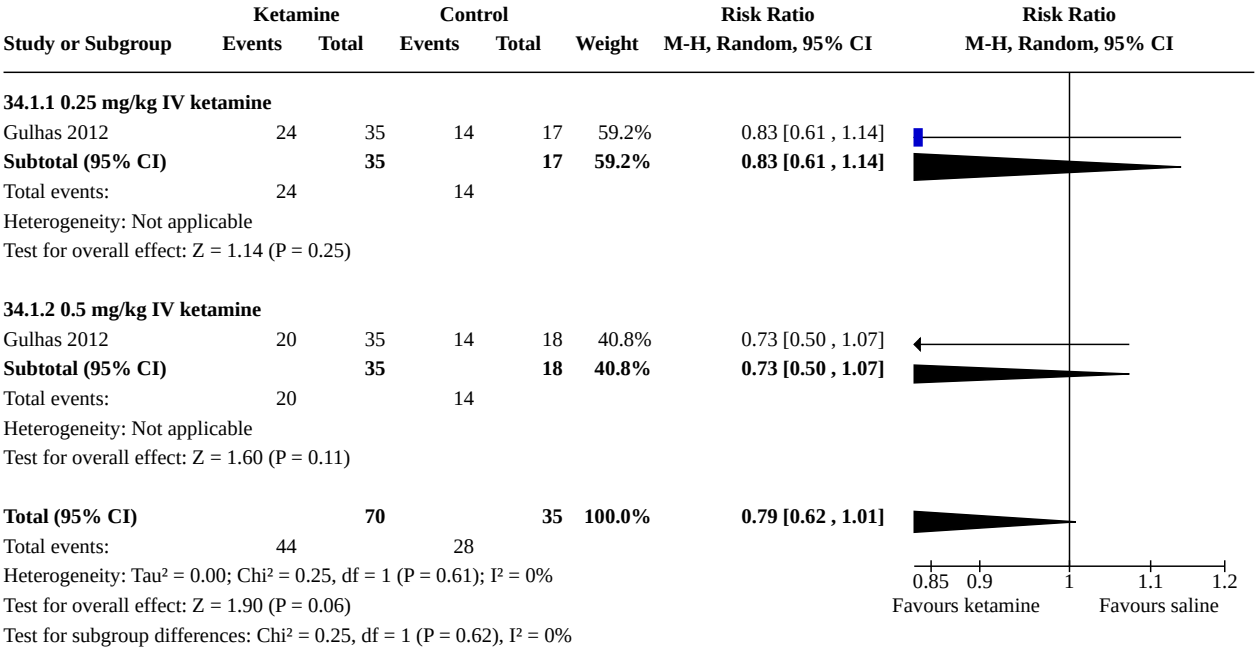
Heterogeneity: Not applicable
Test for overall effect: Z = 5.34 (P < 0.00001)
Test for subgroup differences: Not applicable



Comparison 34. Ketamine vs saline

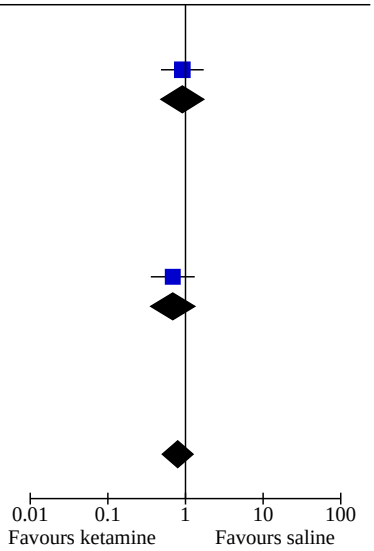
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
34.1 Women with hypotension requiring intervention	1	105	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.62, 1.01]
34.1.1 0.25 mg/kg IV ketamine	1	52	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.14]
34.1.2 0.5 mg/kg IV ketamine	1	53	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.07]
34.2 Women with nausea and/or vomiting	1	105	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.25]
34.2.1 0.25 mg/kg IV ketamine	1	52	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.48, 1.71]
34.2.2 0.5 mg/kg IV ketamine	1	53	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.31]
34.3 Apgar score < 8 at 5 min	1	105	Risk Ratio (M-H, Random, 95% CI)	Not estimable
34.3.1 0.25 mg/kg IV ketamine	1	52	Risk Ratio (M-H, Random, 95% CI)	Not estimable
34.3.2 0.5 mg/kg IV ketamine	1	53	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 34.1. Comparison 34: Ketamine vs saline, Outcome 1: Women with hypotension requiring intervention



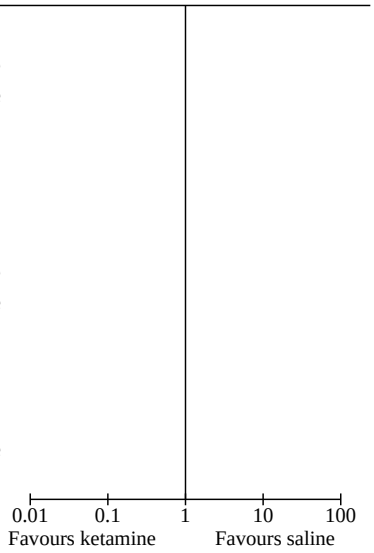
Analysis 34.2. Comparison 34: Ketamine vs saline, Outcome 2: Women with nausea and/or vomiting

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
34.2.1 0.25 mg/kg IV ketamine						
Gulhas 2012	15	35	8	17	51.4%	0.91 [0.48 , 1.71]
Subtotal (95% CI)		**35**		**17**	**51.4%**	**0.91 [0.48 , 1.71]**
Total events:	15		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
34.2.2 0.5 mg/kg IV ketamine						
Gulhas 2012	12	35	9	18	48.6%	0.69 [0.36 , 1.31]
Subtotal (95% CI)		**35**		**18**	**48.6%**	**0.69 [0.36 , 1.31]**
Total events:	12		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.26)						
Total (95% CI)		**70**		**35**	**100.0%**	**0.79 [0.50 , 1.25]**
Total events:	27		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%						



Analysis 34.3. Comparison 34: Ketamine vs saline, Outcome 3: Apgar score < 8 at 5 min

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
34.3.1 0.25 mg/kg IV ketamine						
Gulhas 2012	0	35	0	17		Not estimable
Subtotal (95% CI)		**35**		**17**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
34.3.2 0.5 mg/kg IV ketamine						
Gulhas 2012	0	35	0	18		Not estimable
Subtotal (95% CI)		**35**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**70**		**35**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

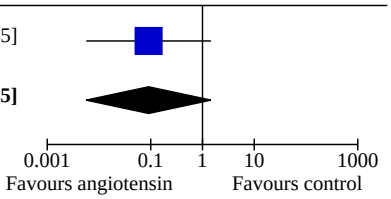


Comparison 35. Angiotensin vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.1 Women with hypotension requiring intervention	1	20	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.45]
35.2 Women with nausea and/or vomiting	1	20	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.70]
35.3 Neonates with acidosis (pH < 7.2)	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable

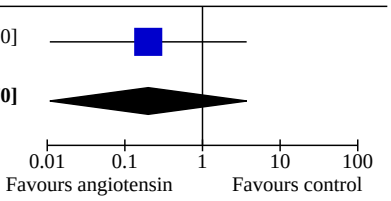
Analysis 35.1. Comparison 35: Angiotensin vs control, Outcome 1: Women with hypotension requiring intervention

	Angiotensin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ramin 1994	0	10	5	10	100.0%	0.09 [0.01 , 1.45]	
Total (95% CI)		**10**		**10**	**100.0%**	**0.09 [0.01 , 1.45]**	
Total events:	0		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.70 (P = 0.09)							
Test for subgroup differences: Not applicable							



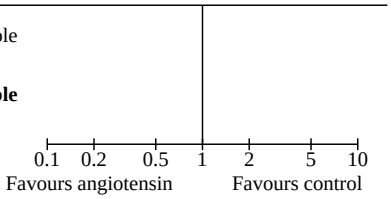
Analysis 35.2. Comparison 35: Angiotensin vs control, Outcome 2: Women with nausea and/or vomiting

	Angiotensin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ramin 1994	0	10	2	10	100.0%	0.20 [0.01 , 3.70]	
Total (95% CI)		**10**		**10**	**100.0%**	**0.20 [0.01 , 3.70]**	
Total events:	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.08 (P = 0.28)							
Test for subgroup differences: Not applicable							



Analysis 35.3. Comparison 35: Angiotensin vs control, Outcome 3: Neonates with acidosis (pH < 7.2)

	Angiotensin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ramin 1994	0	10	0	10		Not estimable	
Total (95% CI)		**10**		**10**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



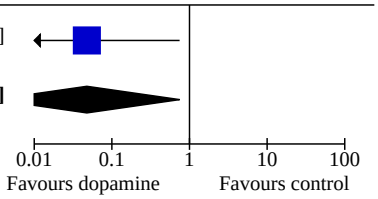
Comparison 36. Dopamine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Women with hypotension requiring intervention	1	30	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.75]
36.2 Neonatal Apgar score < 8 at 5 min	1	30	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 36.1. Comparison 36: Dopamine vs control, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Dopamine Events	Dopamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Yokoyama 1997	0	15	10	15	100.0%	0.05 [0.00 , 0.75]
Total (95% CI)		**15**		**15**	**100.0%**	**0.05 [0.00 , 0.75]**
Total events:	0		10			

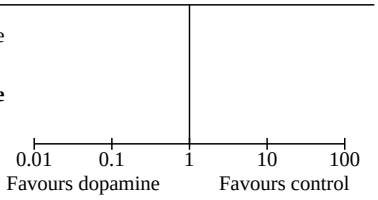
Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 36.2. Comparison 36: Dopamine vs control, Outcome 2: Neonatal Apgar score < 8 at 5 min

Study or Subgroup	Dopamine Events	Dopamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Yokoyama 1997	0	15	0	15		Not estimable
Total (95% CI)		**15**		**15**		**Not estimable**
Total events:	0		0			

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



Comparison 37. Lower limb compression vs control

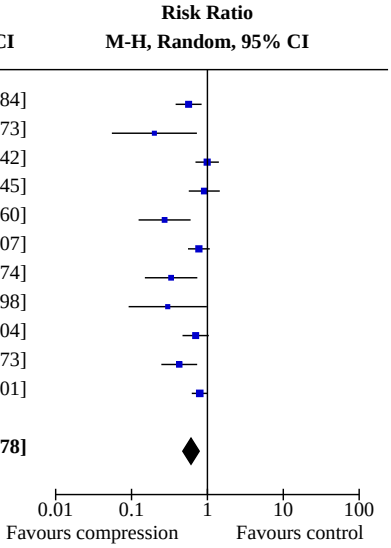
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.1 Women with hypotension requiring intervention	11	705	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.47, 0.78]
37.2 Women with bradycardia	1	74	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.11, 3.56]
37.3 Women with nausea and/or vomiting	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.3.1 Women with nausea and/or vomiting	4	276	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.14, 1.27]
37.3.2 Women with nausea	1	92	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.25, 8.20]
37.3.3 Women with vomiting	1	92	Risk Ratio (M-H, Random, 95% CI)	Not estimable
37.4 Neonates with Apgar score < 8 at 5 min	3	130	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 37.1. Comparison 37: Lower limb compression vs control, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Limb compression Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adsumelli 2003	13	25	23	25	11.5%	0.57 [0.38 , 0.84]
Bhagwanjee 1990	2	12	10	12	3.0%	0.20 [0.06 , 0.73]
James 1973	23	38	25	41	12.2%	0.99 [0.70 , 1.42]
Jorgensen 1996	10	15	11	15	10.3%	0.91 [0.57 , 1.45]
Kohli 2013	6	40	22	40	6.2%	0.27 [0.12 , 0.60]
Kuhn 2016	22	38	27	36	12.6%	0.77 [0.55 , 1.07]
Rout 1993a	6	34	17	32	6.1%	0.33 [0.15 , 0.74]
Singh 2014	3	30	10	30	3.4%	0.30 [0.09 , 0.98]
Sood 1996	14	25	20	25	11.4%	0.70 [0.47 , 1.04]
Sujata 2012	12	47	27	45	9.1%	0.43 [0.25 , 0.73]
Sutherland 2001	33	51	40	49	14.1%	0.79 [0.62 , 1.01]
Total (95% CI)		**355**		**350**	**100.0%**	**0.61 [0.47 , 0.78]**
Total events:	144		232			

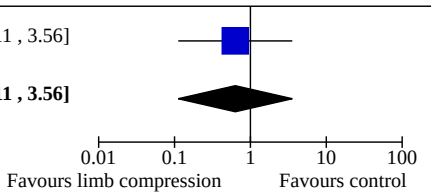
Heterogeneity: Tau² = 0.10; Chi² = 28.94, df = 10 (P = 0.001); I² = 65%
Test for overall effect: Z = 3.93 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 37.2. Comparison 37: Lower limb compression vs control, Outcome 2: Women with bradycardia

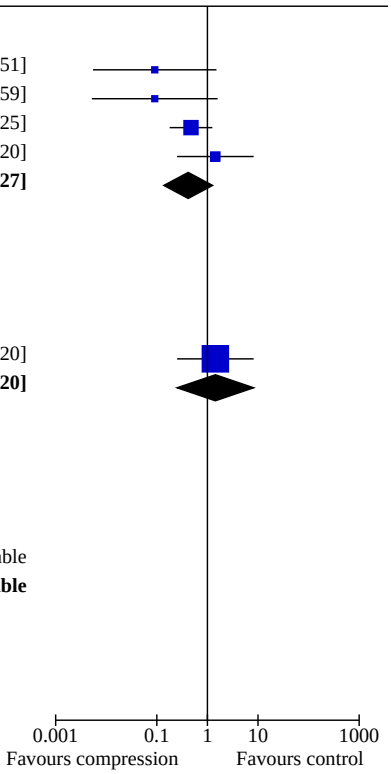
Study or Subgroup	Limb compression Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kuhn 2016	2	38	3	36	100.0%	0.63 [0.11 , 3.56]
Total (95% CI)		**38**		**36**	**100.0%**	**0.63 [0.11 , 3.56]**
Total events:	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



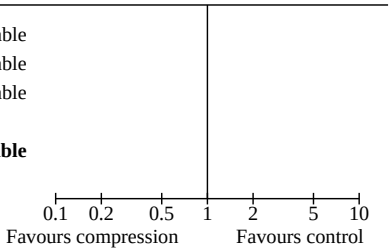
Analysis 37.3. Comparison 37: Lower limb compression vs control, Outcome 3: Women with nausea and/or vomiting

Study or Subgroup	Limb compression Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
37.3.1 Women with nausea and/or vomiting						
Jorgensen 1996	0	15	5	15	12.9%	0.09 [0.01 , 1.51]
Kohli 2013	0	40	5	40	12.6%	0.09 [0.01 , 1.59]
Kuhn 2016	5	38	10	36	48.0%	0.47 [0.18 , 1.25]
Sujata 2012	3	47	2	45	26.5%	1.44 [0.25 , 8.20]
Subtotal (95% CI)		**140**		**136**	**100.0%**	**0.42 [0.14 , 1.27]**
Total events:	8		22			
Heterogeneity: Tau² = 0.42; Chi² = 4.41, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 1.54 (P = 0.12)						
37.3.2 Women with nausea						
Sujata 2012	3	47	2	45	100.0%	1.44 [0.25 , 8.20]
Subtotal (95% CI)		**47**		**45**	**100.0%**	**1.44 [0.25 , 8.20]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
37.3.3 Women with vomiting						
Sujata 2012	0	47	0	45		Not estimable
Subtotal (95% CI)		**47**		**45**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.4%						



Analysis 37.4. Comparison 37: Lower limb compression vs control, Outcome 4: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Limb compression Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adsumelli 2003	0	25	0	25		Not estimable
Jorgensen 1996	0	15	0	15		Not estimable
Sood 1996	0	25	0	25		Not estimable
Total (95% CI)		**65**		**65**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



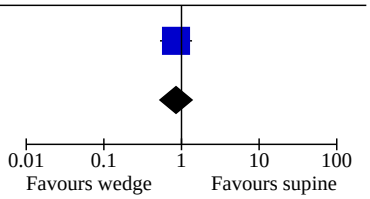
Comparison 38. Wedge vs supine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 Women with hypotension requiring intervention	1	80	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
38.2.1 Women with nausea	1	80	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.60]
38.2.2 Women with vomiting	1	80	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.00]

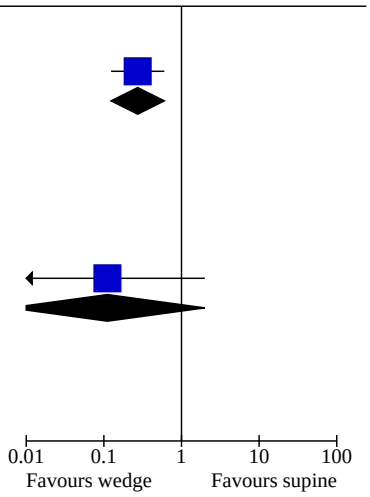
Analysis 38.1. Comparison 38: Wedge vs supine, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	wedge Events	wedge Total	supine Events	supine Total	Weight	Risk Ratio M-H, Random, 95% CI
Calvache 2011	17	40	20	40	100.0%	0.85 [0.53 , 1.37]
Total (95% CI)		**40**		**40**	**100.0%**	**0.85 [0.53 , 1.37]**
Total events:	17		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						



Analysis 38.2. Comparison 38: Wedge vs supine, Outcome 2: Women with nausea and/or vomiting

Study or Subgroup	wedge Events	wedge Total	supine Events	supine Total	Weight	Risk Ratio M-H, Random, 95% CI
38.2.1 Women with nausea						
Calvache 2011	6	40	22	40	100.0%	0.27 [0.12 , 0.60]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.27 [0.12 , 0.60]**
Total events:	6		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.23 (P = 0.001)						
38.2.2 Women with vomiting						
Calvache 2011	0	40	4	40	100.0%	0.11 [0.01 , 2.00]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.11 [0.01 , 2.00]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: $Chi^2 = 0.35$, df = 1 (P = 0.56), $I^2 = 0\%$						



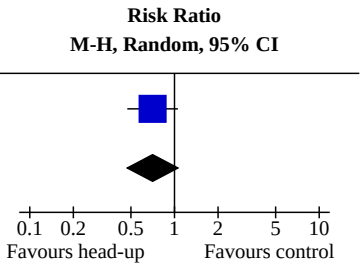
Comparison 39. Head-up tilt vs horizontal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Women with hypotension requiring intervention	1	40	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.47, 1.06]
39.2 Neonates with Apgar score < 8 at 5 min	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 39.1. Comparison 39: Head-up tilt vs horizontal, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Head-up tilt Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Loke 2002	12	20	17	20	100.0%	0.71 [0.47 , 1.06]
Total (95% CI)		**20**		**20**	**100.0%**	**0.71 [0.47 , 1.06]**
Total events:	12		17			

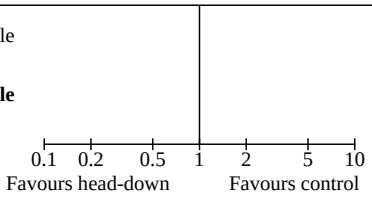
Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 39.2. Comparison 39: Head-up tilt vs horizontal, Outcome 2: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Head-down tilt Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Loke 2002	0	20	0	20		Not estimable
Total (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			

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



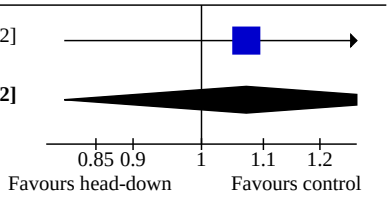
Comparison 40. Head-down tilt vs horizontal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Women with hypotension requiring intervention	1	34	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.81, 1.42]

Analysis 40.1. Comparison 40: Head-down tilt vs horizontal, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Head-down tilt Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Miyabe 1997	15	17	14	17	100.0%	1.07 [0.81 , 1.42]
Total (95% CI)		**17**		**17**	**100.0%**	**1.07 [0.81 , 1.42]**
Total events:	15		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



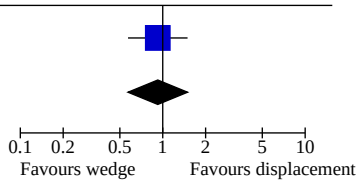
Comparison 41. Crawford's wedge vs manual uterine displacement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Women with hypotension requiring intervention	1	40	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.57, 1.49]
41.2 Neonates with Apgar score < 8 at 5 min	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 41.1. Comparison 41: Crawford's wedge vs manual uterine displacement, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Wedge Events	Total	Manual displacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Amaro 1998	12	20	13	20	100.0%	0.92 [0.57 , 1.49]
Total (95% CI)		**20**		**20**	**100.0%**	**0.92 [0.57 , 1.49]**
Total events:	12		13			

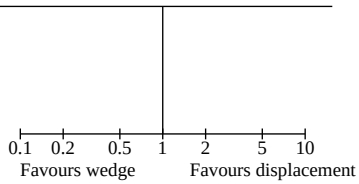
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 41.2. Comparison 41: Crawford's wedge vs manual uterine displacement, Outcome 2: Neonates with Apgar score < 8 at 5 min

Study or Subgroup	Wedge Events	Total	Manual displacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Amaro 1998	0	20	0	20		Not estimable
Total (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			

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



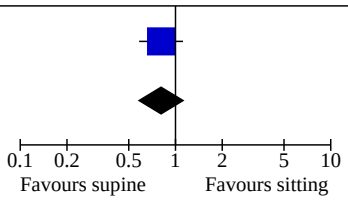
Comparison 42. Supine vs sitting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42.1 Women with hypotension requiring intervention	1	98	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.12]
42.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
42.2.1 Nausea	1	98	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.40, 1.07]
42.2.2 Vomiting	1	98	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.02, 9.01]
42.3 Neonates with acidosis (pH < 7.2)	1	98	Risk Ratio (M-H, Random, 95% CI)	Not estimable
42.4 Neonates with Apgar < 7 at 5 min	1	98	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 42.1. Comparison 42: Supine vs sitting, Outcome 1: Women with hypotension requiring intervention

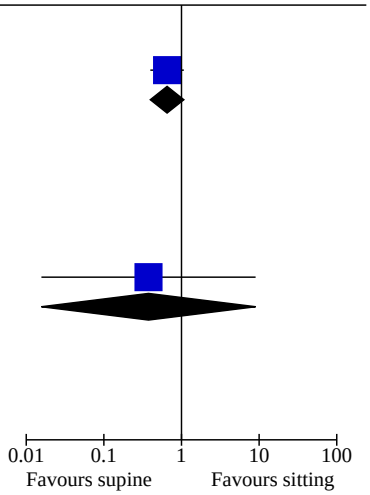
Study or Subgroup	Supine Events	Supine Total	Sitting Events	Sitting Total	Weight	Risk Ratio M-H, Random, 95% CI
Kohler 2002	25	46	35	52	100.0%	0.81 [0.58 , 1.12]
Total (95% CI)		**46**		**52**	**100.0%**	**0.81 [0.58 , 1.12]**
Total events:	25		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



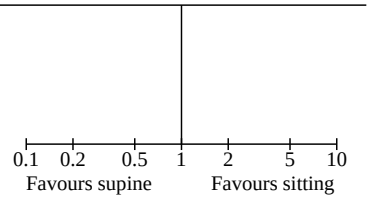
Analysis 42.2. Comparison 42: Supine vs sitting, Outcome 2: Women with nausea and/or vomiting

Study or Subgroup	Supine Events	Supine Total	Sitting Events	Sitting Total	Weight	Risk Ratio M-H, Random, 95% CI
42.2.1 Nausea						
Kohler 2002	15	46	26	52	100.0%	0.65 [0.40 , 1.07]
Subtotal (95% CI)		**46**		**52**	**100.0%**	**0.65 [0.40 , 1.07]**
Total events:	15		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
42.2.2 Vomiting						
Kohler 2002	0	46	1	52	100.0%	0.38 [0.02 , 9.01]
Subtotal (95% CI)		**46**		**52**	**100.0%**	**0.38 [0.02 , 9.01]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						



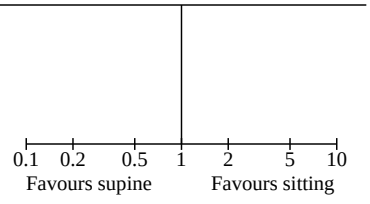
Analysis 42.3. Comparison 42: Supine vs sitting, Outcome 3: Neonates with acidosis (pH < 7.2)

Study or Subgroup	Supine Events	Supine Total	Sitting Events	Sitting Total	Weight	Risk Ratio M-H, Random, 95% CI
Kohler 2002	0	46	0	52		Not estimable
Total (95% CI)		**46**		**52**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 42.4. Comparison 42: Supine vs sitting, Outcome 4: Neonates with Apgar < 7 at 5 min

Study or Subgroup	Supine Events	Supine Total	Sitting Events	Sitting Total	Weight	Risk Ratio M-H, Random, 95% CI
Kohler 2002	0	46	0	52		Not estimable
Total (95% CI)		**46**		**52**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



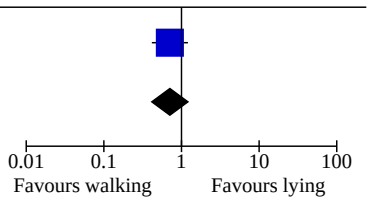
Comparison 43. Walking vs lying

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 Women requiring intervention for hypotension	1	37	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.41, 1.21]

Analysis 43.1. Comparison 43: Walking vs lying, Outcome 1: Women requiring intervention for hypotension

Study or Subgroup	walking Events	walking Total	lying Events	lying Total	Weight	Risk Ratio M-H, Random, 95% CI
Cyna 2010	10	20	12	17	100.0%	0.71 [0.41 , 1.21]
Total (95% CI)		**20**		**17**	**100.0%**	**0.71 [0.41 , 1.21]**
Total events:	10		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



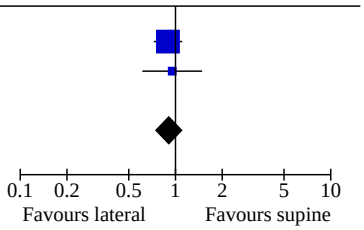
Comparison 44. Lateral vs supine wedged position

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 Women with hypotension requiring intervention	2	126	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.09]
44.2 Women with cardiac dysrhythmia requiring intervention	1	40	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.08]
44.3 Neonates admitted to neonatal intensive care unit	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
44.4 Women with nausea	1	86	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.45, 1.48]

Analysis 44.1. Comparison 44: Lateral vs supine wedged position, Outcome 1: Women with hypotension requiring intervention

Study or Subgroup	Lateral Events	Lateral Total	Supine wedged Events	Supine wedged Total	Weight	Risk Ratio M-H, Random, 95% CI
Hartley 2001	17	20	19	20	81.7%	0.89 [0.73 , 1.10]
Hwang 2012	20	43	21	43	18.3%	0.95 [0.61 , 1.48]
Total (95% CI)		**63**		**63**	**100.0%**	**0.91 [0.75 , 1.09]**
Total events:	37		40			

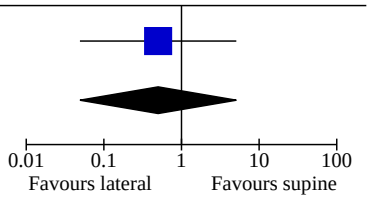
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 44.2. Comparison 44: Lateral vs supine wedged position, Outcome 2: Women with cardiac dysrhythmia requiring intervention

Study or Subgroup	Lateral Events	Lateral Total	Supine wedged Events	Supine wedged Total	Weight	Risk Ratio M-H, Random, 95% CI
Hartley 2001	1	20	2	20	100.0%	0.50 [0.05 , 5.08]
Total (95% CI)		**20**		**20**	**100.0%**	**0.50 [0.05 , 5.08]**
Total events:	1		2			

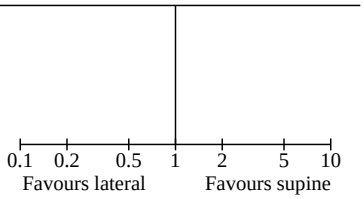
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 44.3. Comparison 44: Lateral vs supine wedged position, Outcome 3: Neonates admitted to neonatal intensive care unit

Study or Subgroup	Lateral Events	Lateral Total	Supine wedged Events	Supine wedged Total	Weight	Risk Ratio M-H, Random, 95% CI
Hartley 2001	0	20	0	20		Not estimable
Total (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			

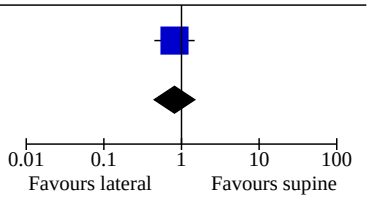
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 44.4. Comparison 44: Lateral vs supine wedged position, Outcome 4: Women with nausea

Study or Subgroup	Lateral Events	Lateral Total	Supine wedged Events	Supine wedged Total	Weight	Risk Ratio M-H, Random, 95% CI
Hwang 2012	13	43	16	43	100.0%	0.81 [0.45 , 1.48]
Total (95% CI)		**43**		**43**	**100.0%**	**0.81 [0.45 , 1.48]**
Total events:	13		16			

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



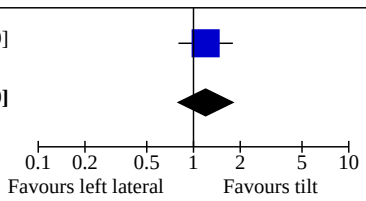
Comparison 45. Left lateral vs left lateral tilt

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45.1 Women with hypotension requiring intervention	1	58	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.80, 1.79]
45.2 Women with cardiac dysrhythmia requiring intervention	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
45.2.1 Bradycardia	1	58	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.68]
45.3 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
45.3.1 Nausea: 15 degree tilt	1	58	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.18, 1.11]
45.3.2 Vomiting: 15 degree tilt	1	58	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.83]

Analysis 45.1. Comparison 45: Left lateral vs left lateral tilt, Outcome 1: Women with hypotension requiring intervention

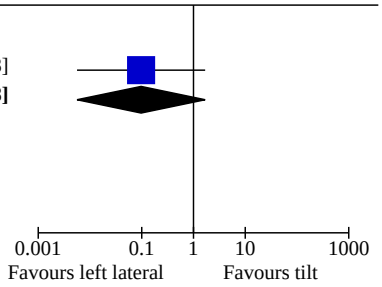
Study or Subgroup	Left lateral Events	Left lateral Total	Left lateral tilt Events	Left lateral tilt Total	Weight	Risk Ratio M-H, Random, 95% CI
Rees 2002	19	28	17	30	100.0%	1.20 [0.80 , 1.79]
Total (95% CI)		**28**		**30**	**100.0%**	**1.20 [0.80 , 1.79]**
Total events:	19		17			

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



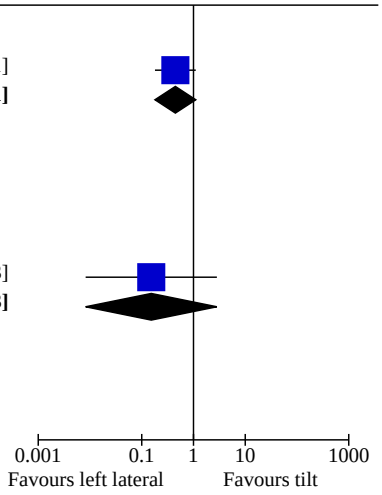
Analysis 45.2. Comparison 45: Left lateral vs left lateral tilt, Outcome 2: Women with cardiac dysrhythmia requiring intervention

Study or Subgroup	Left lateral Events	Left lateral Total	Left lateral tilt Events	Left lateral tilt Total	Weight	Risk Ratio M-H, Random, 95% CI
45.2.1 Bradycardia						
Rees 2002	0	28	5	30	100.0%	0.10 [0.01 , 1.68]
Subtotal (95% CI)		**28**		**30**	**100.0%**	**0.10 [0.01 , 1.68]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						



Analysis 45.3. Comparison 45: Left lateral vs left lateral tilt, Outcome 3: Women with nausea and/or vomiting

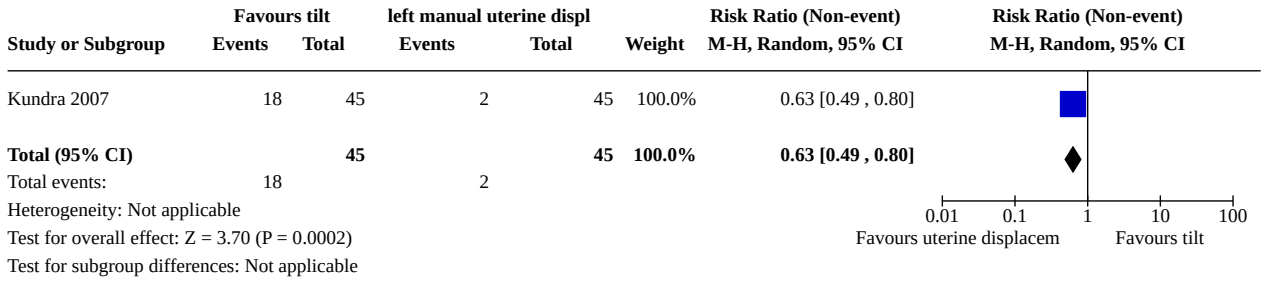
Study or Subgroup	Left lateral Events	Left lateral Total	Left lateral tilt Events	Left lateral tilt Total	Weight	Risk Ratio M-H, Random, 95% CI
45.3.1 Nausea: 15 degree tilt						
Rees 2002	5	28	12	30	100.0%	0.45 [0.18 , 1.11]
Subtotal (95% CI)		**28**		**30**	**100.0%**	**0.45 [0.18 , 1.11]**
Total events:	5		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
45.3.2 Vomiting: 15 degree tilt						
Rees 2002	0	28	3	30	100.0%	0.15 [0.01 , 2.83]
Subtotal (95% CI)		**28**		**30**	**100.0%**	**0.15 [0.01 , 2.83]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						



Comparison 46. Left lateral tilt vs left manual uterine displacement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
46.1 Women with hypotension requiring intervention	1	90	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.80]

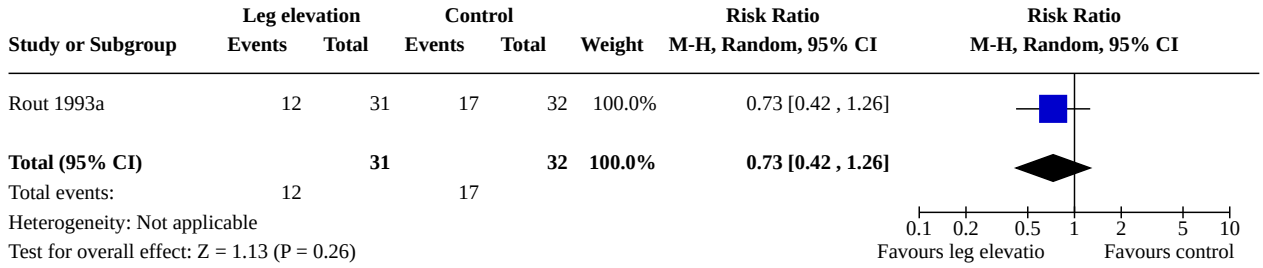
Analysis 46.1. Comparison 46: Left lateral tilt vs left manual uterine displacement, Outcome 1: Women with hypotension requiring intervention



Comparison 47. Leg elevation vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.1 Women with hypotension requiring intervention	1	63	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.42, 1.26]

Analysis 47.1. Comparison 47: Leg elevation vs control, Outcome 1: Women with hypotension requiring intervention



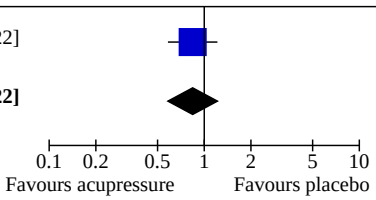
Comparison 48. Acupressure vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48.1 Women with hypotension requiring intervention	1	50	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.58, 1.22]
48.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
48.2.1 Nausea	1	50	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.66]
48.2.2 Vomiting	1	50	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.14, 1.78]
48.3 Neonates with Apgar < 7 at 5 min	1	50	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 48.1. Comparison 48: Acupressure vs placebo, Outcome 1: Women with hypotension requiring intervention

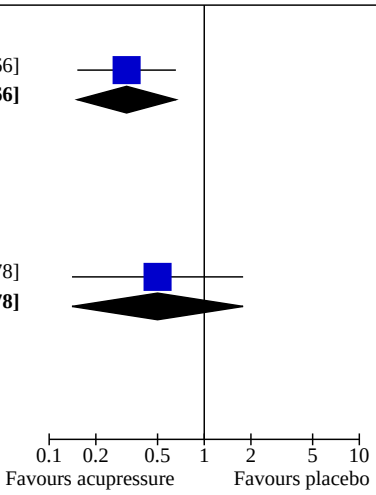
Study or Subgroup	Aupressure Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stein 1997	16	25	19	25	100.0%	0.84 [0.58 , 1.22]
Total (95% CI)		**25**		**25**	**100.0%**	**0.84 [0.58 , 1.22]**
Total events:	16		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 48.2. Comparison 48: Acupressure vs placebo, Outcome 2: Women with nausea and/or vomiting

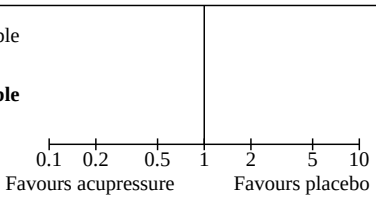
Study or Subgroup	Acupressure Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
48.2.1 Nausea						
Stein 1997	6	25	19	25	100.0%	0.32 [0.15 , 0.66]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**0.32 [0.15 , 0.66]**
Total events:	6		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
48.2.2 Vomiting						
Stein 1997	3	25	6	25	100.0%	0.50 [0.14 , 1.78]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**0.50 [0.14 , 1.78]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						



Analysis 48.3. Comparison 48: Acupressure vs placebo, Outcome 3: Neonates with Apgar < 7 at 5 min

Study or Subgroup	Acupressure Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stein 1997	0	25	0	25		Not estimable
Total (95% CI)		**25**		**25**		**Not estimable**
Total events:	0		0			

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



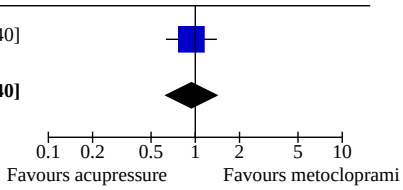
Comparison 49. Acupressure vs metoclopramide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.1 Women with hypotension requiring intervention	1	50	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.63, 1.40]
49.2 Women with nausea and/or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
49.2.1 Nausea	1	50	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.48, 4.68]
49.2.2 Vomiting	1	50	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.92]
49.3 Neonates with Apgar < 7 at 5 min	1	50	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 49.1. Comparison 49: Acupressure vs metoclopramide, Outcome 1: Women with hypotension requiring intervention

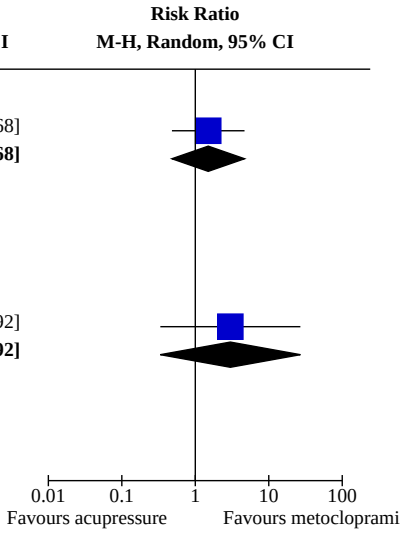
Study or Subgroup	Acupressure Events	Acupressure Total	Metoclopramide Events	Metoclopramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Stein 1997	16	25	17	25	100.0%	0.94 [0.63 , 1.40]
Total (95% CI)		**25**		**25**	**100.0%**	**0.94 [0.63 , 1.40]**
Total events:	16		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 49.2. Comparison 49: Acupressure vs metoclopramide, Outcome 2: Women with nausea and/or vomiting

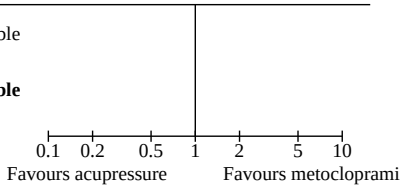
Study or Subgroup	Acupressure Events	Acupressure Total	Metoclopramide Events	Metoclopramide Total	Weight	Risk Ratio M-H, Random, 95% CI
49.2.1 Nausea						
Stein 1997	6	25	4	25	100.0%	1.50 [0.48 , 4.68]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**1.50 [0.48 , 4.68]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
49.2.2 Vomiting						
Stein 1997	3	25	1	25	100.0%	3.00 [0.33 , 26.92]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**3.00 [0.33 , 26.92]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						



Analysis 49.3. Comparison 49: Acupressure vs metoclopramide, Outcome 3: Neonates with Apgar < 7 at 5 min

Study or Subgroup	Acupressure Events	Acupressure Total	Metoclopramide Events	Metoclopramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Stein 1997	0	25	0	25		Not estimable
Total (95% CI)		**25**		**25**		**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. Hypotension definitions (mmHg or % fall in systolic/mean arterial pressure)

Studies	SAP < 80 mmHg	SAP < 90 mmHg	SAP < 95 mmHg	SAP < 100 mmHg	SAP > 10% fall	SAP > 20% fall	SAP > 25% fall	SAP > 30% fall	MAP > 20% fall	MAP > 25% fall	S/MAP > 10 mmHg fall	MAP < 70 mmHg
Ansari 2011; Bouchnak 2012; Doherty 2012; Magalhaes 2009; Muzlifah 2009; Nishikawa 2007; Ueyama 1992	X	—	—	—	—	—	—	—	—	—	—	—
Carvalho 2009; Loke 2002; Mathru 1980; Nazir 2012; Sahoo 2012; Singh 2014; Yorozu 2002	—	X	—	—	—	—	—	—	—	—	—	—
Allen 2010; Jabalameli 2011; Jacob 2012; Kuhn 2016; Kundra 2007; Marciniak 2015; Pouta 1996; Tawfik 2014; Unlugenc 2015	—	X (or)	—	—	—	X	—	—	—	—	—	—
Karinen 1995; Sood 1996	—	X (and)	—	—	—	X	—	—	—	—	—	—
Davies 2006; French 1999; Grubb 2004; Loughrey 2002; Singh 2009	—	X (or)	—	—	—	—	—	X	—	—	—	—
Dahlgren 2005; Damevski 2011; James 1973; Loo 2002; Miyabe 1997	—	—	—	X	—	—	—	—	—	—	—	—
Alimian 2014; Amaro 1998; Cyna 2010; Embu 2011; Jorgensen 1996; Loughrey 2005; Khan 2013; Madi-Jebara 2008; Marciniak 2013; Mohta 2010; Ouerghi 2010; Rees 2002; Stein 1997; Ueya-	—	—	—	X (or)	—	X	—	—	—	—	—	—

Table 1. Hypotension definitions (mmHg or % fall in systolic/mean arterial pressure) *(Continued)*

ma 2002; Ure 1999; Wilson 1999												
Bhagwanjee 1990; Hasan 2012; Ngan Kee 2000; Riley 1995; Rout 1992; Rout 1993a; Siddik 2000; Siddik-Sayyid 2009; Sutherland 2001; Ueyama 1999; Upadya 2016	—	—	—	X (and)	—	X	—	—	—	—	—	—
Chohedri 2007; Inglis 1995; Jorgensen 2000; Kohler 2002; Webb 1998	—	—	—	X (or)	—	—	—	X	—	—	—	—
Bhardwaj 2013; Cardoso 2004a; Yokoyama 1997	—	—	—	—	X	—	—	—	—	—	—	—
Arora 2015; Bottiger 2010; Carvalho 1999a; Carvalho 1999b; Carvalho 2000; Chan 1997; Dahlgren 2007; Das Neves 2010; Dyer 2004; El-Mekawy 2012; Gulhas 2012; Hall 1994; Hartley 2001; Idehen 2014; King 1998; Kundra 2008; Kohli 2013; Mercier 2014; Moslemi 2015; Ngan Kee 2004a; Ngan Kee 2013a; Oh 2014; Ozkan 2004; Perumal 2004; Romdhani 2014; Selvan 2004; Singh 2016; Sujata 2012 Tercanli 2005; Terkawi 2015; Trabelsi 2015; Turkoz 2002; Torres unpub; Wang 2014a; Wang 2014b; Wilson 1998	—	—	—	—	—	X	—	—	—	—	—	—
Calvache 2011; Ortiz-Gomez 2014	—	—	—	—	—	—	X	—	—	—	—	—

Table 1. Hypotension definitions (mmHg or % fall in systolic/mean arterial pressure) *(Continued)*

Lin 1999; Morgan 2000; Ramin 1994	—	—	—	—	—	—	—	X	—	—	—	—
Adsumelli 2003; Faydaci 2011; Farid 2016; Gunaydin 2009; Hwang 2012; Tsen 2000	—	—	—	—	—	—	—	—	X	—	—	—
Gomaa 2003	—	—	—	—	—	—	—	—	—	X	—	—
Alahuhta 1992; Olsen 1994	—	—	—	—	—	—	—	—	—	—	X	—
Gunusen 2010	—	—	X	—	—	X	—	—	—	—	—	—
Eldaba 2015	—	—	—	—	—	—			—	—	—	X

MAP: mean arterial pressure; **SAP**: systolic arterial pressure.

WHAT'S NEW

Date	Event	Description
5 June 2020	Amended	The study by Mitra 2014, previously included in comparison 7 (colloid vs crystalloid), has been retracted. We have therefore re-classified this study from included to excluded and edited the review analysis and text accordingly.
5 June 2020	New citation required but conclusions have not changed	Since publication of this updated review in 2017 (Cyna 2017), the Mitra 2014 study has now been retracted by the Saudi Journal of Anaesthesia because it has "..been found to have a number of unattributed sections of content with high rate of similarity from various other articles along with overwhelming evidence of data fabrication". Removing this study from analysis 7.1, 7.3.2, 7.4.21 and 7.6.2 has not changed the results or the conclusions of this review.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 3, 2001

Date	Event	Description
9 August 2016	New search has been performed	Search updated– last published included 75 trials, now includes 126 trials. Note: we excluded 13 trials included in last update because they assessed combined spinal-epidurals rather than spinal anaesthesia, and we excluded one study because it failed to report our primary outcome. Author list and order updated for this version of the review. We excluded quasi-randomised trials in this version. We also excluded trials where women received epidural anaesthesia or combined spinal-epidural anaesthesia. We have incorporated seven 'Summary of findings' tables into this update.
9 August 2016	New citation required and conclusions have changed	Conclusions changed with this update. Ondansetron may be a useful intervention, and fluid coloading is more effective than preloading.
30 June 2010	Amended	Search updated.Eighty-five trial reports added to Studies awaiting classification.
18 February 2008	Amended	Converted to new review format.
6 June 2006	New search has been performed	The 2006 update now contains 75 included studies. Forty new studies have been added and 10 previously excluded studies have now been included. These studies were previously excluded as there was some variation between women in the dose of anaesthetic.

Date	Event	Description
		An additional 38 studies were excluded and appear in the Characteristics of excluded studies table with reasons for their exclusion. The new studies reinforce the previous conclusions and also show that phenylephrine is also likely to be effective in preventing hypotension.

CONTRIBUTIONS OF AUTHORS

Planning review: Allan Cyna, Scott Simmons.
Writing protocol: Allan Cyna, Scott Simmons.
Revising protocol: Allan Cyna, Richard Emmett, Scott Simmons.
Retrieving papers for review: Richard Emmett.
Extracting data from reviewed papers: Cheryl Chooi, Julia Cox, Richard Lumb.
Writing draft review: Richard Emmett, Allan Cyna.
Revising original review: Scott Simmons, Allan Cyna, Richard Emmett.
First update and amendments: Allan Cyna, Richard Emmett, Philippa Middleton.
Second update (2006) and amendments: Allan Cyna and Philippa Middleton, with comments from the other review authors.
Third update (2017) and amendments: Cheryl Chooi, Julia Cox, Richard Lumb.

DECLARATIONS OF INTEREST

Cheryl Chooi: none known.
Richard S Lumb: none known.
Julia J Cox: none known.
Richard S Emmett: none known.
Philippa Middleton: none known.
Scott W Simmons: none known.
Mark Chemali: none known.
Allan M Cyna: is also an author of one of the included studies (Cyna 2010). CC and RSL extracted data from this study.

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Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia
- Department of Health and Ageing, Australia

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update (2017), the criteria for considering studies for this review were changed to exclude:

- quasi-randomised, cluster or cross-over studies;
- studies in which women received combined spinal-epidural anaesthesia or epidural anaesthesia.

Primary and secondary outcomes were specified from the main and other outcomes.

We reported Apgar scores as they were reported by trialists. This meant that as well as Apgar scores of less than 7 or 8 at five minutes, we reported Apgar scores of less than 9 at five minutes.

We only performed assessment of publication bias through funnel plots for the primary outcome, as it was likely caused by the large amount of small trials that contributed to all the analyses.

NOTES

The study by Mitra 2014, previously included in comparison 7 (colloid vs crystalloid), has been retracted. We have therefore reclassified this study from included to excluded and edited the review analysis and text accordingly.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Obstetrical [*adverse effects]; Anesthesia, Spinal [*adverse effects]; Antiemetics [therapeutic use]; *Cesarean Section; Colloids [therapeutic use]; Crystalloid Solutions [therapeutic use]; Ephedrine [therapeutic use]; Hypotension [chemically induced] [*prevention & control]; Intraoperative Complications [*prevention & control]; Isotonic Solutions [therapeutic use]; Ondansetron [therapeutic use]; Phenylephrine [therapeutic use]; Postoperative Nausea and Vomiting [drug therapy]; Randomized Controlled Trials as Topic; Vasoconstrictor Agents [therapeutic use]; Walking

MeSH check words

Female; Humans; Pregnancy