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Umbilical vein injection for management of retained placenta (Review)

Kumar N, Jahanfar S, Haas DM, Weeks AD

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[Intervention Review]

Umbilical vein injection for management of retained placenta

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ABSTRACT

Background

Retained placenta is a common complication of pregnancy affecting 1% to 6% of all births. If a retained placenta is left untreated, spontaneous delivery of the placenta may occur, but there is a high risk of bleeding and infection. Manual removal of the placenta (MROP) in an operating theatre under anaesthetic is the usual treatment, but is invasive and may have complications. An effective non-surgical alternative for retained placenta would potentially reduce the physical and psychological trauma of the procedure, and costs. It could also be lifesaving by providing a therapy for settings without easy access to modern operating theatres or anaesthetics. Injection of uterotonics into the uterus via the umbilical vein and placenta is an attractive low-cost option for this. This is an update of a review last published in 2011.

Objectives

To assess the use of umbilical vein injection (UVI) of saline solution with or without uterotonics compared to either expectant management or with an alternative solution or other uterotonic agent for retained placenta.

Search methods

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (14 June 2020), and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) comparing UVI of saline or other fluids (with or without uterotonics), either with expectant management or with an alternative solution or other uterotonic agent, in the management of retained placenta. We considered quasi-randomised, cluster-randomised, and trials reported only in abstract form.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data, and checked them for accuracy. We assessed the certainty of the evidence using the GRADE approach. We calculated pooled risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs), and presented results using 'Summary of findings' tables.

Main results

We included 24 trials (n = 2348). All included trials were RCTs, one was quasi-randomised, and none were cluster-randomised. Risk of bias was variable across the included studies. We assessed certainty of evidence for four comparisons: saline versus expectant management, oxytocin versus expectant management, oxytocin versus saline, and oxytocin versus plasma expander. Evidence was moderate to very-low certainty and downgraded for risk of bias of included studies, imprecision, and inconsistency of effect estimates.

Saline solution versus expectant management

There is probably little or no difference in the incidence of MROP between saline and expectant management (RR 0.93, 95% CI 0.80 to 1.10; 5 studies, n = 445; moderate-certainty evidence). Evidence for the following remaining primary outcomes was very-low certainty: severe postpartum haemorrhage 1000 mL or greater, blood transfusion, and infection. There were no events reported for maternal mortality or postpartum anaemia (24 to 48 hours postnatal). No studies reported addition of therapeutic uterotonics.

Oxytocin solution versus expectant management

UVI of oxytocin solution might slightly reduce in the need for manual removal compared with expectant management (mean RR 0.73, 95% CI 0.56 to 0.95; 7 studies, n = 546; low-certainty evidence). There may be little to no difference between the incidence of blood transfusion between groups (RR 0.81, 95% CI 0.47 to 1.38; 4 studies, n = 339; low-certainty evidence). There were no maternal deaths reported (2 studies, n = 93). Evidence for severe postpartum haemorrhage of 1000 mL or greater, additional uterotonics, and infection was very-low certainty. There were no events for postpartum anaemia (24 to 48 hours postnatal).

Oxytocin solution versus saline solution

UVI of oxytocin solution may reduce the use of MROP compared with saline solution, but there was high heterogeneity (RR 0.82, 95% CI 0.69 to 0.97; 14 studies, n = 1370; I^2 = 54%; low-certainty evidence). There were no differences between subgroups according to risk of bias or oxytocin dose for the outcome MROP. There may be little to no difference between groups in severe postpartum haemorrhage of 1000 mL or greater, blood transfusion, use of additional therapeutic uterotonics, and antibiotic use. There were no events for postpartum anaemia (24 to 48 hours postnatal) (very low-certainty evidence) and there was only one event for maternal mortality (low-certainty evidence).

Oxytocin solution versus plasma expander

One small study reported UVI of oxytocin compared with plasma expander (n = 109). The evidence was very unclear about any effect on MROP or blood transfusion between the two groups (very low-certainty evidence). No other primary outcomes were reported.

For other comparisons there were little to no differences for most outcomes examined. However, there was some evidence to suggest that there may be a reduction in MROP with prostaglandins in comparison to oxytocin (4 studies, n = 173) and ergometrine (1 study, n = 52), although further large-scale studies are needed to confirm these findings.

Authors' conclusions

UVI of oxytocin solution is an inexpensive and simple intervention that can be performed when placental delivery is delayed. This review identified low-certainty evidence that oxytocin solution may slightly reduce the need for manual removal. However, there are little or no differences for other outcomes. Small studies examining injection of prostaglandin (such as dissolved misoprostol) into the umbilical vein show promise and deserve to be studied further.

PLAIN LANGUAGE SUMMARY

Umbilical vein injection after childbirth for management of retained placenta

What is the issue?

The placenta provides nourishment for the baby in the womb (uterus) through the umbilical cord. It usually comes out shortly after the baby. If the placenta remains in the womb (a 'retained placenta'), women have an increased risk of bleeding heavily (haemorrhage), infection, and very occasionally death. Manual removal of the placenta involves a doctor passing their hand through the vagina into the womb to remove the placenta. However, it requires an anaesthetic and can have side effects. Use of medicines injected into the placenta through blood vessels (veins) in the umbilical cord is an attractive alternative to remove the placenta.

Why is this important?

The injection of oxytocin (a hormone released from the brain into the blood during labour) solution into the umbilical cord after the cord is cut is a cheap and simple intervention that could be performed to deliver the placenta. It is especially attractive for low-income countries where there is not easy access to doctors or an operating theatre.

What evidence did we find?

We searched for evidence in June 2020 and combined the data from 24 trials involving 2348 women.

Injection of a saline (salt) solution made little or no difference in the need for manual removal of placenta in comparison to waiting for spontaneous delivery. There is some evidence that injecting an oxytocin solution into the umbilical vein may be beneficial, but many of the studies are at high risk of bias, the results are inconsistent, and the benefits are seen only in a few outcomes. Small studies suggest there may be some effect of an injection of a prostaglandin (that stimulate contractions of the womb; misoprostol or carboprost) when

compared to oxytocin solution. One study comparing a carbetocin (which is similar to oxytocin) solution to oxytocin did not show any difference in the need for manual removal.

What does this mean?

The use of umbilical vein injections for retained placenta may or may not have a benefit for women with retained placenta. An umbilical vein injection of prostaglandin shows promise and requires more research.

Summary of findings 1. Saline solution compared to expectant management for management of retained placenta

Saline solution compared to expectant management for management of retained placenta

Patient or population: management of retained placenta
Setting: hospital (Argentina, Denmark, the Netherlands, the UK)
Intervention: saline solution UVI
Comparison: expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with saline solution UVI				
Manual removal of the placenta	**Study population**		**RR 0.93** (0.80 to 1.10)	445 (5 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	—
	579 per 1000	539 per 1000 (463 to 637)				
Maternal mortality	**Study population**		0 events – not estimable	87 (2 RCTs)	⊕⊖⊖⊖ **Very low** [b,c]	—
	See comment	See comment				
Severe PPH (≥ 1000 mL)	**Study population**		**RR 0.73** (0.17 to 3.11)	122 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,d,e]	—
	67 per 1000	49 per 1000 (11 to 207)				
Blood transfusion	**Study population**		**Mean RR 0.41** (0.10 to 1.73)	277 (3 RCTs)	⊕⊖⊖⊖ **Very low** [a,d,f,g]	—
	241 per 1000	99 per 1000 (24 to 417)				
Addition of therapeutic uterotonics	—		—	—	—	No trial reported this outcome.
Need for treatment with antibiotics (infection)	**Study population**		**RR 0.48** (0.09 to 2.54)	176 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,d,e]	—
	47 per 1000	22 per 1000 (4 to 118)				

Maternal postpartum anaemia (haemoglobin 24–48 hours postpartum)	—	**MD 0.1 higher** (0.59 lower to 0.79 higher)	—	163 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,h]	—

*__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; **UVI:** umbilical vein injection; **MD:** mean difference; **PPH:** postpartum haemorrhage; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

[a]Downgraded one level for study design limitations: majority of pooled effect provided by study (or studies) at moderate risk of bias.
[b]Downgraded two levels for serious study design limitations: majority of pooled effect provided by study (or studies) at moderate or high risk of bias.
[c]Downgraded two levels for serious imprecision: small sample size, no events, not estimable.
[d]Downgraded one level for imprecision: wide confidence intervals crossed the line of no effect.
[e]Downgraded two levels for serious imprecision: single study with small sample size and few events.
[f]Downgraded one level for inconsistency: severe unexplained heterogeneity ($I^2 > 30$).
[g]Downgraded one level for imprecision: small sample size.
[h]Downgraded two levels for serious imprecision: single study with small sample size.

Summary of findings 2. Oxytocin solution compared to expectant management for management of retained placenta

Oxytocin solution compared to expectant management for management of retained placenta

Patient or population: management of retained placenta
Setting: hospital (Argentina, Belgium, Denmark, Malaysia, Netherlands, the UK)
Intervention: oxytocin solution UVI
Comparison: expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with oxytocin solution UVI				
Manual removal of the placenta	**Study population**		**Mean RR 0.73** (0.56 to 0.95)	546 (7 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
	602 per 1000	440 per 1000				

		(337 to 572)				
Maternal mortality	**Study population**		0 events – not estimable	93 (2 RCTs)	⊕⊖⊖⊖ **Very low** [c,d]	—
	0 per 1000	0 per 1000 (0 to 0)				
Severe PPH (≥ 1000 mL)	**Study population**		**RR 1.23** (0.41 to 3.74)	190 (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,e,f]	—
	56 per 1000	68 per 1000 (23 to 208)				
Blood transfusion	**Study population**		**RR 0.81** (0.47 to 1.38)	339 (4 RCTs)	⊕⊕⊖⊖ **Low** [a,f]	—
	140 per 1000	114 per 1000 (66 to 194)				
Addition of therapeutic uterotonics	**Study population**		**RR 0.50** (0.28 to 0.88)	60 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,g,h]	—
	667 per 1000	333 per 1000 (187 to 587)				
Need for treatment with antibiotics (infection)	**Study population**		**RR 1.16** (0.32 to 4.16)	179 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,f,g,h]	—
	47 per 1000	54 per 1000 (15 to 193)				
Postpartum anaemia (haemoglobin 24–48 hours postpartum, g%)	**Study population**		0 events – not estimable	166 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,h]	—
	0 per 1000	0 per 1000 (0 to 0)				

*__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; **UVI:** umbilical vein injection; **PPH:** postpartum haemorrhage; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

[a]Downgraded one level for study design limitations: majority or all of pooled effect provided by study (or studies) at moderate risk of bias.
[b]Downgraded one level for inconsistency: severe unexplained heterogeneity ($I^2 > 30\%$).
[c]Downgraded two levels for serious study design limitations: majority of pooled effect provided by study (or studies) at moderate or high risk of bias.
[d]Downgraded two levels for serious imprecision: small sample size, no events, not estimable.
[e]Downgraded two levels for serious imprecision: small sample size, few events.
[f]Downgraded one level for imprecision: wide confidence intervals crossed the line of no effect.
[g]Downgraded one level for imprecision: few events.
[h]Downgraded two levels for serious imprecision: single study with small sample size.

Summary of findings 3. Oxytocin solution compared to saline solution for management of retained placenta

Oxytocin solution compared to saline solution for management of retained placenta

Patient or population: management of retained placenta
Setting: hospital (Argentina, Denmark, Hong Kong, India, Italy, Malaysia, the Netherlands; Pakistan, Uganda, the UK)
Intervention: oxytocin solution UVI
Comparison: saline solution UVI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with saline solution UVI	Risk with oxytocin solution UVI				
Manual removal of the placenta	**Study population**		**RR 0.82** (0.69 to 0.97)	1370 (14 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
	626 per 1000	513 per 1000 (432 to 607)				
Maternal mortality	**Study population**		**RR 2.93** (0.12 to 71.59)	782 (5 RCTs)	⊕⊕⊖⊖ **Low** [c,d]	—
	0 per 1000	0 per 1000 (0 to 0)				
Severe PPH (≥ 1000 mL)	**Study population**		**RR 1.08** (0.70 to 1.68)	766 (4 RCTs)	⊕⊕⊕⊖ **Moderate** [c]	—
	88 per 1000	95 per 1000 (62 to 148)				
Blood transfusion	**Study population**		**RR 1.08** (0.78 to 1.49)	974 (7 RCTs)	⊕⊕⊕⊖ **Moderate** [c]	—
	121 per 1000	130 per 1000 (94 to 180)				

Addition of therapeutic uterotonics	**Study population**		**RR 0.85** (0.59 to 1.23)	678 (4 RCTs)	⊕⊕⊖⊖ **Low** [b,c]	—
	139 per 1000	118 per 1000 (82 to 170)				
Need for treatment with antibiotics (infection)	**Study population**		**RR 1.26** (0.81 to 1.96)	635 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [c]	—
	99 per 1000	124 per 1000 (80 to 194)				
Maternal postpartum anaemia (haemoglobin 24–48 hours postpartum)	**Study population**		0 events – not estimable	167 (1 RCT)	⊕⊖⊖⊖ **Very low** [d,e]	—
	No events – not estimable	**MD 0.1 lower** (0.76 lower to 0.56 higher)				

*__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; **UVI:** umbilical vein injection; **MD:** mean difference; **PPH:** postpartum haemorrhage; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

[a]Downgraded one level for study design limitations: majority or all pooled effect provided by study (or studies) at moderate risk of bias.
[b]Downgraded one level for inconsistency: severe unexplained heterogeneity ($I^2 > 30\%$).
[c]Downgraded one level for imprecision: wide confidence intervals crossed the line of no effect.
[d]Downgraded one level for imprecision: few events.
[e]Downgraded two levels for serious imprecision: single study with small sample size.

Summary of findings 4. Oxytocin solution compared to plasma expander for management of retained placenta

Oxytocin solution compared to plasma expander for management of retained placenta

Patient or population: management of retained placenta
Setting: hospital (Finland)
Intervention: oxytocin solution UVI
Comparison: plasma expander UVI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with plasma expander UVI	Risk with oxytocin solution UVI				
Manual removal of the placenta	**Study population**		**RR 1.34** (0.97 to 1.85)	109 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b]	—
	537 per 1000	719 per 1000 (520 to 993)				
Maternal mortality	—		—	—	—	No trial reported this outcome.
Severe PPH (≥ 1000 mL)	**Study population**		**RR 0.96** (0.34 to 2.75)	109 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b]	—
	122 per 1000	117 per 1000 (41 to 335)				
Blood transfusion	—		—	—	—	No trial reported this outcome.
Additional therapeutic uterotonics	—		—	—	—	No trial reported this outcome.
Need for treatment with antibiotics (infection)	—		—	—	—	No trial reported this outcome.
Maternal postpartum anaemia (haemoglobin 24–48 hours postpartum)	—		—	—	—	No trial 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; **UVI:** umbilical vein injection; **PPH:** postpartum haemorrhage; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

[a]Downgraded two levels for serious study design limitations: all pooled effect provided by study at high risk of bias.
[b]Downgraded two levels for serious imprecision: single study, small sample size, few events. Wide confidence intervals crossed the line of no effect.

BACKGROUND

Description of the condition

Normally, the uterine contractions that occur immediately after the delivery of the baby result in spontaneous detachment of the placenta from the uterine wall and subsequent delivery. The term 'retained placenta' is used when the placenta has not been delivered within one hour after the birth of the baby (WHO 1990). It occurs in up to 6% of births depending on setting and third-stage management (Cheung 2011). Weeks 2008a describes the three subtypes of retained placenta as *placenta adherens* (failure of the retroplacental myometrium to contract), *trapped placenta* (expulsion from the uterus into the lower segment, but prevented expulsion by a closed cervix), and *partial accreta* (prevention of complete detachment due to an area of abnormal implantation of the placenta into the myometrium).

Retained placenta is a potentially life-threatening complication of the third stage of labour. If untreated, as may happen after home births in low- and middle-income countries, there is a high risk of maternal death from haemorrhage or infection. The current expectant management of retained placenta, by manual removal, aims to prevent these problems, but it is unsatisfactory as it involves the clinician reaching a hand through the vagina into the cavity of uterus to remove the placenta. Furthermore, it usually requires general or regional anaesthesia in hospital. It is an invasive procedure with its own potentially serious complications of haemorrhage, infection, or genital tract trauma.

Description of the intervention

Any management simple and safe enough to be performed at the place of delivery, reducing the need for manual removal of placenta, could be of major benefit to women worldwide. The umbilical vein injection (UVI) of saline solution or any other fluid alone or plus an uterotonic drug seems a promising intervention to help push out the placenta by inducing uterine contractions. Uterotonic drugs are those that increase the uterine tone or contractility (or both) and include ergot alkaloids, oxytocin, and prostaglandins. Injection of the solution into the umbilical vein in the cord after delivery of the baby is an inexpensive and simple intervention.

UVI for the management of retained placenta was first described by both Mojon and Asdrubali independently in 1826 (Koerting 1926). In the early 20th century, various authors reported the use of UVI of saline solution with volumes that have varied widely between 200 mL and 400 mL (Gabaston 1914; Jarcho 1928). Subsequent studies have concentrated on smaller volumes of UVI of saline solution plus oxytocin, although most of these were uncontrolled (Golan 1983; Golan 1984; Hauksson 1986; Heinonen 1985; Neri 1966).

How the intervention might work

The hypothesised beneficial effect of the UVI is that it may reduce the need for manual removal of the placenta (Carroli 1991). The aim is to treat the *placenta adherens* subtype by delivering the uterotonic drug directly to the retroplacental myometrium, which would then contract, thus shearing away the placenta and leading to its expulsion. The uterotonic drug would need to pass down the umbilical vein into the placental bed capillaries, across the syncytiotrophoblast into the maternal blood flowing over the placental bed and into the myometrium. It is unlikely that this mechanism would have any effect on *partial accreta* (which is an anatomical rather than functional abnormality), or *trapped placenta* where the placenta had already detached from the uterus and delivery could be made more difficult by cervical contraction (Akol 2016).

Why it is important to do this review

The aim of this review was to evaluate the available evidence about the possible benefits and risks of the use of UVI versus expectant management for retained placenta. We also evaluated benefits and risks of the use of umbilical injection with different fluids and uterotonic drugs. This is an update of a review last published in 2011.

OBJECTIVES

To assess the use of umbilical vein injection (UVI) of saline solution with or without uterotonics compared to either expectant management or with an alternative solution or other uterotonic agent for retained placenta.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials comparing UVI of saline solution or other fluids, with or without uterotonic drugs, either with expectant management or with an alternative UVI injection, in the management of retained placenta. We considered quasi-randomised, cluster-randomised, and trials reported only in abstract form.

Types of participants

We included all women having a vaginal delivery with a retained placenta. For this review, we considered trials including women in whom the placenta was not delivered spontaneously at least 15 minutes after delivery of the baby.

Types of interventions

1. UVI saline versus expectant management.
2. UVI oxytocin in saline versus expectant management.
3. UVI oxytocin in saline versus UVI saline alone.
4. UVI oxytocin in saline versus UVI plasma expander.
5. UVI oxytocin in saline versus UVI ergometrine in saline.
6. UVI prostaglandin in saline versus UVI saline alone.
7. UVI prostaglandin in saline versus UVI oxytocin in saline.
8. UVI prostaglandin in saline versus UVI ergometrine in saline.
9. UVI ergometrine in saline versus UVI saline alone.
10. UVI carbetocin in saline versus UVI oxytocin in saline.

Types of outcome measures

We evaluated the following maternal outcomes. We chose seven to be primarily representative of the important clinical measures of ineffectiveness and complications.

Primary outcomes

1. Manual removal of the placenta.
2. Maternal mortality.

3. Severe postpartum haemorrhage (PPH) (defined as clinically estimated blood loss of 1000 mL or greater).
4. Blood transfusion.
5. Addition of therapeutic uterotonics.
6. Need for treatment with antibiotics (infection).
7. Maternal postpartum anaemia (defined by the haemoglobin concentration according to local standards).

Secondary outcomes

1. Serious maternal morbidity (hysterectomy, admission to intensive care, renal or respiratory failure, and other additional surgical procedures to treat PPH other than manual removal of placenta, related to the randomised interventions).
2. PPH (defined as clinically estimated or measured blood loss of 500 mL or greater).
3. Mean blood loss (mL).
4. Mean time from injection to placental removal (minutes).
5. Perinatal fall in haemoglobin levels (defined as decrease in previous haemoglobin concentration levels by at least 10%).
6. Iron tablets during the puerperium.
7. Subsequent surgical evacuation of retained products of conception.
8. Diastolic blood pressure greater than 100 mmHg between injection and discharge from the labour ward.
9. Vomiting between injection and discharge from the labour ward.
10. Shivering between injection and discharge from the labour ward.
11. Nausea between injection and discharge from the labour ward.
12. Headache between injection and discharge from the labour ward.
13. Fever between injection and discharge from the labour ward.
14. Maternal pain between injection and discharge from the labour ward.
15. Maternal dissatisfaction with third-stage management.
16. Secondary PPH (after 24 hours and before six weeks).
17. Bleeding needing readmission.
18. Maternal fatigue.
19. Breastfeeding at discharge from hospital.

Search methods for identification of studies

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

Electronic searches

In this update, we searched Cochrane Pregnancy and Childbirth's Trials Register of Controlled Trials (14 June 2020) by contacting their Information Specialist.

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for Cochrane Central Register of Controlled Trials (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 refer to the website (pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register).

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

1. monthly searches of 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 the search results and review the full text of all relevant trial reports identified through the searching activities. Based on the intervention described, they assign each trial report a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and add it to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies).

In addition, we searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for unpublished, planned, and ongoing trial reports (9 July 2019) using the search methods detailed in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We applied no language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Nardin 2011.

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

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

Selection of studies

Two review authors (NK and SJ) independently assessed for inclusion all the potential studies identified by the search strategy. We resolved any disagreements through discussion or, if required, we consulted the third review author (AW). If a review author was involved in a trial that was identified by the search strategy as a possibility for inclusion, that review author did not participate in consideration of that study (e.g. Weeks 2009).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (NK and SJ) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author (AW). We entered data into

Review Manager 5 (Review Manager 2014), and checked them for accuracy. We used the GRADE approach to assess the overall certainty of the evidence (Langer 2012). We used GRADE Profiler to import data from Review Manager 5 and create 'Summary of findings' tables (gradepro.org/). We used five GRADE elements (study limitation, consistency of effect, imprecision, indirectness, and publication bias) to assess the overall certainty of evidence. Then, we provided justifications to downgrade the certainty of the evidence from 'high certainty' by one level (for serious biases or high heterogeneity), or by two levels (for very serious biases such as imprecision of effect estimates) using footnotes.

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

If a review author was involved in an included trial, that review author did not participate in data extraction or analysis (e.g. Weeks 2009).

Assessment of risk of bias in included studies

Two review authors (NK and SJ) 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 review author (AW). If a review author was involved in an included trial, that review author did not participate in assessment of risk of bias (e.g. Weeks 2009).

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

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

We assessed the method as:

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

2. Allocation concealment (checking for possible selection bias)

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

1. low, high, or unclear risk of bias.

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

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

We assessed methods as:

1. low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
2. 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);
3. unclear risk of bias.

5. Selective reporting (checking for reporting bias)

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

We assessed the methods as:

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

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

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could have put it at risk of bias:

1. low risk of other bias;
2. high risk of other bias;
3. unclear whether there is risk of other bias.

7. Overall risk of bias

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

Measures of treatment effect

Dichotomous data

For dichotomous data, we performed a meta-analysis using pooled risk ratio (RR) with 95% confidence intervals (CIs).

Continuous data

We calculated the mean difference (MD) with 95% CIs for continuous data, if outcomes were measured in the same way between trials. If data had used different methods, we planned to calculate the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods, with 95% CIs.

Unit of analysis issues

Cluster-randomised trials

We intended to include cluster-randomised trials in the analyses along with individually randomised trials. We would have adjusted their sample sizes or standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.4 or 16.3.6) using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we had used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. We intended to identify both cluster-randomised trials and individually randomised trials, and synthesise the relevant information. We would have considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was unlikely. However, we did not identify any cluster-randomised trials.

We also would acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

Given the nature of the intervention and condition, we planned to exclude any cross-over trials. However, we did not identify any cross-over trials with this search strategy.

Other unit of analysis issues

We did not plan to include any studies with multiple pregnancies and did not identify any with our search strategy.

We included eight studies with multiple treatment groups (Bider 1996; Carroli 1998; Chauhan 2004; Gazvani 1998; Harara 2011; Huber 1991; Kristiansen 1987; Rogers 2007). Seven had three treatment groups (Carroli 1998; Chauhan 2004; Gazvani 1998; Harara 2011; Huber 1991; Kristiansen 1987; Rogers 2007), and one had four treatment groups (Bider 1996). In all trials we selected one pair of eligible interventions for each analysis and excluded irrelevant groups. This meant that trial data were included in more than one comparison depending on the treatment groups being analysed. In this way, we were able to avoid unit of analysis issues.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect 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. 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. We regarded heterogeneity as substantial if I^2 was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

We assessed reporting bias 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 asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it. There was no asymmetry for any of the funnel plots drawn.

Data synthesis

We carried out statistical analysis using the Review Manager 5 (Review Manager 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect (i.e. where trials were examining the same intervention, and the trials' populations and methods were sufficiently similar).

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if there was substantial statistical heterogeneity, we used random-effects

meta-analysis to produce an overall summary if a mean treatment effect across trials was considered clinically meaningful. In future updates, the random-effects summary will be treated as the mean range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the mean treatment effect is not clinically meaningful, we will not combine trials. If we used random-effects analyses, we presented the results as the mean treatment effect with 95% CIs, and the estimates of Tau^2 and I^2 statistics.

Subgroup analysis and investigation of heterogeneity

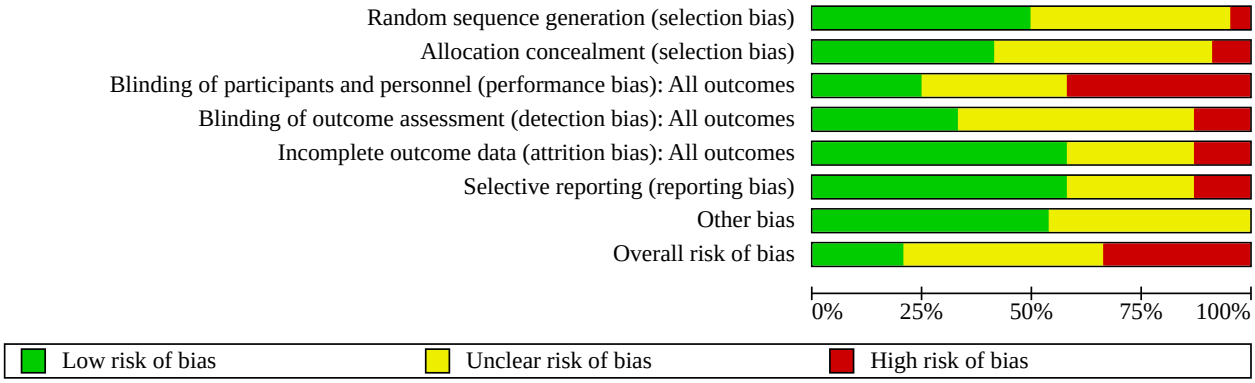
If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We then considered whether an overall summary was meaningful and, if it was, we used random-effects analysis to summarise it.

We carried out the following subgroup analyses.

1. High versus low risk of bias.
2. Dose of international unit (30 or greater or less than 30).

The dichotomisation of studies into high and low risk of bias involved analyses based on each trial's risk of bias rating (low/high/unclear) for allocation, incomplete outcome data, and blinding (Figure 1). Those rated as high or unclear were considered at high risk of bias. We considered only studies that were rated at 'low risk' for allocation concealment and 'low risk' for blinding (due to the nature of the intervention, blinding was considered critical) as 'low risk of bias' (except if the study was rated as 'high risk' or 'unclear' for incomplete outcome data).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



We assessed subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2014). We reported the results of subgroup analyses quoting the effect measure, 95% CI value, and the interaction test I^2 value.

Summary of findings and assessment of the certainty of the evidence

For this update, we assessed the certainty of the evidence using the GRADE approach as outlined in the *GRADE Handbook* to assess the certainty of the body of evidence relating to the main comparisons (gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html).

1. UVI of oxytocin solution versus saline solution.
2. UVI of saline solution versus expectant management.
3. UVI of oxytocin plus saline solution versus expectant management.
4. UVI of oxytocin plus saline solution versus UVI of plasma expander.

We selected the following outcomes as most clinically important.

1. Manual removal of the placenta.
2. Maternal mortality.
3. Severe PPH (defined as clinically estimated blood loss of 1000 mL or greater).
4. Blood transfusion.
5. Addition of therapeutic uterotonics.
6. Need for treatment with antibiotics (or infection).
7. Maternal postpartum anaemia (defined by the haemoglobin concentration according to local standards).

RESULTS

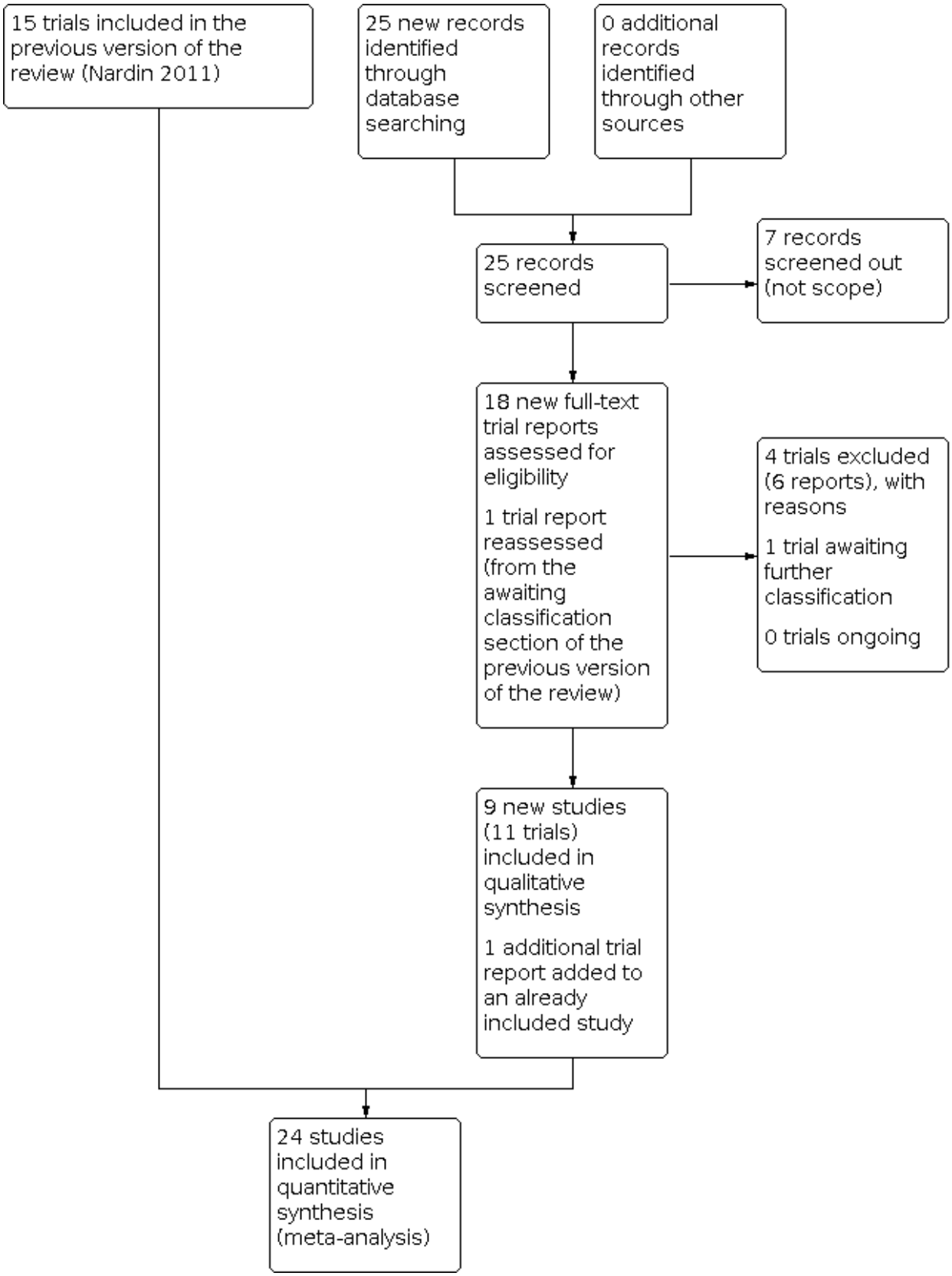
Description of studies

Results of the search

In the previous version of this review (Nardin 2011), we searched the databases to 28 February 2011 and included 15 studies.

In this updated review, we searched to June 2020. We retrieved 18 additional reports for assessment (Figure 2). We also reassessed Chauhan 2004, which was awaiting classification in the previous version of the review. We included nine new trials (11 reports), added one additional report to a previously included study, and excluded four studies (six reports). One trial is awaiting further classification.

Figure 2. Study flow diagram.



Included studies

We included randomised controlled trials that administered normal saline or uterotonic drugs, or both, via the umbilical cord compared with other alternatives including administration of similar agents intravenously or intramuscularly or no injection/placebo. Any of the above interventions were considered regardless of whether the intervention was provided as a part of active management of the third stage of labour. All included trials were RCTs, one was quasi-randomised (Rajab 2014), and none were cluster-randomised.

In this update, we included 24 trials that enrolled 2348 women. The sample size of trials varied between 28 and 577 participants. Full details of participants, interventions, and outcomes of each included trial are provided in the Characteristics of included studies table.

Five included trials compared UVI of saline solution versus expectant management (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987). Seven compared UVI of oxytocin solution versus expectant management (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987; Lim 2011; Thiery 1987). Fourteen compared UVI of oxytocin solution versus UVI of saline solution Calderale 1994; Carroli 1998; Chauhan 2004; Frappell 1988; Gazvani 1998; Hansen 1987; Huber 1991; Kristiansen 1987; Rogers 2007; Samanta 2013; Selinger 1986; Sivalingam 2001; Weeks 2009; Wilken-Jensen 1989). Only Makkonen 1995 compared UVI of oxytocin solution versus UVI of plasma expander (dextran). Three compared UVI of prostaglandin solution versus UVI of saline solution (Bider 1996; Rajab 2014; Rogers 2007). Four compared UVI of prostaglandin solution to UVI of oxytocin solution (Bider 1996; Harara 2011; Nazeer 2016; Rogers 2007). One compared UVI of prostaglandin solution to UVI of ergometrine solution and the same three-arm study compared UVI of oxytocin solution to UVI of ergometrine solution (Harara 2011). One compared UVI of carbetocin solution to UVI of oxytocin solution (Salem 2019).

Setting

Four trials recruited women in Denmark (Chauhan 2004; Hansen 1987; Kristiansen 1987; Wilken-Jensen 1989) and four in the UK (Frappell 1988; Gazvani 1998; Selinger 1986; Weeks 2009). Three trials recruited in Malaysia (Lim 2011; Sivalingam 2001; Ting 2015), two in Egypt (Harara 2011; Salem 2019), and two in Pakistan (Nazeer 2016; Weeks 2009). One study each recruited women in Israel (Bider 1996), Italy (Calderale 1994), Argentina (Carroli 1998), Netherlands (Huber 1991), Finland (Makkonen 1995), Iran (Najafian 2018), Iraq (Rajab 2014), Hong Kong (Rogers 2007), India (Samanta 2013), Belgium (Thiery 1987), and Uganda (Weeks 2009).

Postpartum haemorrhage status at trial entry

Fourteen studies excluded women with PPH or bleeding requiring immediate treatment (Bider 1996; Gazvani 1998; Lim 2011; Nazeer 2016; Rogers 2007; Samanta 2013; Selinger 1986; Sivalingam 2001; Weeks 2009; Wilken-Jensen 1989), hypovolaemic shock (Carroli 1998; Salem 2019), or haemodynamic instability (Najafian 2018; Rajab 2014) at the time of randomisation. One study did not exclude on the grounds of PPH, but reported that no women had a PPH at the time of randomisation (Harara 2011). It was not reported or not made explicit in the remaining studies (Calderale 1994; Chauhan 2004; Frappell 1988; Hansen 1987; Huber 1991; Kristiansen 1987; Makkonen 1995; Thiery 1987; Ting 2015).

Management of third stage

Six studies did not report the management of third stage (Chauhan 2004; Hansen 1987; Kristiansen 1987; Najafian 2018; Thiery 1987; Ting 2015). Of the remaining 18, 15 reported that all women in both treatment and control groups had active management of the third stage. Oxytocic drug, dose, and route varied considerably within the studies. Oxytocics included oxytocin (Calderale 1994; Huber 1991; Rajab 2014), ergometrine (Wilken-Jensen 1989 who used methylergotamine), oxytocin plus ergometrine (Frappell 1988; Gazvani 1998; Harara 2011; Makkonen 1995; Salem 2019; Selinger 1986), oxytocin or ergometrine depending on maternal condition (Lim 2011; Rogers 2007; Samanta 2013; Sivalingam 2001), or unspecified oxytocics (Nazeer 2016; Weeks 2009). For dosages and routes, see Characteristics of included studies table.

The remaining three studies gave oxytocics to some of the women in both treatment and control groups: Bider 1996 gave intravenous oxytocin 10 IU to the women who had not received oxytocin in previous stages of labour (prostaglandin F2α (PGF2α) group: 4/10 women; oxytocin group: 6/11 women); Carroli 1998 did not specify drug, dose, or route (oxytocin group: 45/98 women; control group: 40/95 women); Huber 1991 gave oxytocin but did not specify dose or route (oxytocin group: 46/72 women; control group: 39/59 women).

Dates of study, funding sources, and declarations of interest

The studies were conducted between 1985 and 2018. Six studies did not state their study dates (Chauhan 2004; Gazvani 1998; Kristiansen 1987; Makkonen 1995; Selinger 1986; Wilken-Jensen 1989), and one we could not assess due to language (Calderale 1994). Four studies were completed between 1980 and 1990 (1985 to 1987: Frappell 1988; 1985 to 1986: Hansen 1987; 1986 to 1989: Huber 1991; 1987: Thiery 1987); three were completed between 1991 and 2000 (1989 to 1992: Bider 1996; 1991 to 1994: Carroli 1998; 1998: Sivalingam 2001); three were completed between 2001 and 2010 (2008 to 2009: Harara 2011; 2002 to 2004: Lim 2011; 2004 to 2005: Rogers 2007; 2004 to 2008: Weeks 2009); and the remaining six were completed between 2011 and 2018 (2012 to 2015: Najafian 2018; 2011: Nazeer 2016; 2011 to 2012: Rajab 2014; 2014 to 2018: Salem 2019; 2010 to 2011: Samanta 2013; 2013 to 2014: Ting 2015).

Most studies did not state their funding sources (Bider 1996; Chauhan 2004; Gazvani 1998; Harara 2011; Huber 1991; Kristiansen 1987; Lim 2011; Makkonen 1995; Najafian 2018; Nazeer 2016; Rajab 2014; Rogers 2007; Salem 2019; Samanta 2013; Selinger 1986; Sivalingam 2001; Ting 2015). Two studies were in different languages so it was unclear if they stated their funding sources (Calderale 1994; Hansen 1987). Thiery 1987 stated that no special funding was required for their study. The remaining studies disclosed their funding sources: Carroli 1998 received funding from the World Health Organization (Special Programme of Research, Development and Research Training Human Reproduction, Maternal health and Safe Motherhood Programme); Frappell 1988 received oxytocin and placebo ampoules from Sandoz Products Ltd; Weeks 2009 received funding from the World Health Organisation, WellBeing of Women, and Pakistan Higher Education Commission; and Wilken-Jensen 1989 received a grant from the Danish Hospital Foundation for Medical Research.

Seven study author teams declared they had no conflicts of interest (Lim 2011; Najafian 2018; Rajab 2014; Salem 2019; Samanta 2013; Ting 2015; Weeks 2009). Two studies were in different languages

so it was unclear if they declared any conflicts (Calderale 1994; Hansen 1987). The remaining studies made no statement regarding conflicts of interest (Bider 1996; Carroli 1998; Chauhan 2004; Frappell 1988; Gazvani 1998; Harara 2011; Huber 1991; Kristiansen 1987; Makkonen 1995; Nazeer 2016; Rogers 2007; Selinger 1986; Sivalingam 2001; Thiery 1987; Wilken-Jensen 1989).

Excluded studies

In this update, we excluded four new trials, making a total of six. One trial compared two doses of the same prostaglandin (Alalaf 2020). Three had a route of administration in the comparator arm that did not fit our inclusion criteria (Das 2008; Elfayomy 2015; Maher 2017). Two were excluded due to uncertainty if the trials were randomised (Das 2008; Habek 2007). One was a non-randomised prospective study (Habek 2001).

See Characteristics of excluded studies table.

Studies awaiting classification

We were unable to access one trial report in the online WHO registry, which was undergoing maintenance at the time of writing (IRCT2015102824754N1). We will revisit this report in the next update.

See Characteristics of studies awaiting classification table

Ongoing studies

There are no ongoing studies to our knowledge.

Risk of bias in included studies

Figure 1 and Figure 3 show an overview of risk of bias across the included studies.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

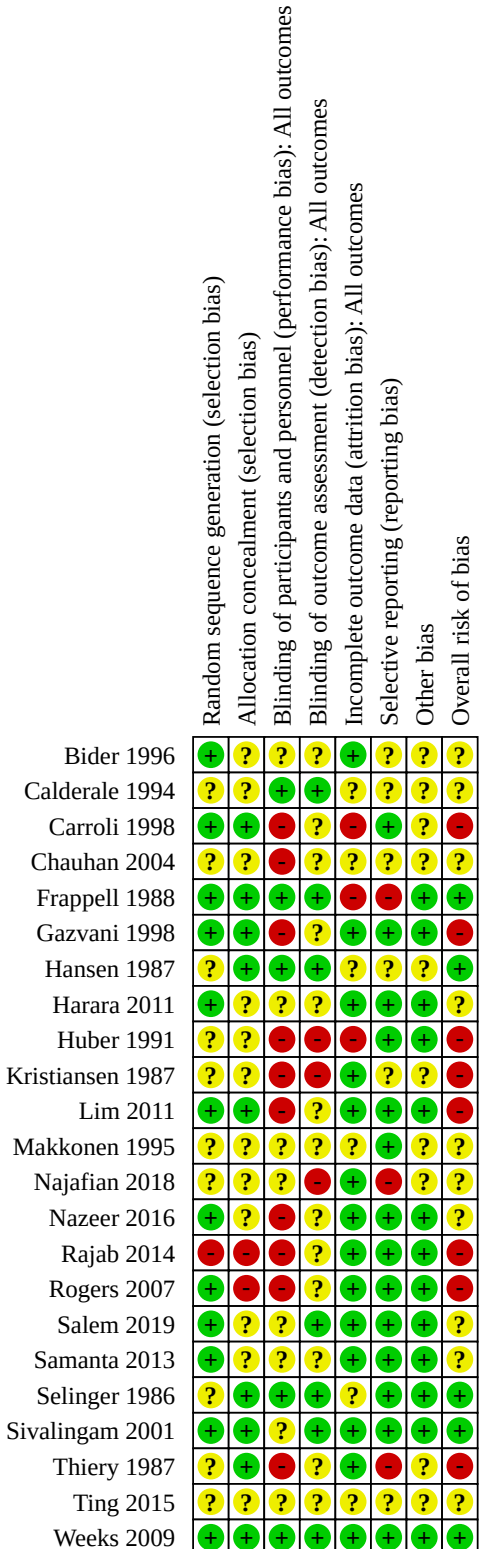
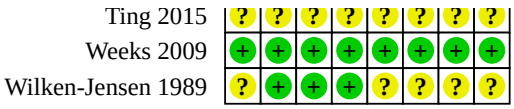


Figure 3. (Continued)



Allocation

Sequence generation

Thirteen trials described clearly the random method generation making selection bias at entry to the trials unlikely (Bider 1996; Carroli 1998; Chauhan 2004; Frappell 1988; Gazvani 1998; Harara 2011; Lim 2011; Nazeer 2016; Rogers 2007; Salem 2019; Samanta 2013; Sivalingam 2001; Weeks 2009). Eleven trials did not describe the random generation method, and thus had a slight potential of selection bias (unclear risk) (Calderale 1994; Chauhan 2004; Hansen 1987; Huber 1991; Kristiansen 1987; Makkonen 1995; Najafian 2018; Selinger 1986; Thiery 1987; Ting 2015; Wilken-Jensen 1989). Rajab 2014 alternately allocated their envelopes ('quasi randomised') and thus had a high potential for selection bias.

Allocation concealment

Ten trials described concealment of allocation succinctly (Carroli 1998; Frappell 1988; Gazvani 1998; Hansen 1987; Lim 2011; Selinger 1986; Sivalingam 2001; Thiery 1987; Weeks 2009; Wilken-Jensen 1989). Twelve trials did not clearly state the method of allocation concealment and, therefore, could be prone to selection bias (unclear risk) (Bider 1996; Calderale 1994, Chauhan 2004; Harara 2011; Huber 1991; Kristiansen 1987; Makkonen 1995; Najafian 2018; Nazeer 2016; Salem 2019; Samanta 2013; Ting 2015). Rajab 2014 alternately allocated their envelopes ('quasi randomised') and thus had a high potential for selection bias. Rogers 2007 had a method of allocation concealment, but the misoprostol solution was more opaque than the other two solutions, which increases likelihood of selection bias.

Blinding

Performance bias

Six studies were described as double blind and were at low risk of performance bias (Calderale 1994; Frappell 1988; Hansen 1987; Selinger 1986; Weeks 2009; Wilken-Jensen 1989). Eight studies did not describe blinding, or there was some blinding of participants, but it was unclear whether blinding could have been breached (Bider 1996; Harara 2011; Makkonen 1995; Najafian 2018; Salem 2019; Samanta 2013; Sivalingam 2001; Ting 2015). In the remaining studies, there was no blinding or it was not possible to blind and so these were at high risk of performance bias (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987; Lim 2011; Nazeer 2016; Rajab 2014; Rogers 2007; Thiery 1987).

Detection bias

Eight studies were at low risk of detection bias because there was some form of blinding of assessors and evaluators and MROP was set with a time limit (Calderale 1994; Frappell 1988; Hansen 1987; Salem 2019; Selinger 1986; Sivalingam 2001; Weeks 2009; Wilken-Jensen 1989). Thirteen studies did not describe blinding, although there was a set time limit for MROP, but other outcomes were open to bias and so these were assessed at unclear risk of bias (Bider 1996; Carroli 1998; Chauhan 2004; Gazvani 1998; Harara 2011; Lim 2011; Makkonen 1995; Nazeer 2016; Rajab 2014; Rogers 2007; Samanta 2013; Thiery 1987; Ting 2015). In three studies, there was no blinding or time limit set for MROP and so these were at high risk (Huber 1991; Kristiansen 1987; Najafian 2018).

In summary, performance bias was assessed high risk in 10 studies (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987; Lim 2011; Nazeer 2016; Rajab 2014; Rogers 2007; Thiery 1987) and detection bias high risk in three studies (Huber 1991; Kristiansen 1987; Najafian 2018).

Incomplete outcome data

Fourteen trials reported no withdrawals, so the likelihood of attrition bias after entry to these trials was low (Bider 1996; Gazvani 1998; Harara 2011; Kristiansen 1987; Lim 2011; Najafian 2018; Nazeer 2016; Rajab 2014; Rogers 2007; Salem 2019; Samanta 2013; Sivalingam 2001; Thiery 1987; Weeks 2009).

Carroli 1998 lost 1.7% of participants to follow-up. Huber 1991 excluded 4.5% of women due to violations of the treatment protocol. Neither included these exclusions in final analysis and thus had a slight risk of attrition bias. Frappell 1988 excluded 18% due to various protocol errors, inadequate data collection, or spontaneous delivery prior to injection, indicating a high risk of attrition bias.

In the remaining studies, it was unclear whether there was any attrition bias as withdrawals were not clearly described.

Selective reporting

Only two studies had a protocol published online that we were able to find. Weeks 2009 presented all primary and secondary outcomes and thus is unlikely to have reporting bias. Rajab 2014 also presented all outcomes, but was retrospectively registered in April 2013, when the trial was completed in 2012, and thus has the potential for reporting bias.

The remaining studies did not have a prepublished protocol. However, 12 presented the relevant outcomes of interest and were unlikely to have significant reporting bias (Carroli 1998; Gazvani 1998; Harara 2011; Huber 1991; Lim 2011; Makkonen 1995; Nazeer 2016; Rogers 2007; Salem 2019; Samanta 2013; Selinger 1986; Sivalingam 2001). Three studies only presented one outcome and were assessed as high risk (Frappell 1988; Najafian 2018; Thiery 1987). The remaining studies were at unclear risk of bias. Six only presented a limited number of outcomes (Bider 1996; Calderale 1994; Chauhan 2004; Hansen 1987; Kristiansen 1987; Wilken-Jensen 1989); and one did not contribute any usable data (Ting 2015). These 10 were more likely to have reporting biases.

Other potential sources of bias

In Bider 1996, three women were not randomised due to excessive bleeding from the manual removal group.

In Carroli 1998, there was a change in treatment protocol during the study (after the first 64 women were recruited, the injected volume was increased to 40 mL), due to publication of an article on the topic while the study was underway, and so this was assessed as being at unclear risk of bias.

We could not assess two studies fully as they were not published in English (Calderale 1994; Hansen 1987).

Seven studies were limited in their overall presentation of the study, and thus there may have had other unknown biases (Chauhan 2004; Kristiansen 1987; Makkonen 1995; Najafian 2018; Thiery 1987; Ting 2015; Wilken-Jensen 1989).

Two trials did not contribute data to the analyses: Najafian 2018 because data reported were inconsistent, and Ting 2015 because an abstract only was available and the number of women in each group was unclear.

Studies had considerable heterogeneity in regards to the primary outcome of manual removal of the placenta, as they each had a different endpoint for when to proceed (e.g. 15 minutes after UVI, 30 minutes after UVI, at discretion of physician). Determination of the need for additional uterotonics and criteria for infection were also similarly highly variable. The other primary outcomes have clearer criteria and were more likely to be similar between studies.

Effects of interventions

See: **Summary of findings 1** Saline solution compared to expectant management for management of retained placenta; **Summary of findings 2** Oxytocin solution compared to expectant management for management of retained placenta; **Summary of findings 3** Oxytocin solution compared to saline solution for management of retained placenta; **Summary of findings 4** Oxytocin solution compared to plasma expander for management of retained placenta

Saline solution versus expectant management

Five studies compared saline solution versus expectant management (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987). See Summary of findings 1.

Primary outcomes

There was no evidence of a difference for any of the outcomes between saline and expectant management including controlled cord traction.

Five studies (n = 445) reported that saline probably makes little or no difference in manual removal of the placenta (RR 0.93, 95% CI 0.80 to 1.10; moderate-certainty evidence; Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987; Analysis 1.1). Evidence for the remaining primary outcomes was of very low certainty due to high imprecision and moderate risk of bias in study design. Therefore, it is uncertain whether injection of saline solution reduces maternal mortality (no events; Gazvani 1998; Kristiansen 1987; Analysis 1.2); severe blood loss (1000 mL or greater) (RR 0.73, 95% CI 0.17 to 3.11; 1 study, n = 122; Carroli 1998; Analysis 1.3), or postpartum anaemia, reported as mean haemoglobin levels at 24 to 48 hours postpartum (MD 0.10, 95% CI −0.59 to 0.79; 1 study, n = 163; Carroli 1998; Analysis 1.6). The evidence is very uncertain about the effect of saline in comparison to expectant management on risk of blood transfusion (mean RR 0.41, 95% CI 0.10 to 1.73; $Tau^2 = 0.81$; $Chi^2 = 3.86$ (P = 0.05); $I^2 = 74\%$; 3 studies, n = 277; very low-certainty evidence; Carroli 1998; Chauhan 2004; Gazvani 1998; Analysis 1.4).

None of the studies reported additional therapeutic uterotonics in this comparison.

Secondary outcomes

Two studies reported serious maternal morbidity, but there were no events recorded (Gazvani 1998; Kristiansen 1987; Analysis 1.8).

Maternal dissatisfaction with third stage management may be reduced with saline solution compared to expectant management (RR 0.51, 95% CI 0.30 to 0.87; 1 study, n = 42; Analysis 1.13).

There were little to no differences between saline solution and expectant management for the following outcomes.

1. Haemoglobin 40 to 45 days postpartum (MD 0.40, 95% CI −0.23 to 1.03; 1 study, n = 93; Analysis 1.7).
2. Blood loss (500 mL or greater) (RR 0.98, 95% CI 0.52 to 1.82; 2 studies, n = 177; Analysis 1.9).
3. Mean blood loss (MD −20.65 mL, 95% CI −128.77 to 87.48; 2 studies, n = 164; Analysis 1.10).
4. Time from injection to placental removal (MD 5.00 minutes, 95% CI −18.63 to 28.63; 1 study; n = 42; Analysis 1.11).
5. Subsequent surgical evacuation of retained products of conception (RR 0.79, 95% CI 0.51 to 1.22; 1 study, n = 178; Analysis 1.12).
6. Stay at hospital for more than two days (RR 1.19, 95% CI 0.66 to 2.15; 1 study, n = 176; Analysis 1.14).

Oxytocin solution versus expectant management

Seven studies (n = 546) investigated the risk of injecting oxytocin solution in comparison with expectant management (Carroli 1998; Chauhan 2004; Gazvani 1998; Huber 1991; Kristiansen 1987; Lim 2011; Thiery 1987). See Summary of findings 2.

Primary outcomes

UVI of oxytocin solution may slightly reduce the incidence of manual removal of the placenta compared with expectant management (mean RR 0.73, 95% CI 0.56 to 0.95; 7 studies, n = 546; $Tau^2 = 0.06$; $Chi^2 = 13.30$ (P = 0.04); $I^2 = 55\%$; low-certainty evidence; Analysis 2.1). Given the high statistical heterogeneity present in these results, they should be interpreted with caution. Two trials studies maternal mortality but there were no cases reported (n = 93; very low-certainty evidence; Gazvani 1998; Kristiansen 1987; Analysis 2.2). It is uncertain whether UVI of oxytocin reduces severe PPH of 1000 mL or greater because the certainty of the evidence was very low (RR 1.23, 95% CI 0.41 to 3.74; 2 studies, n = 190). Four studies reported blood transfusion and found little to no difference between the groups (RR 0.81, 95% CI 0.47 to 1.38; n = 339; low-certainty evidence; Carroli 1998; Chauhan 2004; Gazvani 1998; Lim 2011). Use of additional uterotonics appeared to be reduced with oxytocin solution although the certainty of this evidence was very low (RR 0.50, 95% CI 0.28 to 0.88; 1 study, n = 60; Analysis 2.5). Single

studies reported need for treatment with antibiotics (reported as 'infection:' RR 1.16, 95% CI 0.32 to 4.16; n = 179; Analysis 2.6), and postpartum anaemia (reported as haemoglobin 24 to 48 hours postpartum: MD 0.00, 95% CI −0.61 to 0.61; n = 166; Analysis 2.7); however, it is uncertain what effect UVI of oxytocin has on these outcomes because the certainty of evidence was very low.

Secondary outcomes

Two trials studied serious maternal morbidity but there were no cases reported (Gazvani 1998; Kristiansen 1987).

There were little to no differences between use of oxytocin solution versus expectant management for the following outcomes.

1. Haemoglobin 40 to 45 days postpartum (MD 0.50, 95% CI −0.14 to 1.14; 1 study, n = 96; Analysis 2.8).
2. PPH 500 mL or greater (RR 1.00, 95% CI 0.45 to 2.22; 3 studies, n = 245; I^2 = 49%; Analysis 2.10).
3. Mean total blood loss (MD −20.92 mL, 95% CI −233.56 to 191.71; 2 studies, n = 172; I^2 = 80%; Analysis 2.11). Very high heterogeneity in this result gives very little certainty in the effect estimate.
4. Time from injection to placental removal (MD 2.00 minutes, 95% CI −21.63 to 25.63; 1 study, n = 42; Analysis 2.12).
5. Surgical evacuation of retained products of conception (RR 0.68, 95% CI 0.43 to 1.06; 2 studies, n = 242; Analysis 2.13).
6. Stay at hospital more than two days (RR 1.09, 95% CI 0.60 to 1.97; 1 study; n = 180; Analysis 2.15).

Maternal dissatisfaction with third stage management may be reduced with UVI oxytocin compared to expectant management (RR 0.38, 95% CI 0.19 to 0.74; 1 trial; n = 42; Analysis 2.14).

Oxytocin solution versus saline solution

Fourteen studies (n = 1370) compared oxytocin solution versus saline solution (Calderale 1994; Carroli 1998; Chauhan 2004; Frappell 1988; Gazvani 1998; Hansen 1987; Huber 1991; Kristiansen 1987; Rogers 2007; Samanta 2013; Selinger 1986; Sivalingam 2001; Weeks 2009; Wilken-Jensen 1989). See Summary of findings 3.

Primary outcomes

Injection of oxytocin solution may reduce the need for manual removal of placenta when compared with saline (mean RR 0.82, 95% CI 0.69 to 0.97; 14 studies, n = 1370; Tau^2 = 0.04; Chi^2 = 28.11 (P = 0.009); I^2 = 54%; low-certainty evidence; Analysis 3.1). However, there is high heterogeneity in this analysis and the results should be interpreted with caution. To explore this heterogeneity, we performed two subgroup analysis; one by risk of bias, and the other by dose of oxytocin. We also created funnel plots for each subgroup to explore other forms of biases (Figure 4; Figure 5).

Figure 4. Funnel plot of comparison: 3 Oxytocin solution versus saline solution, outcome: 3.1 Manual removal of the placenta – by overall risk of bias.

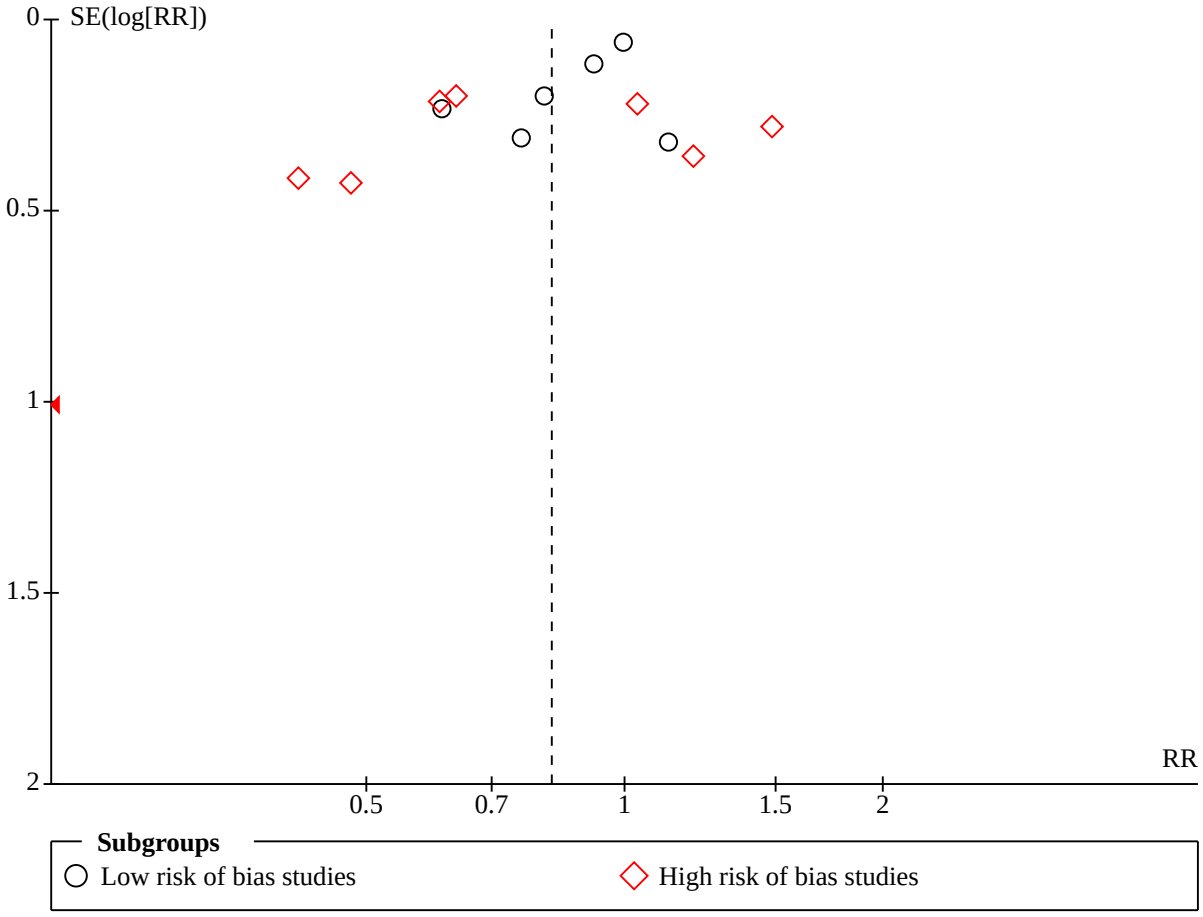
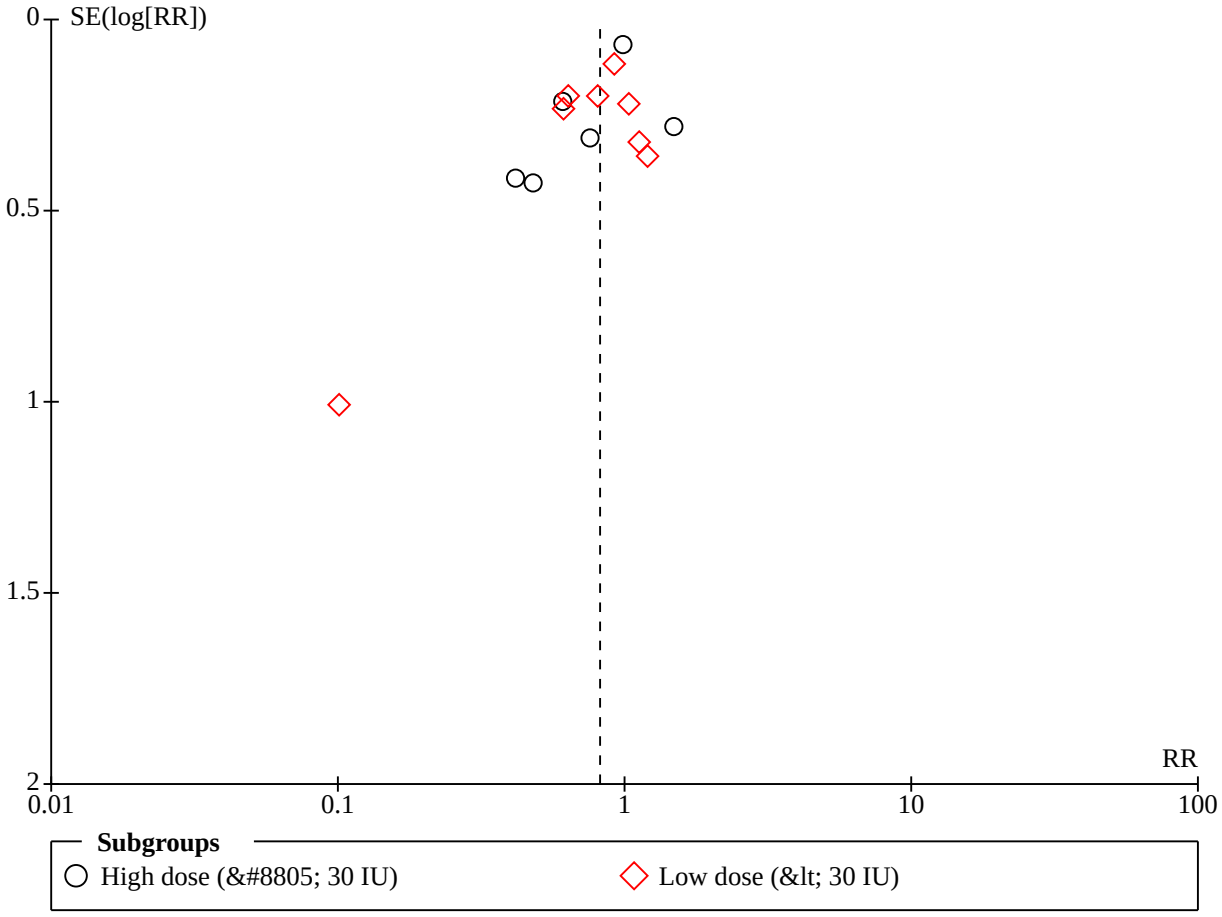


Figure 5. Funnel plot of comparison: 3 Oxytocin solution versus saline solution, outcome: 3.2 Manual removal of the placenta – by oxytocin dose.



There was no evidence of a difference for both CIs for low (mean RR 0.87, 95% CI 0.72 to 1.05; 7 studies, n = 978; I^2 = 45%) and high (mean RR 0.78, 95% CI 0.57 to 1.08; 7 studies, n = 392; I^2 = 58%) risk of bias studies (Analysis 3.1). Heterogeneity remained high within both subgroups (Analysis 3.1), and there was no evidence of a subgroup difference (Chi^2 = 0.28, df = 1 (P = 0.59), I^2 = 0%).

There was no evidence of a difference for both CIs for high dose (mean RR 0.78, 95% CI 0.56 to 1.09; 6 studies, n = 776; I^2 = 65%) and low dose (mean RR 0.83, 95% CI 0.67 to 1.02; 8 studies, n = 594; I^2 = 40%) oxytocin (Analysis 3.2). Heterogeneity remained substantial within the groups, and there was no evidence of a subgroup difference (Chi^2 = 0.28, df = 1 (P = 0.59), I^2 = 0%).

The CIs for the remaining primary outcomes were wide and were unlikely to differ between the two interventions: maternal mortality (RR 2.93, 95% CI 0.12 to 71.59; 5 studies, n = 782; low-certainty evidence; Analysis 3.3); severe PPH of 1000 mL or greater (RR 1.08, 95% CI 0.70 to 1.68; 4 studies, n = 766; moderate-certainty evidence; Analysis 3.4); blood transfusion (RR 1.08, 95% CI 0.78 to 1.49; 7 studies, n = 974; moderate-certainty evidence; Analysis 3.5); use of additional therapeutic uterotonics (RR 0.85, 95% CI 0.59 to 1.23; 4 studies, n = 678; I^2 = 48%; low-certainty evidence; Analysis 3.6); antibiotic use (RR 1.26, 95% CI 0.81 to 1.96; 2 studies, n = 635; moderate-certainty evidence; Analysis 3.7); infection (RR 1.35, 95% CI 0.87 to 2.09; 3 studies, n = 820; Analysis 3.8), and postpartum anaemia, reported as haemoglobin levels at 24 to 48 hours postpartum (MD –0.10, 95% CI –0.76 to 0.56; 1 study, n = 167; very low-certainty evidence; Analysis 3.10).

Secondary outcomes

There were little to no differences in the following outcomes between use of oxytocin and saline solution.

1. Serious maternal morbidity (RR 0.14, 95% CI 0.01 to 2.69; 4 studies, n = 724; Analysis 3.9).
2. Haemoglobin 40 to 45 days postpartum (MD –0.10, 95% CI –0.58 to 0.78; 1 study, n = 167; Analysis 3.11).
3. Blood loss of 500 mL or greater after entry (RR 0.98, 95% CI 0.80 to 1.20; 6 studies, n = 887; I^2 = 31%; Analysis 3.12).
4. Mean blood loss (MD –13.56 mL, 95% CI –118.83 to 91.71; 5 studies, n = 274; I^2 = 78%; Analysis 3.13).
5. Time from injection to placental removal (MD 8.26 minutes, 95% CI –2.00 to 18.53; 2 studies, n = 577; Analysis 3.14).
6. Haemoglobin levels fall (RR 1.01, 95% CI 0.90 to 1.14; 1 study, n = 541; Analysis 3.15).

7. Surgical evacuation of retained products of conception (RR 0.89, 95% CI 0.56 to 1.40; 4 studies, n = 826; Analysis 3.16).
8. Hypertension (no events; Analysis 3.17).
9. Shivering following injection (no events; 1 study, n = 60; Analysis 3.18).
10. Nausea following injection (no events; 1 study, n = 60; Analysis 3.19).
11. Headache following injection (no events; 1 study, n = 60; Analysis 3.20).
12. Abdominal pain (RR 2.00, 95% CI 0.09 to 43.22; 1 study, n = 18; Analysis 3.21).
13. Maternal dissatisfaction with third-stage management (RR 0.75, 95% CI 0.33 to 1.72; 1 study, n = 36; Analysis 3.22).
14. Fever (RR 1.67, 95% CI 0.76 to 3.64; 4 studies, n = 707; Analysis 3.23).
15. Length of third stage of labour (MD 16.20 minutes, 95% CI −15.22 to 47.62; 1 study, n = 30; Analysis 3.24).
16. Stay at hospital more than two days (RR 0.91, 95% CI 0.52 to 1.59; 1 study, n = 184; Analysis 3.25).

Oxytocin solution versus plasma expander

One study (n = 109) reported oxytocin solution versus plasma expanders (Makkonen 1995). See Summary of findings 4.

This study provided data only on use of manual placenta removal (RR 1.34, 95% CI 0.97 to 1.85; Analysis 4.1) and blood transfusion (RR 0.96, 95% CI 0.34 to 2.75; Analysis 4.2). It was of very low certainty so it is uncertain whether oxytocin solution reduces either outcome compared to plasma expander.

Oxytocin solution versus ergometrine solution

One study (n = 52) reported use of oxytocin solution versus ergometrine solution (Harara 2011).

Primary outcomes

Oxytocin UVI reduced the need for manual removal of the placenta compared to ergometrine (RR 0.43, 95% CI 0.21 to 0.86; Analysis 5.1).

The study reported no other primary outcomes.

Secondary outcomes

There was no evidence of a difference between oxytocin and ergometrine on time to placental delivery (MD 0.60 minutes, 95% CI −1.59 to 2.79; Analysis 5.2).

The study reported no other secondary outcomes.

Prostaglandin solution versus saline solution

Three studies (n = 97) compared injection of prostaglandin solution with saline solution (Bider 1996; Rajab 2014; Rogers 2007).

Primary outcomes

The risk of manual removal of the placenta is unlikely to differ between prostaglandin solution and saline solution, given a wide CI and high degree of heterogeneity (mean RR 0.32, 95% CI 0.07 to 1.49; 3 studies, n = 97; $Tau^2 = 1.21$; $Chi^2 = 6.53$ (P = 0.04); $I^2 = 69\%$; Analysis 6.1). There was also high statistical heterogeneity present for this outcome. One small study reported use of additional uterotonics and found little to no difference between the groups (RR 1.05, 95% CI 0.46 to 2.38; n = 17; Analysis 6.2).

The studies reported no other primary outcomes.

Secondary outcomes

Two studies reported mean blood loss and found little to no difference between groups (MD −78.56 mL, 95% CI −161.94 to 4.82; n = 63; random-effects model; $Tau^2 = 2562.08$; $Chi^2 = 2.83$ (P = 0.09); $I^2 = 65\%$; Bider 1996; Rajab 2014; Analysis 6.3). There was high statistical heterogeneity noted for this outcome.

The following outcomes either did not differ between use of prostaglandin solution versus saline solution, or had no events.

1. Vomiting following injection (no events; 1 study, n = 46; Analysis 6.4).
2. Shivering following injection (RR 3.00, 95% CI 0.13 to 70.02; 1 study, n = 46; Analysis 6.5).
3. Nausea following injection (no events; 1 study, n = 46; Analysis 6.6).
4. Headache following injection (no events; 1 study, n = 46; Analysis 6.7).
5. Maternal pain following injection (no events; 1 study, n = 46; Analysis 6.8).
6. Abdominal pain (RR 5.09, 95% CI 0.30 to 85.39; 1 study, n = 17; Analysis 6.9).
7. Fever (RR 2.18, 95% CI 0.10 to 46.92; 2 studies, n = 63; Analysis 6.10).

The studies reported no other secondary outcomes.

Prostaglandin solution versus oxytocin solution

Four studies (n = 173) compared injection of prostaglandin solution with oxytocin solution (Bider 1996; Harara 2011; Nazeer 2016; Rogers 2007).

Primary outcomes

There may be a reduction in the risk of manual removal of the placenta with prostaglandin solution (RR 0.55, 95% CI 0.36 to 0.84; 4 studies, n = 173; $I^2 = 38\%$; Bider 1996; Harara 2011; Nazeer 2016; Rogers 2007; Analysis 7.1). There were little to no differences between groups for use of additional therapeutic uterotonics (RR 1.32, 95% CI 0.58 to 3.00; 1 study; n = 21; Analysis 7.2).

The studies reported no other primary outcomes.

Secondary outcomes

The MD of time from injection to placenta delivery was about seven minutes less in prostaglandin solution versus oxytocin (MD −6.70 minutes, 95% CI −7.58 to −5.82; 3 studies, n = 132; Analysis 7.4).

There were little to no differences between prostaglandin and oxytocin solutions for the following outcomes.

1. Mean blood loss (MD −19.00 mL, 95% CI −118.19 to 80.19; 1 study, n = 21; Analysis 7.3).
2. Shivering following injection (RR 3.00, 95% CI 0.13 to 70.83; 1 study, n = 60; Analysis 7.5).

3. Abdominal pain (RR 3.30, 95% CI 0.41 to 26.81; 1 study, n = 21; Analysis 7.6).
4. Fever (RR 1.10, 95% CI 0.08 to 15.36; 1 study, n = 21; Analysis 7.7).

The studies reported no other secondary outcomes.

Prostaglandin solution versus ergometrine solution

One study (n = 52) reported use of prostaglandin solution versus ergometrine solution (Harara 2011).

Primary outcomes

The comparison of misoprostol and ergometrine solutions showed there may be a reduction in the need for manual removal of placenta with misoprostol (RR 0.32, 95% CI 0.14 to 0.73; Analysis 8.1)

The study reported no other primary outcomes.

Secondary outcomes

The comparison of misoprostol and ergometrine solutions showed there may be a shorter time from injection to placental delivery (MD −15.50 minutes, 95% CI −17.36 to −13.64; Analysis 8.2).

The study reported no other secondary outcomes.

Ergometrine solution versus saline solution

We found no studies comparing ergometrine solution versus saline solution.

Carbetocin solution versus oxytocin solution

One study (n = 200) compared carbetocin solution versus oxytocin solution (Salem 2019).

Primary outcomes

There were little to no differences between carbetocin injection and oxytocin solution for manual removal of the placenta (RR 0.53, 95% CI 0.25 to 1.13; Analysis 9.1), and blood transfusion (RR 0.14, 95% CI 0.02 to 1.14; Analysis 9.2). Carbetocin reduced the use of additional uterotonics (RR 0.26, 95% CI 0.17 to 0.40; Analysis 9.3), and postpartum anaemia, reported as postpartum haemoglobin concentration (MD 0.87 g/dL, 95% CI 0.08 to 1.66; Analysis 9.4).

Secondary outcomes

This single study reported little to no difference between carbetocin injection and oxytocin solution in the number of women with PPH of 500 mL or greater (RR 0.30, 95% CI 0.09 to 1.06; Analysis 9.5). Carbetocin may reduce total blood loss in the third and fourth stages of labour compared to oxytocin (MD −98.00 mL, 95% CI −192.47 to −3.53; Analysis 9.6), and result in a lower change in haemoglobin concentration between admission and six hours postnatal (MD −0.55 g/dL, 95% CI −0.59 to −0.51; Analysis 9.7). There was little to no difference in the incidence of adherent placenta, piecemeal removal, and uterine curettage between carbetocin injection and oxytocin solution (RR 0.40, 95% CI 0.08 to 2.01; Analysis 9.8).

DISCUSSION

Retained placenta affects up to 6% of women having vaginal birth, where it causes morbidity and psychological trauma for the parents. However, in low-resource settings, where there is limited access to operating theatres and blood transfusions, they are a major contributor to the 150,000 haemorrhage deaths each year. A simple, low-cost therapeutic option that could be implemented without need for expensive medical care would therefore be beneficial to mothers, babies, and health systems.

Summary of main results

Saline versus expectant management

This analysis was based in only five small randomised controlled trials, none of which could be blinded. Nevertheless, there seems to be no clear benefits to using saline, with probably little or no difference in the incidence of MROP and evidence for the remaining outcomes being of very-low certainty: severe PPH 1000 mL or greater, blood transfusion, and infection. There were no events reported for maternal mortality or postpartum anaemia (24 to 48 hours postnatal).

Oxytocin solution versus expectant management

UVI of oxytocin solution may reduce the incidence of manual removal of placenta by 27% compared to expectant management (low-certainty evidence), but this meta-analysis was heterogeneous (I^2 = 55%) and the benefit was not reflected in any improvement in other outcomes including mean blood loss, PPH rates, or blood transfusion.

Oxytocin solution versus saline

Oxytocin solution versus saline was the most frequent comparison with 14 studies and the largest sample size (n = 1370) of all the comparisons. There may be a reduction in need for manual removal (low-certainty evidence with high heterogeneity (I^2 = 54%)). As discussed below, with an outcome such as manual removal of the placenta that can be affected by the clinician, having studies that are blinded and of high methodological quality is critical. Subgroup analysis of the studies by risk of bias found the CIs of the low risk of bias group crossed the line of no effect, and showed only a slightly lower heterogeneity (45%), although there was no evidence of a subgroup difference between low-risk and high-risk bias subgroups according to the subgroup interaction tests. Post-hoc exploration by oxytocin dose and by funnel plot revealed no alternative source of heterogeneity. Dealing with these data will, therefore, be controversial, especially as one of our review team (AW) is first author for the largest study.

Overall, it appears unlikely that there is a major effect of umbilical oxytocin injection on main outcomes. However, with a number needed to treat to prevent a retained placenta of 18 (95% CI 9 to 948), it could be argued that with no harmful effects found with its administration, and as an inexpensive and simple intervention that could be performed while placental delivery is awaited, it could still have a role in the management of retained placenta. If the intervention is performed within 15 to 30 minutes after delivery of the baby, it may slightly reduce the need for further interventions for retained placenta. This small potential beneficial effect could still be important in settings where resources are scarce and there is no immediate availability of facilities for manual removal of the placenta.

It should be noted that we found no benefit for UVI of oxytocin solution in length of third stage of labour, blood loss, PPH, haemoglobin, blood transfusion, curettage, infection, hospital stay, fever, abdominal pain, and addition of therapeutic uterotonics.

Oxytocin solution versus plasma expander

UVI of oxytocin solution compared with UVI of plasma expander showed little to no difference in the need for manual removal of placenta or blood loss of 1000 mL or greater.

Oxytocin solution versus ergometrine solution

One study compared oxytocin to ergometrine. There may be a reduction in the need for manual removal of placenta by 43% in favour of oxytocin, but not in time to placental delivery.

Prostaglandin solution versus saline solution

Three studies compared the use of UVI of prostaglandin solution with UVI of saline alone (n = 97) and they found little or no difference in risk of manual removal of placenta or mean blood loss. Furthermore, there was little to no difference in fever, abdominal pain, or use of additional therapeutic uterotonics. The prostaglandin used in two of the studies was dissolved misoprostol, which would be useful in low-resource settings because of its tolerance to heat, low cost, and simple storage.

Prostaglandin solution versus oxytocin solution

The UVI of prostaglandin solution compared with UVI of oxytocin solution may show a reduction in manual removal of placenta by 55%, and for time to placental delivery favouring prostaglandin. All other reported outcomes had wide CIs that crossed the line of no effect with little to no differences. Three of the four studies used misoprostol dissolved in saline, showing promise for low-resource settings.

Prostaglandin solution versus ergometrine solution

One study compared misoprostol to ergometrine. There may be a reduction in the need for manual removal of placenta by 32% as well as time to placental delivery by 15.5 minutes in favour of prostaglandin.

Ergometrine solution versus saline solution

We found no studies comparing ergometrine solution versus saline solution

Carbetocin solution versus oxytocin solution

Only one study compared carbetocin to oxytocin. Carbetocin reduced the use of additional uterotonics and total blood loss. Women who received carbetocin also had higher postpartum haemoglobin concentrations and smaller changes in haemoglobin between admission to hospital and six hours after birth.

Overall completeness and applicability of evidence

Most (but not all) retained placentas are caused by the failure of the retroplacental myometrium to contract. This failure prevents the shearing away of the placenta from the underlying myometrium and its expulsion. UVI of a uterotonic drug seeks to rectify this by delivering a contractile agent directly to this area through the placental vasculature. To do this, the following are required.

1. The drug injected into the placental vein must reach the capillaries in the placental bed. Pipingas demonstrated that the best way of doing this was to thread a catheter along the umbilical vein, and then inject the drug in at least 30 mL of saline (the 'Pipingas' technique) (Pipingas 1993).
2. The drug must pass from the capillaries across the syncytiotrophoblast of the placenta to reach the maternal circulation. Oxytocin only does this very slowly (Malek 1996). However, prostaglandins are a form of fatty acid, and these are actively and rapidly transferred across the placenta (Duttaroy 2009).
3. The drug must pass from the pool of maternal blood that washes across the back of the placenta to the myometrium. However, the blood flowing across the back of the placenta passes directly into the radial veins and thus to the maternal venous circulation. Retrograde flow of the drug from the uterine veins into the myometrial capillaries is unlikely, and so it would probably only reach the myometrial capillaries on its second pass around the body. This is the same as if the drug was given as a systemic maternal intravenous injection.

The above hypothesised mechanism casts doubt on the potential of many (if not all) of the studies in this review to be effective.

A further problem is that the diagnosis of 'retained placenta' is a clinical one and consists of at least three underlying pathologies (see Background). Umbilical injection aims to treat *placenta adherens* only – delivery of a trapped placenta could be made more difficult if any uterotonic passed through the placenta into the uterine tissue, and *partial accreta* is unlikely to be affected as an anatomical, rather than functional, abnormality. One study of 355 retained placentas over five years found that although 74% of retained placenta are of the *adherens* type, 20% were *trapped placentas* and just 5% were *partial accreta* (LWH 2019). Thus, we could only expect the UVI technique to have an effect on about 75% of the cases of retained placenta. Thus, even if UVI were effective for *placenta adherens*, then the demonstrable benefits would be reduced in studies in which all retained placenta types were included irrespective of subgroup. In groups in which intravenous ergometrine is routinely used for prophylaxis, there is a high rate of retained placenta thought to be the *trapped placenta* variety (Begley 1990). In settings using this prophylaxis technique, the efficacy of the UVI could be expected to be even lower.

Quality of the evidence

The problems described in Overall completeness and applicability of evidence are compounded by the subjectivity of many of the PPH outcomes: both the decision to perform a manual removal and the decision to give a blood transfusion are subjective, and blood loss volume is often visually estimated. Even the need for manual removal can be influenced by the tenacity of the doctor attempting to deliver the placenta by cord traction. This means that the study results are prone to assessment bias, unless the clinician attempting delivery of the placenta, deciding on the need for manual removal, and reporting the outcomes is blinded to the intervention being studied. This is best done through a double-blind methodology using placebos, although in theory there could be a separate clinician providing the intervention. It is disappointing that only nine of the studies were able to blind their studies, but it increases the importance of the results from this subgroup of 'low risk of bias' studies, which were graded with a moderate level of certainty due to high heterogeneity.

The drugs discussed in this review (with the exception of misoprostol) require a strict 'cold chain' of refrigeration to maintain their efficacy. This is often unavailable or poorly maintained, even in high-income settings. This could have contributed to the low

efficacy of the technique in some studies – but equally could cause the technique to be less effective once operationalised and so may reflect 'real world' efficacy.

The certainty of evidence as presented in the four 'Summary of findings' tables ranged from very low- to moderate-certainty evidence (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4). Downgrading decisions mainly related to imprecision (small number of events, studies, and wide CIs), limitations in study design, and some inconsistency of effects.

Potential biases in the review process

One of the authors (AW) was chief investigator for the largest of the umbilical oxytocin studies (Weeks 2009), which found no effect of the technique. This could have led to a subconscious desire for this review not to contradict the results of that study. AW has also championed the use and recognition of retained placenta subtypes (Weeks 2008a), which offer further evidence that the current research around retained placentas is somewhat crude. Other review authors assessed, extracted, and analysed the data for this one study (NK and SJ) (Weeks 2009).

Agreements and disagreements with other studies or reviews

The results and conclusions of this update are largely unchanged from the previous Cochrane Review (Nardin 2011), despite the addition of nine new studies. A further systematic review was conducted in 2014 by the UK National Institute for Health and Care Excellence (NICE 2014), which was an update of Nardin 2011 and included a cost-effectiveness analysis. It concluded that "The guideline development group noted that the evidence was of varying quality, but considering the number of trials that evaluated UVI oxytocin, the group was confident that the demonstrated lack of significant overall benefit was likely to be a trustworthy finding."

Since then there have been 3 further systematic reviews of umbilical published. Grillo-Ardila 2018, Patrick 2020 and Duffy 2015 all considered all pharmacological interventions for retained placenta. Grillo-Ardila 2018 and Duffy 2015 found no benefit. Patrick 2020, similar to this review, found no statistically significant benefit of oxytocin over control, but concluded that "Pooled estimates for oxytocin via umbilical vein injection, prostaglandin agents, and nitroglycerin performed favorably compared with placebo or control for the management of retained placenta. Carbetocin and prostaglandin agents were superior to oxytocin in reducing the need for manual extraction or dilation and curettage."

The results of this review are, therefore, largely consistent with previous systematic reviews.

AUTHORS' CONCLUSIONS

Implications for practice

This review identified low-certainty evidence that oxytocin solution may slightly reduce the need for manual removal. However, there are little or no differences for other outcomes. Given that the meta-analysis of the three main comparisons showed no consistent benefit, there is insufficient evidence at this time to warrant changes to clinical practice for the treatment of retained placenta. Furthermore, if there is an effect, it does not appear to be large; the number of cases that need to be treated to prevent one manual removal is unlikely to be less than nine and could be high as 948. However, those who persist in using the technique can be reassured that there is no evidence of harm, and they may, therefore, wish to continue using it. Indeed, many retained placenta deliver spontaneously with no intervention, so there may be a benefit to just waiting a further 30 minutes to allow time for this spontaneous expulsion. However, the risk of bleeding increases with the length of the third stage and so facilities for manual removal and blood transfusion should be readily available.

Implications for research

There is little evidence of the optimal time to wait prior to manual removal of placenta, and a study of immediate versus delayed manual removal would help evaluate the risks and benefits of this strategy.

The anatomical flow of blood through the placental and maternal vasculature casts doubt on whether umbilical injection actually delivers the uterotonic drug directly to the myometrium. Therefore, it may be that other ways of delivering the drug directly to the retroplacental myometrium (for example, through nano-medicine techniques) would be more effective.

At least three subgroups of retained placenta exist, and while *placenta adherens* should respond to uterotonics directed at the retroplacental myometrium, a *trapped placenta* may instead benefit from tocolytics. If all types of retained placenta are therefore included in a study, a uterotonic could help deliver some types of retained placenta while preventing the delivery of others. This would result in no overall effect on the need for manual removal, even if it was effective in the treatment of *placenta adherens*. Future studies should use ultrasound to determine the subtype of retained placenta prior to administering therapy to prevent a falsely negative study.

Sixteen randomised trials (nine of which were low risk of bias) studied UVI oxytocin and overall found no clear benefit. Further research on oxytocin UVI does not, therefore, seem to be justified, although the evidence was not of high certainty. There is some evidence (albeit from studies at high risk of bias) that an UVI of plasma expander or dissolved misoprostol could be beneficial, and so further research in this area is required. If further studies are done, however, they should use the Pipingas method for injection, ultrasound assessment of placental type, and a double-blind methodology to prevent operator bias. Small studies examining injection of prostaglandin (such as dissolved misoprostol) into the umbilical vein show promise and deserve to be studied further.

The evidence extracted from this review suggests that further research on the use of UVI of saline solution alone in comparison to expectant management is not warranted, although the evidence was again either moderate to very-low certainty.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bider 1996

Study characteristics	
Methods	Randomised controlled trial **Setting**: not explicit, but appeared to be 1 hospital in Israel
Participants	37 women with singleton vaginal delivery with retained placenta 60 minutes after delivery of baby
Interventions	Group 1: UVI prostaglandin F2α 20 mg + saline solution 20 mL Group 2: UVI oxytocin 30 IU 3 mL + saline solution 20 mL Group 3: UVI saline solution 20 mL and then either prostaglandin or oxytocin 'randomly' after 30 minutes if still undelivered Group 4: manual removal ('control')
Outcomes	Manual removal of placenta 30 minutes after entry to trial, time to placental delivery, blood loss, fever, abdominal pain, addition of therapeutic uterotonics
Notes	Groups 3 and 4 were excluded from analysis. Dates of study: 3-year period ending September 1992 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: PGF2α: 6/10 augmented, the remaining 4 given oxytocin 10 IU by IV injection after birth of baby. Oxytocin: 5/11 augmented, remaining 6 given oxytocin 10 IU by IV injection PPH status of women at randomisation: women bleeding excessively were not randomised. Only those with firm uterus and 'no bleeding' included.

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

Bider 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised randomisation.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but set a limit for MROP (30 minutes). Other outcomes are likely to have been influenced by clinical judgement (e.g. use of additional uterotonics, blood loss), so if clinicians or outcome assessors (or both) were not blinded, this could have impacted on results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data appeared to be reported for all 37 women.
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol, but did have the main expected outcomes of interest.
Other bias	Unclear risk	3 women from the manual group were not randomised due to excessive bleeding. This group were not included in our analyses, but it was unclear how they could have been allocated to the 'manual' group while also not having been randomised.
Overall risk of bias	Unclear risk	Several unclear factors

Calderale 1994

Study characteristics	
Methods	Randomised controlled trial **Setting**: 1 hospital in Asiago, Italy
Participants	42 women with vaginal delivery of a singleton fetus at 34–42 weeks of gestation. Retained placenta was diagnosed when it was still undelivered 30 minutes after delivery of baby
Interventions	Group 1: UVI oxytocin 10 IU 1 mL + saline solution 20 mL Group 2: UVI placebo + saline solution 20 mL
Outcomes	Manual removal of placenta 30 minutes after UVI, blood loss, time to placental delivery
Notes	**Dates of study**: unable to assess as article is in Italian **Funding sources**: unable to assess as article is in Italian **Declarations of interest**: unable to assess as article is in Italian Oxytocic used in third stage: all women given IV oxytocin. Dose not reported PPH status of women at randomisation: not described in translation

Calderale 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization list" used. No further description.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"il doppio cieco" (double blind).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded with MROP time limit (30 minutes).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess as article is in Italian.
Selective reporting (reporting bias)	Unclear risk	Unable to assess as article is in Italian.
Other bias	Unclear risk	Unable to assess as article is in Italian.
Overall risk of bias	Unclear risk	Several unclear factors.

Carroli 1998

Study characteristics	
Methods	Randomised controlled trial **Setting**: 11 hospitals in Argentina (Buenos Aires, Corrientes, Rosario, Salta)
Participants	286 women with retained placenta 30 minutes after a vaginal delivery and no uterine scar or signs of hypovolaemic shock
Interventions	Group 1: UVI oxytocin 20 IU 2 mL + saline solution 18 mL Group 2: UVI saline solution 2 mL + saline solution 18 mL Group 3: expectant management After the first 64 women recruited, the injected volume was increased to 40 mL.
Outcomes	Manual removal of placenta (no stated time), blood loss after entry to trial, time to placental delivery, haemoglobin level at 24–48 hours and at 40–45 days after delivery, blood transfusion, curettage, infection, hospital stay
Notes	Dates of study: October 1991 to December 1994 Funding sources: World Health Organization (Special Programme of Research, Development and Research Training Human Reproduction, Maternal health and Safe Motherhood Programme)

Carroli 1998 *(Continued)*

Declarations of interest: no statement

Oxytocic used in third stage: type of oxytocic, dose, and route unspecified

Group 1 (UVI oxytocin): 45/98 (2 unknown)

Group 2 (UVI saline): 40/95 (2 unknown)

Group 3 (expectant management): 37/93 (4 unknown)

PPH status of women at randomisation: women with signs of hypovolaemic shock excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1:1 within balanced blocks of 3–9, stratified by centre; generated by customised computer program.
Allocation concealment (selection bias)	Low risk	Sealed consecutively numbered treatment packs. The packs were prepared by the statistician who kept the personnel involved in the recruitment unaware of the pack content. The packs were similar in size, shape, weight, and feel, and were sealed with wax after preparation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Oxytocin vs saline blinded. In expectant management group neither clinicians nor participants blinded (all treatment packs contained 1 ampoule and a bottle, but in the expectant management inside the lid and on the bottles was a label stating: 'do not use! expectant management;' furthermore, to be sure the fluid would not be injected, the bottles contained small black particles in the fluid). Lack of blinding could have influenced clinical decision-making.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Expectant management group not blinded, but MROP time limit set (30 minutes). Some other outcomes reflect decisions made by the attending clinician (e.g. blood loss), so where clinicians were not blinded, this could have impacted on results.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the saline + oxytocin group, 7/98 women did not receive standard intervention as allocated and 6/98 were unknown; these numbers were (respectively) 5/97 and 8/97 in the saline group and 0/96 and 9/96 in the expectant management group. All were followed up. None were lost to follow-up in saline + oxytocin, 2 in the saline group, and 3 in the expectant management group. These 5 lost to follow-up were not included in final analysis.
Selective reporting (reporting bias)	Low risk	The main expected outcomes of interest were reported, and reflect unpublished protocol seen by review authors.
Other bias	Unclear risk	In addition to some women not being treated per protocol as described above, there was a change in treatment protocol during the study (after the first 64 women were recruited, the injected volume was increased to 40 mL), due to publication of an article on the topic while the study was underway.
Overall risk of bias	High risk	Not blinded in 1 comparison and had a high attrition rate.

Chauhan 2004

Study characteristics

Chauhan 2004 *(Continued)*

Methods	Randomised controlled trial **Setting**: 2 hospitals in Denmark (Kolding and Odense)
Participants	60 women with retained placenta 30 minutes after vaginal delivery
Interventions	Group 1: UVI oxytocin 100 IU in 10 mL + saline solution 20 mL Group 2: UVI saline solution 30 mL Group 3: no active treatment given for 30 minutes
Outcomes	Time from injection to placental delivery, blood loss
Notes	Only abstract found. Data presented as percentages with results favourable to oxytocin group. Raw data provided by author. Dates of study: not stated Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: not described PPH status of women at randomisation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" but no further description given.
Allocation concealment (selection bias)	Unclear risk	No explanation is given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No explanation is given; however, it would not have been possible to blind clinicians or women to allocation to expectant management.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear, report describes percentages only.
Selective reporting (reporting bias)	Unclear risk	Not clear.
Other bias	Unclear risk	Not clear.
Overall risk of bias	Unclear risk	Not clear.

Frappell 1988

Study characteristics	
Methods	Randomised controlled trial **Setting**: 2 hospitals in London, UK
Participants	50 women with singleton vaginal delivery. Retained placenta was diagnosed by vaginal examination if the placenta was not located in the vagina or cervix 15 minutes after the delivery of baby.
Interventions	Group 1: UVI oxytocin 10 IU in 1 mL + saline solution 20 mL Group 2: UVI placebo (saline solution) 1 mL + saline solution 20 mL
Outcomes	Manual removal of placenta 15 minutes after the UVI, PPH, blood loss
Notes	Dates of study: August 1985 to February 1987 Funding sources: Sandoz Products Ltd (oxytocin and placebo ampoules) Declarations of interest: no statement Oxytocic used in third stage: all women received oxytocin + ergometrine IM PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables to generate sequential ampoules prepared by pharmacist.
Allocation concealment (selection bias)	Low risk	Sequentially randomly numbered ampoules prepared by pharmacist who took no further participation in the study. Active or placebo ampoules diluted in 20 mL saline.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind." Placebo ampoules used, and random allocation done by pharmacist who took no further part in the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded, MROP time limit (15 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 women (18%) post randomisation exclusions, ITT not used.
Selective reporting (reporting bias)	High risk	No prepublished protocol. Only presented outcome of method of placenta removal (spontaneous or manual).
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Low risk	High exclusion rate, but double-blind nature means bias was unlikely.

Gazvani 1998

Study characteristics	
Methods	Randomised controlled trial **Setting**: 2 hospitals in UK (Liverpool and Swansea)
Participants	81 women with placenta undelivered 20 minutes after completion of the second stage of labour and the following criteria: intact umbilical cord, maternal age > 18 years, gestational age ≥ 28 weeks, no PPH requiring immediate intervention, no known uterine malformations, no previous caesarean delivery
Interventions	IUVI given 30 minutes after delivery of baby Group 1: UVI oxytocin 20 IU in 2 mL + saline solution 20 mL Group 2: UVI saline solution 20 mL Group 3: expectant management
Outcomes	Manual removal of placenta (15 minutes after UVI), expulsion of placenta within 45 minutes, PPH, blood transfusion, maternal morbidity
Notes	Dates of study: not stated Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: all women received oxytocin + ergometrine IM PPH status of women at randomisation: women with PPH requiring immediate intervention were excluded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Consecutively numbered opaque, sealed envelopes. Quote: "There were no violations of the randomization sequence."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described. However, it would not have been possible to blind either clinicians or women to treatment allocation for expectant management group. It was not stated whether clinicians and participants were blinded to the treatments for the other 2 intervention groups. Lack of blinding could have influenced clinical decision-making.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but time limit set for MROP (45 minutes). However, some other outcomes such as blood transfusion reflect decisions made by the attending clinician, who may not have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 81 women randomised included in the analysis on an ITT basis.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, but expected outcomes presented.

Gazvani 1998 *(Continued)*

Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	High risk	Not blinded.

Hansen 1987

Study characteristics	
Methods	Randomised controlled trial **Setting**: 2 'maternity units' in Denmark (Randers and Aalborg)
Participants	60 women with retained placenta 30 minutes after delivery of baby. 1 woman with heavy bleeding was not entered.
Interventions	Group 1: UVI oxytocin 10 IU in 1 mL + saline solution 20 mL Group 2: UVI placebo (saline solution) 1 mL + saline solution 20 mL
Outcomes	Manual removal of placenta 15 minutes after UVI
Notes	No response to a letter sent requesting additional information. Dates of study: January 1985 to January 1986 Funding sources: not able to assess as article in Danish Declarations of interest: not able to assess as article in Danish Oxytocic used in third stage: not reported PPH status of women at randomisation: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized." No further description.
Allocation concealment (selection bias)	Low risk	Adequate. Identical consecutively numbered vials containing oxytocin or saline solution coded by pharmaceutical company (code was broken after completion of trial).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind, with MROP time limit (15 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess as article in Danish.

Hansen 1987 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Unable to assess as article in Danish.
Other bias	Unclear risk	Unable to assess as article in Danish.
Overall risk of bias	Low risk	Double-blinded trial with a time-limit set (15 minutes)

Harara 2011

Study characteristics	
Methods	Randomised controlled trial **Setting**: maternity hospital in Cairo, Egypt
Participants	78 women with a prolonged third-stage labour (retained placenta ≥ 30 minutes after delivery of fetus) despite administration of uterotonics after delivery of anterior shoulder.
Interventions	IUVI given 30 minutes after delivery of baby Group 1: UVI oxytocin 20 IU in saline solution 30 mL Group 2: UVI misoprostol 800 mg dissolved in saline solution 30 mL Group 3: UVI ergometrine 0.2 mg in saline solution 30 mL
Outcomes	Successful placental separation within 30 minutes, injection-separation time interval
Notes	Dates of study: April 2008 to March 2009 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: all women received oxytocin 5 IU + methyl ergometrine 0.2 mg IM PPH status of women at randomisation: no women had PPH when randomised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated using a "computer-generated randomization system."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but time limit set for MROP (30 minutes).

Harara 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, but expected outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Unclear risk	Many aspects not described.

Huber 1991

Study characteristics	
Methods	Randomised controlled trial **Setting**: 8 hospitals in the Netherlands (4 in Amsterdam; 1 in each of Amstelveen, Utrecht, Zaandam, and Zwolle).
Participants	220 women with a vaginal delivery of a singleton baby of ≥ 28 weeks' gestational age and placenta undelivered ≥ 30 minutes after delivery of baby
Interventions	Group 1: UVI oxytocin 10 IU in 1 mL + saline solution 20 mL Group 2: UVI saline solution 1 mL + saline solution 20 mL Group 3: expectant management
Outcomes	Manual removal of placenta after a time based on the clinical judgement of the obstetrician, time interval from injection to spontaneous expulsion of placenta, blood loss
Notes	No response to a letter sent requesting additional information. Dates of study: February 1986 to January 1989 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: oxytocin, dose and route unspecified Group 1 (UVI oxytocin): 46/72 women Group 2 (UVI saline): 37/59 women Group 3 (expectant management): 39/59 women PPH status of women at randomisation: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described. Used a "blocking procedure" to allow balance within small blocks (of 6), but no further information given.

Huber 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Identical white sealed boxes in numeric order with a serial code, by which randomisation occurred in 3 groups. Each box contained an unmarked ampoule. The code was kept by the principal investigator and was broken after completion of trial. However, trial used small block randomisation (of 6). If any recruiting personnel knew that this blocking method was in use, it could have biased treatment allocation at enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Instructions for each group differed based on allocation, and primary outcome (MROP) subject to clinical judgement.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, MROP based on subjective clinical judgement of obstetrician.
Incomplete outcome data (attrition bias) All outcomes	High risk	20/220 (9.1%) women excluded due to protocol violations, and although there was incomplete information in the report, the exclusions did not appear to have been balanced between groups.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, but expected outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	High risk	Not blinded, significant and unbalanced exclusions, unclear randomisation and allocation methods.

Kristiansen 1987

Study characteristics	
Methods	Randomised controlled trial **Setting**: not explicit but appeared to be 1 hospital in Aarhus, Denmark
Participants	51 women with retained placenta for > 20 minutes after delivery of baby
Interventions	Group 1: UVI oxytocin 10 IU in saline solution 10 mL Group 2: UVI saline solution 10 mL Group 3: expectant management
Outcomes	Manual removal of placenta
Notes	No response to a letter sent requesting additional information Dates of study: not stated Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: not reported

Kristiansen 1987 *(Continued)*

PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized." No further description.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participant blinded, but investigator not blind. Lack of blinding could have affected clinical decision-making.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, no clear time limit for MROP reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed.
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol, limited outcomes presented.
Other bias	Unclear risk	Insufficient information to assess.
Overall risk of bias	High risk	Several unclear factors and no blinding.

Lim 2011

Study characteristics

Methods	Randomised controlled trial **Setting**: hospital in Kuala Lumpur, Malaysia
Participants	61 women with placenta undelivered 20 minutes after delivery of baby and the following criteria: singleton pregnancies, > 28 weeks' gestation, vaginal delivery, failure to deliver the placenta after 20 minutes of delivering baby, active management of third stage, no placenta praevia, no PPH, no snapped umbilical cord, no emergency caesarean section in labour, no haemodynamically instability or illness, no presence of severe anaemia, and no chorioamnionitis
Interventions	IUVI given 20 minutes after delivery of baby Group 1: UVI oxytocin 100 IU + saline solution 30 mL Group 2: controlled cord traction
Outcomes	Manual removal of placenta, blood loss, need for blood transfusion, need for additional uterotonic agents to control PPH, incidence of PPH (500 mL), need for uterine curettage, uterine atony, drop in haemoglobin level
Notes	Dates of study: December 2002 to March 2004

Lim 2011 *(Continued)*

Funding sources: not described

Declarations of interest: "We declare that we have no conflicts of interest."

Oxytocic used in third stage:

Group 1 (UVI oxytocin): oxytocin 1/30; oxytocin + ergometrine 29/30

Group 2 (controlled cord traction): oxytocin 3/31; oxytocin + ergometrine 28/31

PPH status of women at randomisation: women with PPH were not randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Box containing an equal number of envelopes for Group 1 and Group 2." Envelopes prepared by a medical officer not involved in the study. They were (quote) "shuffled in a random order."
Allocation concealment (selection bias)	Low risk	Sealed opaque envelope, which was taken randomly from the box by the attending midwife.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It would not have been possible to blind women or attending clinicians to the treatment allocation. Lack of blinding could have influenced clinical decision-making.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but time limit set for MROP (30 minutes). Blood loss assessed by (quote) "collecting all blood and clots in a graduated container and counting swabs and linen;" this appears to be reasonably objective. However, other outcomes (e.g. use of additional uterotonics) reflect decisions made by attending clinicians who were probably not blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women for whom an envelope was opened were followed up and analysed. No withdrawals occurred.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, but presented expected outcomes.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	High risk	Not blinded.

Makkonen 1995

Study characteristics

Methods	Randomised controlled trial **Setting**: not explicit but appeared to be 1 hospital in Kuopio, Finland
Participants	109 women with retained placenta 30 minutes after delivery of baby

Makkonen 1995 *(Continued)*

Interventions	Group 1: UVI oxytocin 50 IU in 5 mL + saline solution 15 mL Group 2: UVI plasma expander (Dextran 70) 20 mL
Outcomes	Manual removal of placenta 30 minutes after entry to trial, duration of third stage, blood loss
Notes	Dates of study: not stated Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: all women received IV oxytocin 5 IU + ergometrine maleate 0.2 mg IM PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized." No further description, but groups were imbalanced in size (68 vs 41), which suggests either a simple method of randomisation or possible flaws with the process (impossible to know without more information).
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but MROP time limit (30 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There appeared to be no losses to follow-up (table 1); however, this was not explicitly stated.
Selective reporting (reporting bias)	Low risk	No prepublished protocol. Presents many relevant outcomes.
Other bias	Unclear risk	Insufficient information to assess.
Overall risk of bias	Unclear risk	Several unclear factors.

Najafian 2018

Study characteristics

Methods	Randomised controlled trial **Setting**: 2 hospitals in Iran (Tehran and Bandar Abbas)
Participants	44 women with placenta undelivered after 30 minutes and successful first and second parturition stages, but no instability of mother's haemodynamic situation

Najafian 2018 *(Continued)*

Interventions	IUVI given 30 minutes after delivery of baby Group 1: UVI oxytocin 50 IU + saline solution 30 mL Group 2: UVI misoprostol 800 µg + saline solution 30 mL
Outcomes	Final time of placenta delivery, haemoglobin drop
Notes	Dates of study: 2012–2015 Funding sources: not stated Declarations of interest: "Authors declare that they have no conflict of interests." Oxytocic used in third stage: not reported PPH status of women at randomisation: excluded women with haemodynamic instability

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided" by "tetra blocking method." Unclear what this method involved. No other information.
Allocation concealment (selection bias)	Unclear risk	Not described, but "tetra-blocking method" suggests small block randomisation (blocks of 4).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described, and MROP time limit not set.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed; none were lost to follow-up.
Selective reporting (reporting bias)	High risk	No prepublished protocol, and limited outcomes presented.
Other bias	Unclear risk	Insufficient information to assess.
Overall risk of bias	Unclear risk	Unclear.

Nazeer 2016

Study characteristics

Methods	Randomised controlled trial **Setting**: hospital in Karachi, Pakistan

Nazeer 2016 *(Continued)*

Participants	60 women with placenta undelivered 30 minutes after completion of second stage of labour and the following criteria: term pregnancies (≥ 37 weeks) delivering vaginally at Jinnah Postgraduate Medical Centre, haemodynamically stable, no twin pregnancies, no blood loss > 500 mL, no high-risk pregnancies (hypertension, diabetes, previous caesarean section)
Interventions	IUVI given 30 minutes after delivery of baby Group 1: UVI oxytocin 50 IU + saline solution 30 mL Group 2: UVI misoprostol 800 µg + saline solution 30 mL
Outcomes	Injection to placenta delivery time, blood loss, maternal morbidity
Notes	Dates of study: February to August 2011 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: all women had active management – no details given PPH status of women at randomisation: excluded women with blood loss > 500 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Envelope method."
Allocation concealment (selection bias)	Unclear risk	Envelope not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded, but investigator was not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigator not blinded, but MROP time limit set (30 minutes). Blood loss measured weighing pad that had been placed under woman's buttocks at time of injection (reasonably objective). However, knowledge of allocation may have influenced assessment of outcome 'shivering.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed.
Selective reporting (reporting bias)	Low risk	No prepublished protocol. Relevant outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Unclear risk	No blinding, but attempted to make subjective outcomes more objective.

Rajab 2014

Study characteristics

Rajab 2014 *(Continued)*

Methods	Quasi-randomised controlled trial **Setting**: hospital in Erbil, Iraq (Kurdistan)
Participants	46 women with an undelivered placenta 30 minutes after delivery of the infant despite active management and the following criteria: ≥ 28 weeks' gestation, no significant bleeding, singleton pregnancy, no previous caesarean delivery, no haemodynamic instability, no severe anaemia (haemoglobin < 8 g/dL), no chorioamnionitis
Interventions	IUVI given 30 minutes after delivery of the infant Group 1: UVI misoprostol 800 µg + saline solution 20 mL Group 2: UVI saline solution 20 mL
Outcomes	Time and method of placental delivery, volume of blood loss, maternal morbidity
Notes	Dates of study: April 2011 to February 2012 Funding sources: not stated Declarations of interest: "The authors declare that they have no competing interests." Oxytocic used in third stage: all women received oxytocin 5 IU IM PPH status of women at randomisation: excluded women with haemodynamic instability

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternately allocated (quasi-randomised).
Allocation concealment (selection bias)	High risk	Allocation was alternate sequence, so entirely predictable.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded, investigator administering the injection was not. There was no indication that other attending clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, MROP time limit (30 minutes) set. Blood loss measured weighing pad that had been placed under patient's buttocks at time of injection (reasonably objective). However, knowledge of allocation may have influenced assessment of other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed.
Selective reporting (reporting bias)	Low risk	No prepublished protocol. Relevant outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	High risk	Quasi-randomised, not blinded.

Rogers 2007

Study characteristics	
Methods	Randomised controlled trial Setting: 2 hospitals in Hong Kong (New Territories and Kowloon)
Participants	54 women with retained placenta 45 minutes after vaginal delivery of a single fetus of > 37 weeks' gestation
Interventions	Group 1: UVI oxytocin 50 IU in 5 mL + saline solution 25 mL Group 2: UVI prostaglandin E1 analogue (misoprostol) 800 µg + saline solution 30 mL Group 3: UVI saline solution 30 mL All intraumbilical injections given through an umbilical catheter.
Outcomes	Manual removal of placenta 30 minutes after trial entry
Notes	Dates of study: 2004–2005 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: all women received oxytocin + ergometrine 1 mL IM or oxytocin 10 IU IV PPH status of women at randomisation: excluded women with significant bleeding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of computer-generated random numbers.
Allocation concealment (selection bias)	High risk	Quote: "[Patient] enrolled by opening the next in a series of randomized treatment packs." Packs contained a 50 mL syringe of 1 of the 3 preparations. Not stated whether packs were opaque. Misoprostol resulted in an opaque suspension compared which was not as 'clear' as the saline and oxytocin solutions.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Midwifery and medical staff could not be entirely blinded, because misoprostol resulted in an opaque suspension compared to clear saline and oxytocin solutions. Participant enrolled by opening their own treatment pack, so could have been aware of whether receiving misoprostol or not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, MROP time limit (30 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, and no loss to follow-up.
Selective reporting (reporting bias)	Low risk	No prepublished protocol. Relevant outcomes presented.

Rogers 2007 *(Continued)*

Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	High risk	Blinding of outcome assessment (detection bias) and allocation concealment.

Salem 2019

Study characteristics	
Methods	Randomised controlled trial **Setting**: Zagazig University Hospital, Egypt
Participants	227 women eligible for inclusion; 200 randomised. **Inclusion criteria**: pregnant women > 34 weeks' gestation with a singleton living fetus, vertex presentation, vaginal spontaneous delivery without the need for episiotomy with failure of placental delivery (retained non-separated placenta) after 30 minutes of IV injections of oxytocin 10 IU and methylergometrine 0.2 mg (uterotonics were injected immediately after delivery of the anterior shoulder of baby) in presence of an intact umbilical cord. After delivery of baby, cord was clamped and cut, and clamp was left in position. After diagnosis of retained placenta, controlled cord traction was performed again and a container placed under woman's buttocks for blood collection. If placenta was still not delivered, woman was randomised.
Interventions	Group 1: IUVI 1 mL of carbetocin 100 µg diluted in 20 mL normal saline 0.9% Group 2: IUVI oxytocin 20 IU (Syntocynon, Novartis) diluted in 20 mL normal saline 0.9%
Outcomes	Blood loss in third and fourth stage of labour (2 hours following placental delivery – volume of blood was measured by estimating the volume of blood present in a container in millilitres from the point of diagnosis of retained placenta to 2 hours after delivery of placenta), duration of third stage of labour in minutes, postpartum haemoglobin concentration (grams per decilitre) measured 6 hours after delivery, change in the haemoglobin concentration in grams per decilitre (difference between haemoglobin on admission and 6 hours after delivery), percentage of spontaneously expelled placenta following intra-umbilical injection of the ecbolic drug, percentage of still retained placenta following intra-umbilical injection of the ecbolic drug (removed manually completely or adherent placenta which needed piecemeal removal and uterine curettage), need for additional uterotonic drugs following complete placental delivery, incidence of PPH (loss > 500 mL of blood), need for blood transfusion, adverse effects at time of injection (anaphylactic reactions, hypotension, and cardiac arrhythmias)
Notes	Dates of study: October 2014 to October 2018 Funding sources: not stated Declarations of interest: "There are no conflicts of interest." Oxytocic used in third stage: all women received oxytocin 10 IU + methylergometrine 0.2 mg IV PPH status of women at randomisation: excluded women with hypovolaemic shock but less severe PPH not mentioned

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Probably low risk, they referred to using a computerised program to randomise participants.

Salem 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Drugs prepared by a nurse and given to operator without any information about the type of drug and all participants were reported as being blinded about the used drug (refer to 'double blind study'). It is possible that blinding could have been breached – relies on no indication from nurse.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reports that all evaluators were blinded about groups during the data collection. Midwives estimating blood loss at 2 hours postpartum were reported as being "blinded." MROP time limit set to 30–45 minutes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	227 eligible for inclusion but 27 were not recruited (7 women had severe atonic PPH necessitating immediate manual removal of placenta; 20 women experienced cervical, vaginal, vulvar, and perineal tears). It reported that these 27 were not included in the final analysis, so that a total of 200 women were finally recruited. So probably low as loss was before randomisation. Results reported for all 200 women.
Selective reporting (reporting bias)	Low risk	All outcomes documented in the methods were reported in results.
Other bias	Low risk	Baseline characteristics similar.
Overall risk of bias	Unclear risk	Unclear.

Samanta 2013

Study characteristics	
Methods	Randomised controlled trial **Setting**: hospital in Bengal, India
Participants	58 women with an undelivered placenta 30 minutes after delivery and the following criteria: aged > 18 years with a singleton pregnancy, gestation > 34 weeks who underwent vaginal delivery, no maternal haemodynamic instability (pulse > 100 beats/minute or systolic blood pressure < 100 mmHg) or PPH requiring immediate intervention, no pre-eclampsia, no stillborn baby, no severe anaemia, no associated medical disorders (e.g. cardiac disease/hypertension/diabetes), no previous placenta previa, no known uterine malformations, no previous caesarean section
Interventions	IUVI given 30 minutes after active management of the third stage of labour Group 1: UVI oxytocin 50 IU 5 mL + saline solution 25 mL Group 2: UVI saline solution 30 mL
Outcomes	Expulsion of placenta within 30 minutes of oxytocin injection, manual removal of placenta, PPH (> 500 mL), drop in haemoglobin concentration, blood transfusion, extra oxytocics for continued bleeding, fall in blood pressure, increase in pulse, maternal pyrexia, need for therapeutic antibiotics, maternal mortality, duration of hospital stay, readmission rate to hospital within 2 weeks of delivery
Notes	Dates of study: June 2010 to May 2011 Funding sources: not stated

Samanta 2013 *(Continued)*

	Declarations of interest: "None of the authors has anything to disclose."
	Oxytocic used in third stage: all women received oxytocin 10 IU IM or methylergometrine 0.2 mg IM
	PPH status of women at randomisation: excluded PPH requiring immediate intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers used. Quote: "There were no violations of the randomization sequence."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No statement on blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, with gentle cord traction and eventual MROP after 30 minutes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed.
Selective reporting (reporting bias)	Low risk	No prepublished protocol. Relevant outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Unclear risk	Overall, unclear how blinding and concealment were performed.

Selinger 1986

Study characteristics

Methods	Randomised controlled trial **Setting**: 2 hospitals in the UK (not explicit but appeared to be Bristol and Oxford)
Participants	30 women with vaginal delivery, singleton pregnancy, and diagnosis of retained placenta by bimanual examination 20 minutes after delivery of baby. Excluded shocked (haemodynamically unstable) or heavily bleeding women
Interventions	Group 1: UVI oxytocin 10 IU 1 mL + saline solution 19 mL Group 2: UVI saline solution 20 mL
Outcomes	Manual removal of placenta 15 minutes after injection, duration of third stage of labour, postpartum blood loss.
Notes	Response to a letter sent requesting additional information specified 'fully blinded.'

Selinger 1986 *(Continued)*

	Dates of study: not stated
	Funding sources: not stated
	Declarations of interest: no statement
	Oxytocic used in third stage: all women received oxytocin 5 IU + ergometrine 500 µg in 1 mL IM (Syntometrine)
	PPH status of women at randomisation: excluded heavily bleeding women

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized." No further description.
Allocation concealment (selection bias)	Low risk	Appears adequate, the same volume of solution was taken from (quote) "identical, randomly numbered ampoules."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded, MROP done after 15 minutes of controlled cord traction.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 (17%) women excluded due to prior damage to the umbilical cord. It appeared that this exclusion may have been prior to treatment and, therefore, prior to randomisation (which occurred upon administration of solution from randomly numbered ampoule); however, this was not entirely clear.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, relevant outcomes presented.
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Low risk	Exclusions made while still blinded.

Sivalingam 2001

Study characteristics

Methods	Randomised controlled trial **Setting**: hospital in Ipoh, Malaysia
Participants	35 women with retained placenta 20 minutes after vaginal delivery of 1 fetus with gestational age ≥ 28 weeks. Reasons for exclusion included: placenta previa, primary PPH, snapped umbilical cord, emergency caesarean section, haemodynamically unstable or ill women, severe anaemia, chorioamnionitis
Interventions	Group 1: UVI oxytocin 30 IU 3 mL + saline solution 27 mL Group 2: UVI saline solution 30 mL

Sivalingam 2001 *(Continued)*

Outcomes	Manual removal of placenta after 30 minutes of UVI, addition of therapeutic uterotonics, blood transfusion, blood loss, curettage
Notes	Dates of study: July to September 1998 Funding sources: not stated Declarations of interest: no statement Oxytocic used in third stage: Group 1 (UVI oxytocin): oxytocin 2/19; oxytocin + ergometrine 17/19. Route not specified Group 2 (UVI saline): oxytocin 2/16; oxytocin + ergometrine 14/16 PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Box of equal number of envelopes prepared by 2 medical officers not involved in the study. Midwife then selected an envelope randomly to prepare solution during delivery.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The envelopes contained different instructions according to the allocation. The treatment was then prepared by a midwife, who did not reveal the allocation to the attending doctor. Women were blinded to allocation. Although blinding of some clinicians attending was attempted, it would have been very easy to breach.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded, with MROP time limit (30 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were analysed.
Selective reporting (reporting bias)	Low risk	No prepublished protocol, relevant outcomes were reported
Other bias	Low risk	No other sources of bias identified.
Overall risk of bias	Low risk	No high or unclear risks of bias found

Thiery 1987

Study characteristics

Methods	Randomised controlled trial **Setting**: not explicit but appeared to be 1 hospital in Gent, Belgium

Thiery 1987 *(Continued)*

Participants	32 women with diagnosis of retained placenta 15 minutes after delivery of baby
Interventions	Group 1: UVI oxytocin 10 IU 1 mL + saline solution 20 mL Group 2: expectant management
Outcomes	Manual removal of placenta 15 minutes after entry to trial
Notes	Unpublished data only Dates of study: 1987 Funding sources: no special funding required Declarations of interest: no statement Oxytocic used in third stage: not reported PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized." No further description.
Allocation concealment (selection bias)	Low risk	Sealed numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Unblinded."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Unblinded," with MROP after 15 minutes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, < 5% lost to follow-up.
Selective reporting (reporting bias)	High risk	Only reported MROP. No prepublished protocol.
Other bias	Unclear risk	Unpublished data only, insufficient information to assess.
Overall risk of bias	High risk	Not blinded, and unclear randomisation method.

Ting 2015

Study characteristics

Methods	Randomised controlled trial **Setting**: tertiary teaching hospital in Malaysia

Ting 2015 *(Continued)*

Participants	37 women delivering singleton fetus, who had no sign of placental separation 20 minutes after vaginal delivery
Interventions	Group 1: UVI carbetocin 100 µg in 39 mL 0.9% sodium chloride Group 2: UVI oxytocin 100 IU in 30 mL 0.9% sodium chloride
Outcomes	Manual removal of placenta after injection, incidence of PPH, additional uterotonic agents, blood transfusion
Notes	Dates of study: May 2013 to April 2014 Funding sources: not reported Declarations of interest: "We declare that we have no conflicts of interest." No data were analysed from this trial due to lack of information on denominators in each intervention group. Oxytocic used in third stage: not reported PPH status of women at randomisation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unable to judge – insufficient information within abstract.
Allocation concealment (selection bias)	Unclear risk	Unable to judge – insufficient information within abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unable to judge – insufficient information within abstract, reported as 'double-blind' but no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to judge – insufficient information within abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to judge – insufficient information within abstract.
Selective reporting (reporting bias)	Unclear risk	Unable to judge – insufficient information within abstract.
Other bias	Unclear risk	Unable to judge – insufficient information within abstract.
Overall risk of bias	Unclear risk	Unable to judge – insufficient information within abstract.

Weeks 2009

Study characteristics

Weeks 2009 *(Continued)*

Methods	Randomised controlled trial **Setting**: 13 hospitals (4 in the UK, 6 in Uganda, and 3 in Pakistan)
Participants	577 women with retained placenta 30 minutes after a vaginal delivery of 1 fetus of > 34 weeks of gestation or > 2 kg birthweight Exclusion criteria: heavy bleeding, evidence of shock (pulse > 100 or systolic blood pressure < 100 mmHg), stillbirth
Interventions	Group 1: UVI oxytocin 50 IU in 5 mL + saline solution 25 mL Group 2: UVI sterile water 5 mL + saline solution 25 mL
Outcomes	Manual removal of placenta, blood loss, blood transfusion, haemoglobin fall, time to placental delivery, maternal mortality, maternal morbidity, curettage, use of antibiotics
Notes	Dates of study: December 2004 to May 2008 Funding sources: WHO, WellBeing of Women, Pakistan Higher Education Commission Declarations of interest: "We declare that we have no conflicts of interest." Oxytocic used in third stage: women excluded who wanted physiological third stage but not detail given on active management PPH status of women at randomisation: excluded women with PPH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list with random permuted blocks of 4, 6, or 8 stratified by recruitment centre.
Allocation concealment (selection bias)	Low risk	Sealed treatment packs consecutively numbered. Packs were prepared by a commercial company who were uninvolved with the remainder of the study. Packs were similar in size, shape, weight, and feel, and were sealed after preparation. Contents of both packs were identical with 5 × 1 mL ampoules labelled with the study name and recruit number. Each pack also contained an extra emergency ampoule hidden in a side compartment for use only in case of breakages.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All blinded to allocation, with MROP time limit (30 minutes) set.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/292 women in oxytocin and 7/285 women in placebo groups did not receive allocated intervention. 0 lost to follow-up, 0 discontinued, and all randomised women were analysed.
Selective reporting (reporting bias)	Low risk	Many prespecified outcomes were reported.

Weeks 2009 *(Continued)*

Other bias	Low risk	No other sources of bias were identified.
Overall risk of bias	Low risk	No high or unclear risks of bias found

Wilken-Jensen 1989

Study characteristics	
Methods	Randomised controlled trial Setting: hospital in Denmark
Participants	40 women with diagnosis of retained placenta 20 minutes after vaginal delivery of baby by intermittent traction on the umbilical cord and light suprapubic pressure
Interventions	Group 1: UVI oxytocin 100 IU 10 mL + saline solution 20 mL Group 2: UVI saline solution 30 mL
Outcomes	Manual removal of placenta 40 minutes after trial entry, time from injection to delivery of placenta, postpartum blood loss
Notes	No response to a letter sent requesting additional information Dates of study: not stated Funding sources: Danish Hospital Foundation for Medical Research (grant) Declarations of interest: no statement Oxytocic used in third stage: all women received methylergotamine 0.2 mg IM PPH status of women at randomisation: excluded women with "heavy bleeding that required the immediate removal of placenta"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"[R]andomized" but method not described.
Allocation concealment (selection bias)	Low risk	Oxytocin and placebo ampoules were supplied by the same pharmaceutical company, and although not explicit, the implication was that they were identical.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind." No further information given. It is plausible that the interventions were identical, and that clinicians and women were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded with MROP time limit set (40 minutes).

Wilken-Jensen 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described. Report stated that 40 women were randomised, but later stated that 18 vs 19 women received the relevant treatment. It was unclear what happened to the 3 other women, or what group they were from.
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol. Only presented time to delivery.
Other bias	Unclear risk	Study was not clearly described, there was insufficient information to assess.
Overall risk of bias	Unclear risk	Several unclear factors.

IM: intramuscular; ITT: intention to treat; IU: international unit; IUVI: intraumbilical vein injection; IV: intravenous; MROP: manual removal of the placenta; PPH: postpartum haemorrhage; UVI: umbilical vein injection.

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

Study	Reason for exclusion
Alalaf 2020	Compared 2 doses of the same prostaglandin.
Das 2008	Comparison of 2 different method of injection of the same solution. Also inadequate data and unclear if randomised.
Elfayomy 2015	Incorrect route of administration.
Habek 2001	Non-randomised prospective study.
Habek 2007	Not clear if randomised.
Maher 2017	Incorrect route of administration.

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

IRCT2015102824754N1

Methods	Women in labour room with retained placenta randomly divided into 2 groups; single-blind, multicentre trial
Participants	44 women who gave birth vaginally diagnosed with retained placenta after 30 minutes
Interventions	Group 1: UVI 50 IU oxytocin in 30 mL saline Group 2: UVI misoprostol 800 mg in 30 mL saline
Outcomes	Primary outcomes: final withdrawal of uterus Secondary outcomes: postpartum bleeding, anaemia
Notes	Recruitment dates: 2016 No further details available. We emailed the authors (Neda_hajiha@yahoo.com; ghafarin2@yahoo.com) on 5 February 2021 and are awaiting a response.

IU: international unit; UVI: umbilical vein injection.

DATA AND ANALYSES

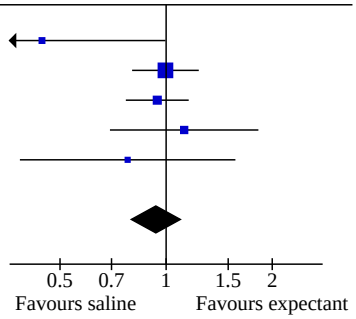
Comparison 1. Saline solution versus expectant management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Manual removal of the placenta	5	445	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.10]
1.2 Maternal mortality	2	87	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Blood loss ≥ 1000 mL after entry	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.17, 3.11]
1.4 Blood transfusion	3	277	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.10, 1.73]
1.5 Infection	1	176	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.54]
1.6 Haemoglobin 24–48 hours postpartum	1	163	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.59, 0.79]
1.7 Haemoglobin 40–45 days postpartum	1	93	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.23, 1.03]
1.8 Serious maternal morbidity	2	87	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.9 Blood loss ≥ 500 mL after entry	2	177	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.52, 1.82]
1.10 Mean blood loss (mL)	2	164	Mean Difference (IV, Fixed, 95% CI)	-20.65 [-128.77, 87.48]
1.11 Time from injection to placental delivery (minutes)	1	42	Mean Difference (IV, Fixed, 95% CI)	5.00 [-18.63, 28.63]
1.12 Surgical evacuation of retained products of conception	1	178	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.22]
1.13 Maternal dissatisfaction with third-stage management	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.30, 0.87]
1.14 Stay at hospital > 2 days	1	176	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.66, 2.15]

Analysis 1.1. Comparison 1: Saline solution versus expectant management, Outcome 1: Manual removal of the placenta

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chauhan 2004	5	18	15	24	10.2%	0.44 [0.20 , 1.00]
Carroli 1998	60	95	59	93	47.1%	1.00 [0.80 , 1.24]
Gazvani 1998	22	26	26	29	19.4%	0.94 [0.77 , 1.16]
Huber 1991	25	69	19	59	16.2%	1.13 [0.69 , 1.83]
Kristiansen 1987	7	16	9	16	7.1%	0.78 [0.38 , 1.57]
Total (95% CI)		**224**		**221**	**100.0%**	**0.93 [0.80 , 1.10]**
Total events:	119		128			

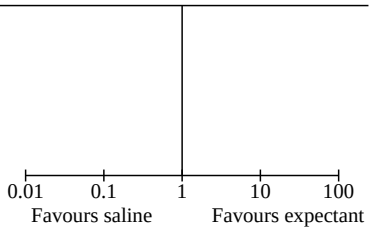
Heterogeneity: Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Saline solution versus expectant management, Outcome 2: Maternal mortality

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	29		Not estimable
Kristiansen 1987	0	16	0	16		Not estimable
Total (95% CI)		**42**		**45**		**Not estimable**
Total events:	0		0			

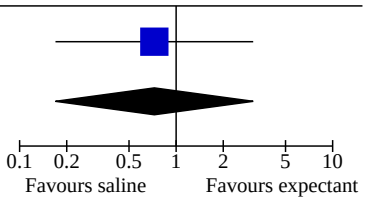
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Saline solution versus expectant management, Outcome 3: Blood loss ≥ 1000 mL after entry

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	3	62	4	60	100.0%	0.73 [0.17 , 3.11]
Total (95% CI)		**62**		**60**	**100.0%**	**0.73 [0.17 , 3.11]**
Total events:	3		4			

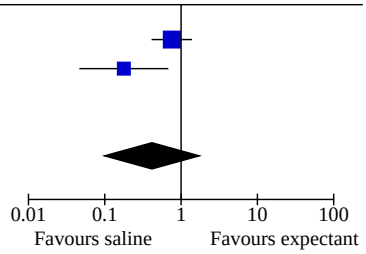
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Saline solution versus expectant management, Outcome 4: Blood transfusion

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Random, 95% CI
Carroli 1998	15	92	19	88	58.5%	0.76 [0.41 , 1.39]
Chauhan 2004	2	18	15	24	41.5%	0.18 [0.05 , 0.68]
Gazvani 1998	0	26	0	29		Not estimable
Total (95% CI)		**136**		**141**	**100.0%**	**0.41 [0.10 , 1.73]**
Total events:	17		34			

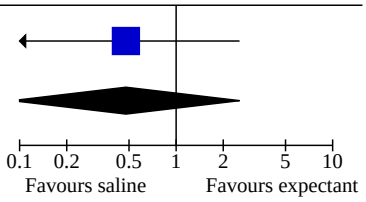
Heterogeneity: Tau² = 0.81; Chi² = 3.86, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Saline solution versus expectant management, Outcome 5: Infection

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	2	90	4	86	100.0%	0.48 [0.09 , 2.54]
Total (95% CI)		**90**		**86**	**100.0%**	**0.48 [0.09 , 2.54]**
Total events:	2		4			

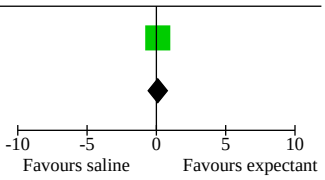
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Saline solution versus expectant management, Outcome 6: Haemoglobin 24–48 hours postpartum

Study or Subgroup	Saline Mean	Saline SD	Saline Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	9.8	2.4	82	9.7	2.1	81	100.0%	0.10 [-0.59 , 0.79]
Total (95% CI)			**82**			**81**	**100.0%**	**0.10 [-0.59 , 0.79]**

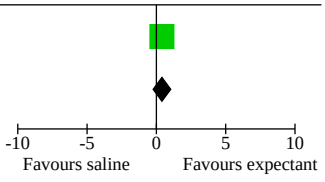
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Saline solution versus expectant management, Outcome 7: Haemoglobin 40–45 days postpartum

Study or Subgroup	Saline Mean	Saline SD	Saline Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	10.8	1.6	44	10.4	1.5	49	100.0%	0.40 [-0.23 , 1.03]
Total (95% CI)			**44**			**49**	**100.0%**	**0.40 [-0.23 , 1.03]**

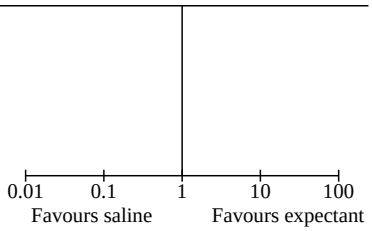
Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Saline solution versus expectant management, Outcome 8: Serious maternal morbidity

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	29		Not estimable
Kristiansen 1987	0	16	0	16		Not estimable
Total (95% CI)		**42**		**45**		**Not estimable**
Total events:	0		0			

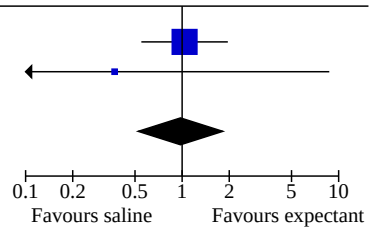
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Saline solution versus expectant management, Outcome 9: Blood loss ≥ 500 mL after entry

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	15	62	14	60	90.9%	1.04 [0.55 , 1.96]
Gazvani 1998	0	26	1	29	9.1%	0.37 [0.02 , 8.71]
Total (95% CI)		**88**		**89**	**100.0%**	**0.98 [0.52 , 1.82]**
Total events:	15		15			

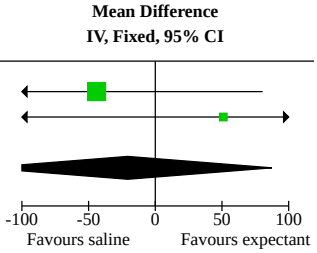
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Saline solution versus expectant management, Outcome 10: Mean blood loss (mL)

Study or Subgroup	Saline Mean	Saline SD	Saline Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	394	305	62	438	390	60	75.4%	-44.00 [-168.51 , 80.51]
Chauhan 2004	434	413	18	383	264	24	24.6%	51.00 [-167.08 , 269.08]
Total (95% CI)			**80**			**84**	**100.0%**	**-20.65 [-128.77 , 87.48]**

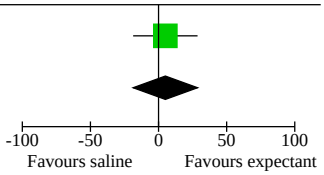
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Saline solution versus expectant management, Outcome 11: Time from injection to placental delivery (minutes)

Study or Subgroup	Saline Mean	Saline SD	Saline Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Chauhan 2004	52	43	18	47	32	24	100.0%	5.00 [-18.63 , 28.63]
Total (95% CI)			**18**			**24**	**100.0%**	**5.00 [-18.63 , 28.63]**

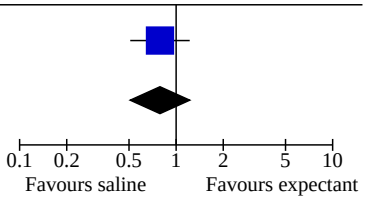
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Saline solution versus expectant management, Outcome 12: Surgical evacuation of retained products of conception

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	25	90	31	88	100.0%	0.79 [0.51 , 1.22]
Total (95% CI)		**90**		**88**	**100.0%**	**0.79 [0.51 , 1.22]**
Total events:	25		31			

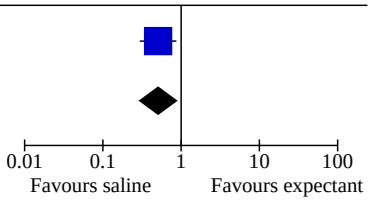
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Saline solution versus expectant management, Outcome 13: Maternal dissatisfaction with third-stage management

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chauhan 2004	8	18	21	24	100.0%	0.51 [0.30 , 0.87]
Total (95% CI)		**18**		**24**	**100.0%**	**0.51 [0.30 , 0.87]**
Total events:	8		21			

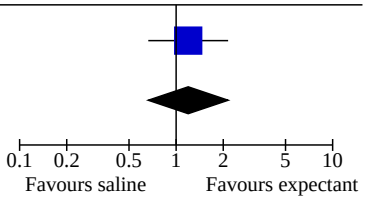
Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Saline solution versus expectant management, Outcome 14: Stay at hospital > 2 days

Study or Subgroup	Saline Events	Saline Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	20	90	16	86	100.0%	1.19 [0.66 , 2.15]
Total (95% CI)		**90**		**86**	**100.0%**	**1.19 [0.66 , 2.15]**
Total events:	20		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable



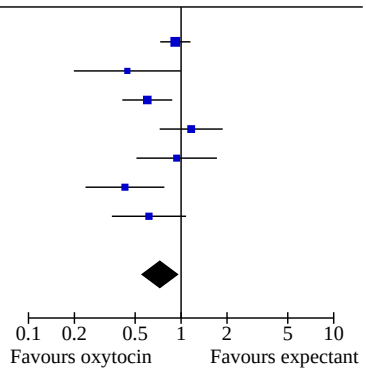
Comparison 2. Oxytocin solution versus expectant management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Manual removal of the placenta	7	546	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.56, 0.95]
2.2 Maternal mortality	2	93	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Blood loss ≥ 1000 mL after entry	2	190	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.41, 3.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Blood transfusion	4	339	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.47, 1.38]
2.5 Additional therapeutic uterotonics	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.28, 0.88]
2.6 Infection	1	179	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.32, 4.16]
2.7 Haemoglobin 24–48 hours postpartum	1	166	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.61, 0.61]
2.8 Haemoglobin 40–45 days postpartum	1	96	Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.14, 1.14]
2.9 Serious maternal morbidity	2	90	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.10 Blood loss ≥ 500 mL after entry	3	245	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.45, 2.22]
2.11 Mean blood loss (mL)	2	172	Mean Difference (IV, Random, 95% CI)	-20.92 [-233.56, 191.71]
2.12 Time from injection to placental delivery (minutes)	1	42	Mean Difference (IV, Fixed, 95% CI)	2.00 [-21.63, 25.63]
2.13 Surgical evacuation of retained products of conception	2	242	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.06]
2.14 Maternal dissatisfaction with third-stage management	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.19, 0.74]
2.15 Stay at hospital > 2 days	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.97]

Analysis 2.1. Comparison 2: Oxytocin solution versus expectant management, Outcome 1: Manual removal of the placenta

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Random, 95% CI
Carroli 1998	57	98	59	93	23.5%	0.92 [0.73 , 1.15]
Chauhan 2004	5	18	15	24	7.8%	0.44 [0.20 , 1.00]
Gazvani 1998	14	26	26	29	18.1%	0.60 [0.41 , 0.88]
Huber 1991	27	72	19	59	14.9%	1.16 [0.72 , 1.87]
Kristiansen 1987	10	19	9	16	11.4%	0.94 [0.51 , 1.72]
Lim 2011	9	30	21	30	11.7%	0.43 [0.24 , 0.78]
Thiery 1987	9	19	10	13	12.6%	0.62 [0.35 , 1.08]
Total (95% CI)		**282**		**264**	**100.0%**	**0.73 [0.56 , 0.95]**
Total events:	131		159			

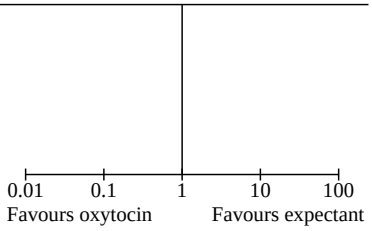


Heterogeneity: Tau² = 0.06; Chi² = 13.30, df = 6 (P = 0.04); I² = 55%
Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2: Oxytocin solution versus expectant management, Outcome 2: Maternal mortality

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	29		Not estimable
Kristiansen 1987	0	19	0	19		Not estimable
Total (95% CI)		**45**		**48**		**Not estimable**
Total events:	0		0			

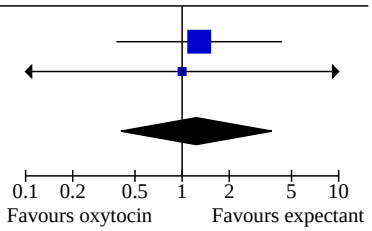
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Oxytocin solution versus expectant management, Outcome 3: Blood loss ≥ 1000 mL after entry

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	6	70	4	60	81.2%	1.29 [0.38 , 4.34]
Lim 2011	1	30	1	30	18.8%	1.00 [0.07 , 15.26]
Total (95% CI)		**100**		**90**	**100.0%**	**1.23 [0.41 , 3.74]**
Total events:	7		5			

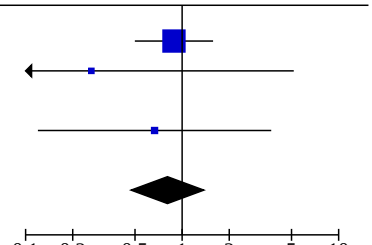
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Oxytocin solution versus expectant management, Outcome 4: Blood transfusion

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	18	94	19	88	79.2%	0.89 [0.50 , 1.58]
Chauhan 2004	0	18	2	24	8.7%	0.26 [0.01 , 5.17]
Gazvani 1998	0	26	0	29		Not estimable
Lim 2011	2	30	3	30	12.1%	0.67 [0.12 , 3.71]
Total (95% CI)		**168**		**171**	**100.0%**	**0.81 [0.47 , 1.38]**
Total events:	20		24			

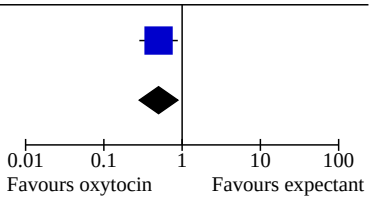
Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Oxytocin solution versus expectant management, Outcome 5: Additional therapeutic uterotonics

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lim 2011	10	30	20	30	100.0%	0.50 [0.28 , 0.88]
Total (95% CI)		**30**		**30**	**100.0%**	**0.50 [0.28 , 0.88]**
Total events:	10		20			

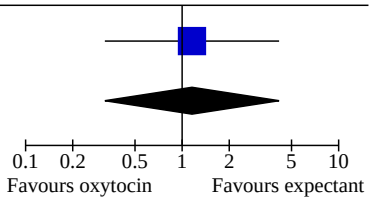
Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Oxytocin solution versus expectant management, Outcome 6: Infection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	5	93	4	86	100.0%	1.16 [0.32 , 4.16]
Total (95% CI)		**93**		**86**	**100.0%**	**1.16 [0.32 , 4.16]**
Total events:	5		4			

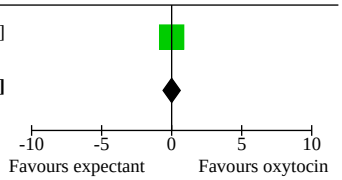
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Oxytocin solution versus expectant management, Outcome 7: Haemoglobin 24–48 hours postpartum

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	9.7	1.9	85	9.7	2.1	81	100.0%	0.00 [-0.61 , 0.61]
Total (95% CI)			**85**			**81**	**100.0%**	**0.00 [-0.61 , 0.61]**

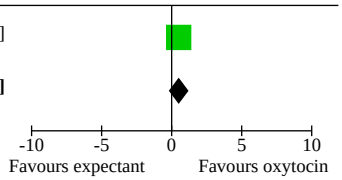
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Oxytocin solution versus expectant management, Outcome 8: Haemoglobin 40–45 days postpartum

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	10.9	1.7	47	10.4	1.5	49	100.0%	0.50 [-0.14 , 1.14]
Total (95% CI)			**47**			**49**	**100.0%**	**0.50 [-0.14 , 1.14]**

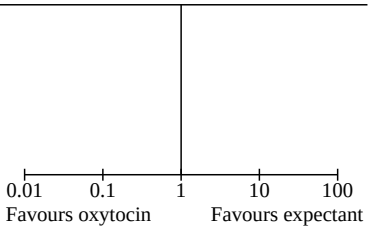
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Oxytocin solution versus expectant management, Outcome 9: Serious maternal morbidity

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	29		Not estimable
Kristiansen 1987	0	19	0	16		Not estimable
Total (95% CI)		**45**		**45**		**Not estimable**
Total events:	0		0			

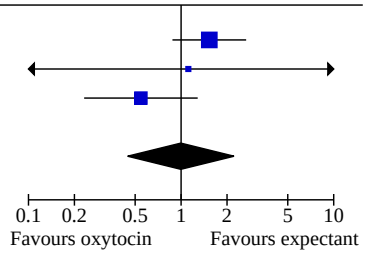
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Oxytocin solution versus expectant management, Outcome 10: Blood loss ≥ 500 mL after entry

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Random, 95% CI
Carroli 1998	25	70	14	60	53.0%	1.53 [0.88 , 2.67]
Gazvani 1998	1	26	1	29	7.7%	1.12 [0.07 , 16.95]
Lim 2011	6	30	11	30	39.3%	0.55 [0.23 , 1.28]
Total (95% CI)		**126**		**119**	**100.0%**	**1.00 [0.45 , 2.22]**
Total events:	32		26			

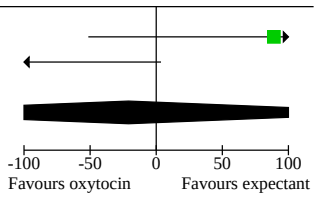
Heterogeneity: Tau² = 0.24; Chi² = 3.92, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Oxytocin solution versus expectant management, Outcome 11: Mean blood loss (mL)

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Random, 95% CI
Carroli 1998	527	426	70	438	390	60	49.3%	89.00 [-51.35 , 229.35]
Chauhan 2004	255	170	18	383	264	24	50.7%	-128.00 [-259.62 , 3.62]
Total (95% CI)			**88**			**84**	**100.0%**	**-20.92 [-233.56 , 191.71]**

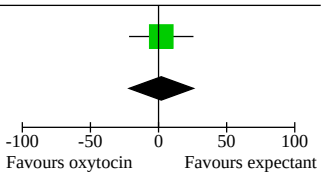
Heterogeneity: Tau² = 18725.97; Chi² = 4.89, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Oxytocin solution versus expectant management, Outcome 12: Time from injection to placental delivery (minutes)

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Expectant Mean	Expectant SD	Expectant Total	Weight	Mean Difference IV, Fixed, 95% CI
Chauhan 2004	49	43	18	47	32	24	100.0%	2.00 [-21.63 , 25.63]
Total (95% CI)			**18**			**24**	**100.0%**	**2.00 [-21.63 , 25.63]**

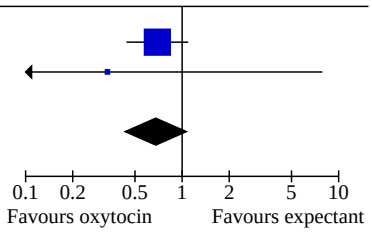
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Oxytocin solution versus expectant management, Outcome 13: Surgical evacuation of retained products of conception

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	23	94	31	88	95.5%	0.69 [0.44 , 1.09]
Lim 2011	0	30	1	30	4.5%	0.33 [0.01 , 7.87]
Total (95% CI)		**124**		**118**	**100.0%**	**0.68 [0.43 , 1.06]**
Total events:	23		32			

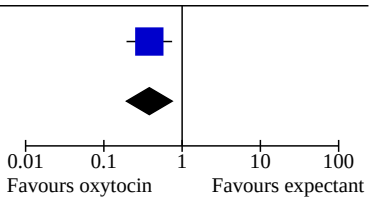
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 2.14. Comparison 2: Oxytocin solution versus expectant management, Outcome 14: Maternal dissatisfaction with third-stage management

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chauhan 2004	6	18	21	24	100.0%	0.38 [0.19 , 0.74]
Total (95% CI)		**18**		**24**	**100.0%**	**0.38 [0.19 , 0.74]**
Total events:	6		21			

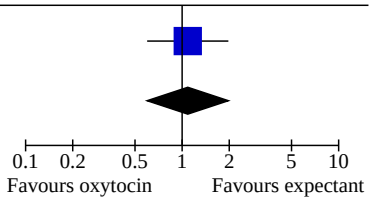
Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.15. Comparison 2: Oxytocin solution versus expectant management, Outcome 15: Stay at hospital > 2 days

Study or Subgroup	Oxytocin Events	Oxytocin Total	Expectant Events	Expectant Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	19	94	16	86	100.0%	1.09 [0.60 , 1.97]
Total (95% CI)		**94**		**86**	**100.0%**	**1.09 [0.60 , 1.97]**
Total events:	19		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



Comparison 3. Oxytocin solution versus saline solution

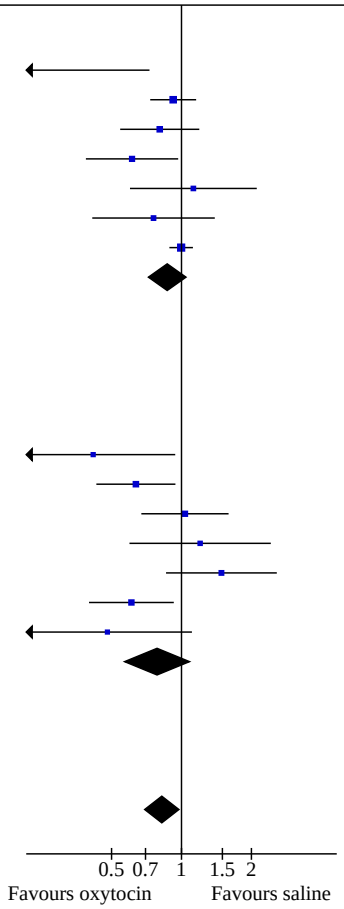
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Manual removal of the placenta – by overall risk of bias	14	1370	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.1 Low risk of bias studies	7	978	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
3.1.2 High risk of bias studies	7	392	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.08]
3.2 Manual removal of the placenta – by oxytocin dose	14	1370	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.97]
3.2.1 High dose (≥ 30 IU)	6	776	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.09]
3.2.2 Low dose (< 30 IU)	8	594	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.02]
3.3 Maternal mortality	5	782	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.59]
3.4 Severe postpartum haemorrhage (≥ 1000 mL after entry)	4	766	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.68]
3.5 Blood transfusion	7	974	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.49]
3.6 Additional therapeutic uterotonics	4	678	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.23]
3.7 Antibiotic use	2	635	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.81, 1.96]
3.8 Infection	3	820	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.87, 2.09]
3.9 Serious maternal morbidity	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.69]
3.10 Haemoglobin 24–48 hours postpartum	1	167	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.76, 0.56]
3.11 Haemoglobin 40–45 days postpartum	1	91	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.58, 0.78]
3.12 Postpartum haemorrhage (≥ 500 mL after entry)	6	887	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.20]
3.13 Mean blood loss (mL)	5	274	Mean Difference (IV, Random, 95% CI)	-13.56 [-118.83, 91.71]
3.14 Time from injection to placental delivery (minutes)	2	577	Mean Difference (IV, Fixed, 95% CI)	8.26 [-2.00, 18.53]
3.15 Haemoglobin levels fall	1	541	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.14]
3.16 Surgical evacuation of retained products of conception	4	826	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.56, 1.40]
3.17 Hypertension following injection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.18 Shivering following injection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.19 Nausea following injection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.20 Headache following injection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.21 Abdominal pain	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.09, 43.22]
3.22 Maternal dissatisfaction with third-stage management	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.33, 1.72]
3.23 Fever	4	707	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.76, 3.64]
3.24 Length of third stage of labour (minutes)	1	30	Mean Difference (IV, Fixed, 95% CI)	16.20 [-15.22, 47.62]
3.25 Stay at hospital > 2 days	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.59]

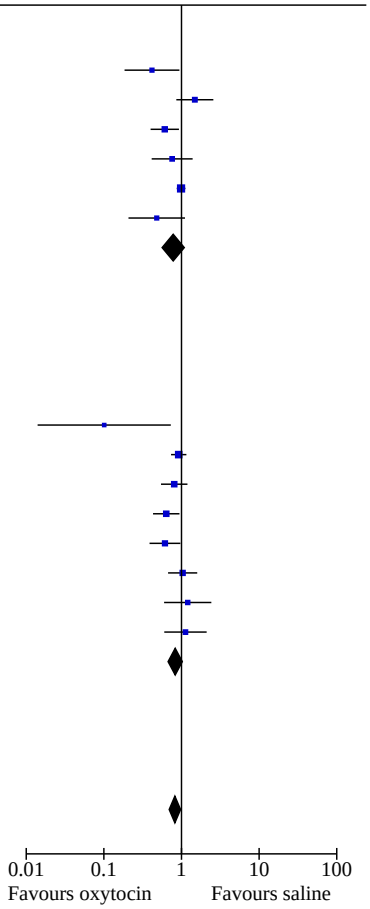
Analysis 3.1. Comparison 3: Oxytocin solution versus saline solution, Outcome 1: Manual removal of the placenta – by overall risk of bias

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Low risk of bias studies						
Calderale 1994	1	22	9	20	0.7%	0.10 [0.01 , 0.73]
Carroli 1998	57	98	60	95	13.2%	0.92 [0.73 , 1.16]
Frappell 1988	14	22	15	19	9.0%	0.81 [0.54 , 1.19]
Hansen 1987	14	32	20	28	7.7%	0.61 [0.39 , 0.97]
Selinger 1986	9	15	8	15	5.1%	1.13 [0.60 , 2.11]
Sivalingam 2001	9	19	10	16	5.4%	0.76 [0.41 , 1.39]
Weeks 2009	193	292	189	285	16.0%	1.00 [0.89 , 1.12]
Subtotal (95% CI)		**500**		**478**	**57.1%**	**0.87 [0.72 , 1.05]**
Total events:	297		311			
Heterogeneity: Tau² = 0.02; Chi² = 10.99, df = 6 (P = 0.09); I² = 45%						
Test for overall effect: Z = 1.49 (P = 0.14)						
3.1.2 High risk of bias studies						
Chauhan 2004	5	18	12	18	3.5%	0.42 [0.18 , 0.94]
Gazvani 1998	14	26	22	26	9.0%	0.64 [0.43 , 0.94]
Huber 1991	27	72	25	69	8.2%	1.03 [0.67 , 1.59]
Kristiansen 1987	10	19	7	16	4.4%	1.20 [0.60 , 2.42]
Rogers 2007	16	20	7	13	6.2%	1.49 [0.86 , 2.57]
Samanta 2013	14	29	23	29	8.4%	0.61 [0.40 , 0.93]
Wilken-Jensen 1989	5	18	11	19	3.3%	0.48 [0.21 , 1.11]
Subtotal (95% CI)		**202**		**190**	**42.9%**	**0.78 [0.57 , 1.08]**
Total events:	91		107			
Heterogeneity: Tau² = 0.10; Chi² = 14.36, df = 6 (P = 0.03); I² = 58%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**702**		**668**	**100.0%**	**0.82 [0.69 , 0.97]**
Total events:	388		418			
Heterogeneity: Tau² = 0.04; Chi² = 28.11, df = 13 (P = 0.009); I² = 54%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.59), I² = 0%						



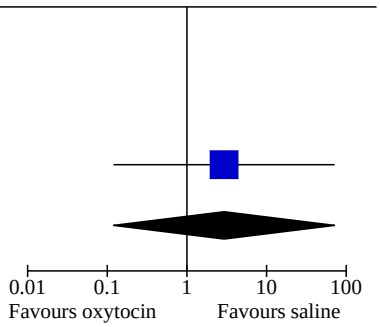
Analysis 3.2. Comparison 3: Oxytocin solution versus saline solution, Outcome 2: Manual removal of the placenta – by oxytocin dose

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 High dose (≥ 30 IU)						
Chauhan 2004	5	18	12	18	3.4%	0.42 [0.18 , 0.94]
Rogers 2007	16	20	7	13	6.1%	1.49 [0.86 , 2.57]
Samanta 2013	14	29	23	29	8.4%	0.61 [0.40 , 0.93]
Sivalingam 2001	9	19	10	16	5.3%	0.76 [0.41 , 1.39]
Weeks 2009	179	292	177	285	16.0%	0.99 [0.87 , 1.12]
Wilken-Jensen 1989	5	18	11	19	3.3%	0.48 [0.21 , 1.11]
Subtotal (95% CI)		**396**		**380**	**42.6%**	**0.78 [0.56 , 1.09]**
Total events:	228		240			
Heterogeneity: Tau² = 0.09; Chi² = 14.28, df = 5 (P = 0.01); I² = 65%						
Test for overall effect: Z = 1.47 (P = 0.14)						
3.2.2 Low dose (< 30 IU)						
Calderale 1994	1	22	9	20	0.7%	0.10 [0.01 , 0.73]
Carroli 1998	57	98	60	95	13.4%	0.92 [0.73 , 1.16]
Frappell 1988	14	22	15	19	9.0%	0.81 [0.54 , 1.19]
Gazvani 1998	14	26	22	26	9.0%	0.64 [0.43 , 0.94]
Hansen 1987	14	32	20	28	7.7%	0.61 [0.39 , 0.97]
Huber 1991	27	72	25	69	8.2%	1.03 [0.67 , 1.59]
Kristiansen 1987	10	19	7	16	4.3%	1.20 [0.60 , 2.42]
Selinger 1986	9	15	8	15	5.1%	1.13 [0.60 , 2.11]
Subtotal (95% CI)		**306**		**288**	**57.4%**	**0.83 [0.67 , 1.02]**
Total events:	146		166			
Heterogeneity: Tau² = 0.03; Chi² = 11.64, df = 7 (P = 0.11); I² = 40%						
Test for overall effect: Z = 1.74 (P = 0.08)						
Total (95% CI)		**702**		**668**	**100.0%**	**0.82 [0.69 , 0.97]**
Total events:	374		406			
Heterogeneity: Tau² = 0.04; Chi² = 27.00, df = 13 (P = 0.01); I² = 52%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



Analysis 3.3. Comparison 3: Oxytocin solution versus saline solution, Outcome 3: Maternal mortality

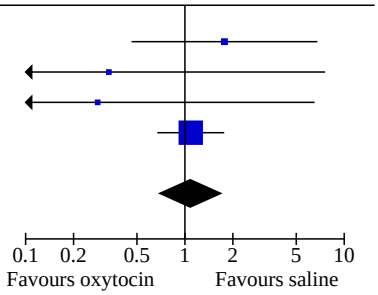
Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	26		Not estimable
Hansen 1987	0	32	0	28		Not estimable
Kristiansen 1987	0	19	0	16		Not estimable
Samanta 2013	0	29	0	29		Not estimable
Weeks 2009	1	292	0	285	100.0%	2.93 [0.12 , 71.59]
Total (95% CI)		**398**		**384**	**100.0%**	**2.93 [0.12 , 71.59]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Not applicable						



Analysis 3.4. Comparison 3: Oxytocin solution versus saline solution, Outcome 4: Severe postpartum haemorrhage (≥ 1000 mL after entry)

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	6	70	3	62	9.2%	1.77 [0.46 , 6.79]
Selinger 1986	0	15	1	15	4.3%	0.33 [0.01 , 7.58]
Sivalingam 2001	0	19	1	16	4.7%	0.28 [0.01 , 6.51]
Weeks 2009	31	287	28	282	81.8%	1.09 [0.67 , 1.76]
Total (95% CI)		**391**		**375**	**100.0%**	**1.08 [0.70 , 1.68]**
Total events:	37		33			

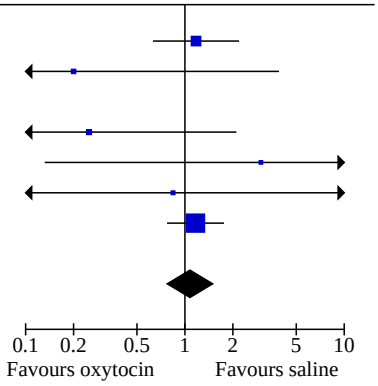
Heterogeneity: Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Oxytocin solution versus saline solution, Outcome 5: Blood transfusion

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	18	94	15	92	25.4%	1.17 [0.63 , 2.19]
Chauhan 2004	0	18	2	18	4.2%	0.20 [0.01 , 3.89]
Gazvani 1998	0	26	0	26		Not estimable
Samanta 2013	1	29	4	29	6.7%	0.25 [0.03 , 2.10]
Selinger 1986	1	15	0	15	0.8%	3.00 [0.13 , 68.26]
Sivalingam 2001	1	19	1	16	1.8%	0.84 [0.06 , 12.42]
Weeks 2009	43	292	36	285	61.0%	1.17 [0.77 , 1.76]
Total (95% CI)		**493**		**481**	**100.0%**	**1.08 [0.78 , 1.49]**
Total events:	64		58			

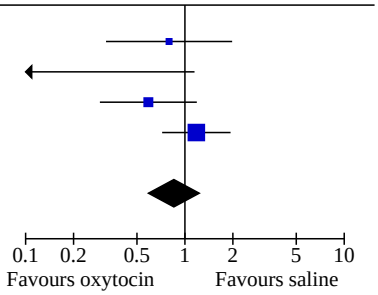
Heterogeneity: Chi² = 3.71, df = 5 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Oxytocin solution versus saline solution, Outcome 6: Additional therapeutic uterotonics

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	5	11	4	7	10.0%	0.80 [0.32 , 1.98]
Hansen 1987	0	32	6	28	14.2%	0.07 [0.00 , 1.15]
Sivalingam 2001	7	19	10	16	22.2%	0.59 [0.29 , 1.19]
Weeks 2009	31	284	26	281	53.6%	1.18 [0.72 , 1.93]
Total (95% CI)		**346**		**332**	**100.0%**	**0.85 [0.59 , 1.23]**
Total events:	43		46			

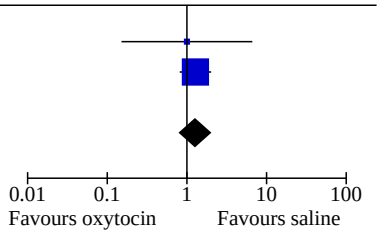
Heterogeneity: Chi² = 5.82, df = 3 (P = 0.12); I² = 48%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Oxytocin solution versus saline solution, Outcome 7: Antibiotic use

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Samanta 2013	2	29	2	29	6.4%	1.00 [0.15 , 6.63]
Weeks 2009	38	292	29	285	93.6%	1.28 [0.81 , 2.02]
Total (95% CI)		**321**		**314**	**100.0%**	**1.26 [0.81 , 1.96]**
Total events:	40		31			

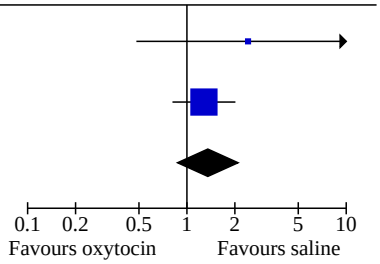
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Oxytocin solution versus saline solution, Outcome 8: Infection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	5	93	2	90	6.5%	2.42 [0.48 , 12.15]
Hansen 1987	0	32	0	28		Not estimable
Weeks 2009	38	292	29	285	93.5%	1.28 [0.81 , 2.02]
Total (95% CI)		**417**		**403**	**100.0%**	**1.35 [0.87 , 2.09]**
Total events:	43		31			

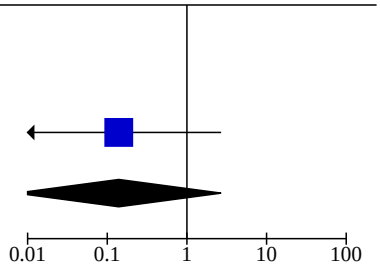
Heterogeneity: Chi² = 0.56, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Oxytocin solution versus saline solution, Outcome 9: Serious maternal morbidity

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gazvani 1998	0	26	0	26		Not estimable
Hansen 1987	0	32	0	28		Not estimable
Kristiansen 1987	0	19	0	16		Not estimable
Weeks 2009	0	292	3	285	100.0%	0.14 [0.01 , 2.69]
Total (95% CI)		**369**		**355**	**100.0%**	**0.14 [0.01 , 2.69]**
Total events:	0		3			

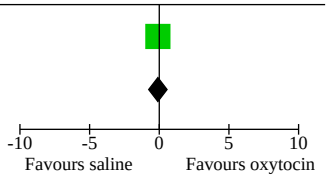
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Oxytocin solution versus saline solution, Outcome 10: Haemoglobin 24–48 hours postpartum

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	9.7	1.9	85	9.8	2.4	82	100.0%	-0.10 [-0.76 , 0.56]
Total (95% CI)			**85**			**82**	**100.0%**	**-0.10 [-0.76 , 0.56]**

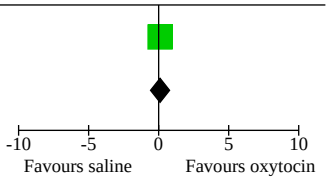
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Oxytocin solution versus saline solution, Outcome 11: Haemoglobin 40–45 days postpartum

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroli 1998	10.9	1.7	47	10.8	1.6	44	100.0%	0.10 [-0.58 , 0.78]
Total (95% CI)			**47**			**44**	**100.0%**	**0.10 [-0.58 , 0.78]**

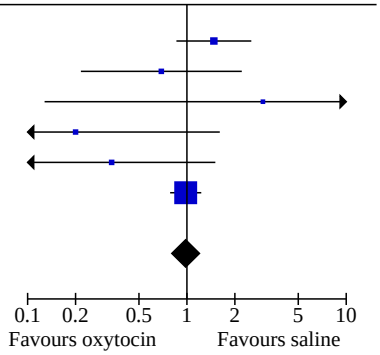
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Oxytocin solution versus saline solution, Outcome 12: Postpartum haemorrhage (≥ 500 mL after entry)

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	25	70	15	62	12.0%	1.48 [0.86 , 2.54]
Frappell 1988	4	22	5	19	4.1%	0.69 [0.22 , 2.21]
Gazvani 1998	1	26	0	26	0.4%	3.00 [0.13 , 70.42]
Samanta 2013	1	29	5	29	3.8%	0.20 [0.02 , 1.61]
Sivalingam 2001	2	19	5	16	4.1%	0.34 [0.08 , 1.51]
Weeks 2009	99	287	99	282	75.6%	0.98 [0.78 , 1.23]
Total (95% CI)		**453**		**434**	**100.0%**	**0.98 [0.80 , 1.20]**
Total events:	132		129			

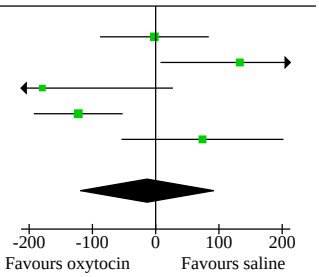
Heterogeneity: Chi² = 7.21, df = 5 (P = 0.21); I² = 31%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 3.13. Comparison 3: Oxytocin solution versus saline solution, Outcome 13: Mean blood loss (mL)

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Random, 95% CI
Bider 1996	229	102.8	11	231	82	7	23.1%	-2.00 [-87.91 , 83.91]
Carroli 1998	527	426	70	394	305	62	19.7%	133.00 [7.61 , 258.39]
Chauhan 2004	255	170	18	434	413	18	13.3%	-179.00 [-385.32 , 27.32]
Samanta 2013	210.34	110.5	29	332.76	158.27	29	24.4%	-122.42 [-192.67 , -52.17]
Selinger 1986	360	221	15	286	123	15	19.5%	74.00 [-53.99 , 201.99]
Total (95% CI)			**143**			**131**	**100.0%**	**-13.56 [-118.83 , 91.71]**

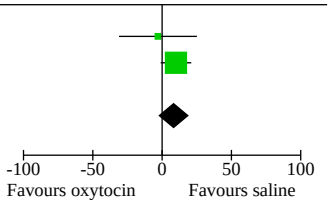
Heterogeneity: Tau² = 10552.54; Chi² = 18.06, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 3.14. Comparison 3: Oxytocin solution versus saline solution, Outcome 14: Time from injection to placental delivery (minutes)

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Chauhan 2004	49	43	18	52	43	18	13.3%	-3.00 [-31.09 , 25.09]
Weeks 2009	95	71.11	272	85	59.26	269	86.7%	10.00 [-1.03 , 21.03]
Total (95% CI)			**290**			**287**	**100.0%**	**8.26 [-2.00 , 18.53]**

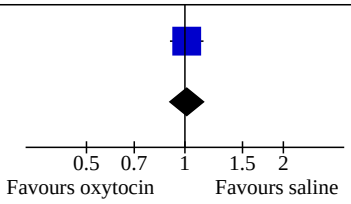
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 3.15. Comparison 3: Oxytocin solution versus saline solution, Outcome 15: Haemoglobin levels fall

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Weeks 2009	185	274	178	267	100.0%	1.01 [0.90 , 1.14]
Total (95% CI)		**274**		**267**	**100.0%**	**1.01 [0.90 , 1.14]**
Total events:	185		178			

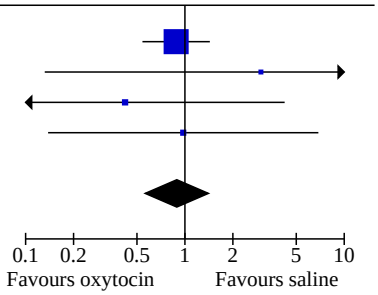
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 3.16. Comparison 3: Oxytocin solution versus saline solution, Outcome 16: Surgical evacuation of retained products of conception

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	23	94	25	90	84.5%	0.88 [0.54 , 1.43]
Selinger 1986	1	15	0	15	1.7%	3.00 [0.13 , 68.26]
Sivalingam 2001	1	19	2	16	7.2%	0.42 [0.04 , 4.23]
Weeks 2009	2	292	2	285	6.7%	0.98 [0.14 , 6.88]
Total (95% CI)		**420**		**406**	**100.0%**	**0.89 [0.56 , 1.40]**
Total events:	27		29			

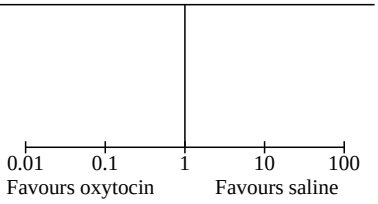
Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 3.17. Comparison 3: Oxytocin solution versus saline solution, Outcome 17: Hypertension following injection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hansen 1987	0	32	0	28		Not estimable
Total (95% CI)		**32**		**28**		**Not estimable**
Total events:	0		0			

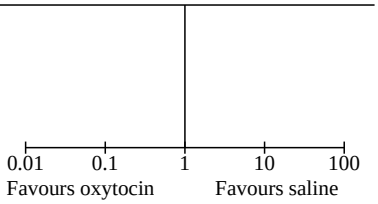
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.18. Comparison 3: Oxytocin solution versus saline solution, Outcome 18: Shivering following injection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hansen 1987	0	32	0	28		Not estimable
Total (95% CI)		**32**		**28**		**Not estimable**
Total events:	0		0			

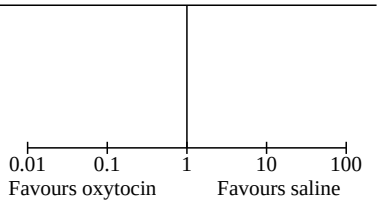
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.19. Comparison 3: Oxytocin solution versus saline solution, Outcome 19: Nausea following injection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hansen 1987	0	32	0	28		Not estimable
Total (95% CI)		**32**		**28**		**Not estimable**
Total events:	0		0			

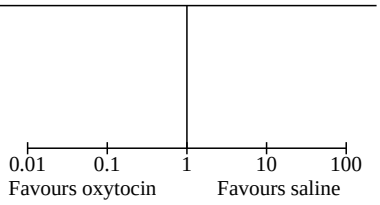
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.20. Comparison 3: Oxytocin solution versus saline solution, Outcome 20: Headache following injection

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hansen 1987	0	32	0	28		Not estimable
Total (95% CI)		**32**		**28**		**Not estimable**
Total events:	0		0			

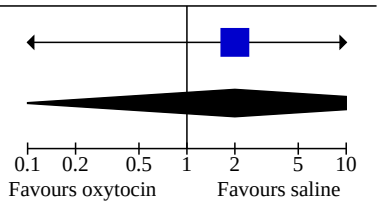
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.21. Comparison 3: Oxytocin solution versus saline solution, Outcome 21: Abdominal pain

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	1	11	0	7	100.0%	2.00 [0.09 , 43.22]
Total (95% CI)		**11**		**7**	**100.0%**	**2.00 [0.09 , 43.22]**
Total events:	1		0			

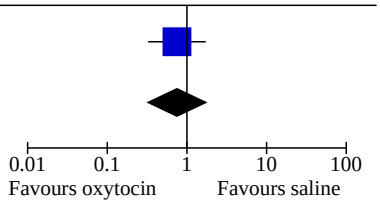
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 3.22. Comparison 3: Oxytocin solution versus saline solution, Outcome 22: Maternal dissatisfaction with third-stage management

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chauhan 2004	6	18	8	18	100.0%	0.75 [0.33 , 1.72]
Total (95% CI)		**18**		**18**	**100.0%**	**0.75 [0.33 , 1.72]**
Total events:	6		8			

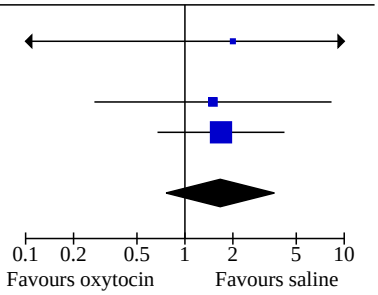
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 3.23. Comparison 3: Oxytocin solution versus saline solution, Outcome 23: Fever

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	1	11	0	7	6.2%	2.00 [0.09 , 43.22]
Hansen 1987	0	32	0	28		Not estimable
Samanta 2013	3	29	2	29	20.7%	1.50 [0.27 , 8.32]
Weeks 2009	12	288	7	283	73.1%	1.68 [0.67 , 4.22]
Total (95% CI)		**360**		**347**	**100.0%**	**1.67 [0.76 , 3.64]**
Total events:	16		9			

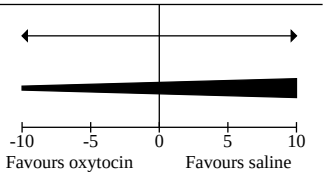
Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 3.24. Comparison 3: Oxytocin solution versus saline solution, Outcome 24: Length of third stage of labour (minutes)

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Fixed, 95% CI
Selinger 1986	111.4	43.2	15	95.2	44.6	15	100.0%	16.20 [-15.22 , 47.62]
Total (95% CI)			**15**			**15**	**100.0%**	**16.20 [-15.22 , 47.62]**

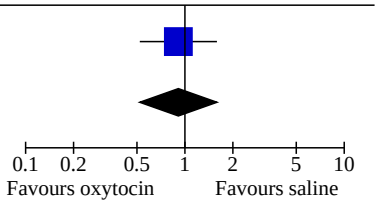
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 3.25. Comparison 3: Oxytocin solution versus saline solution, Outcome 25: Stay at hospital > 2 days

Study or Subgroup	Oxytocin Events	Oxytocin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carroli 1998	19	94	20	90	100.0%	0.91 [0.52 , 1.59]
Total (95% CI)		**94**		**90**	**100.0%**	**0.91 [0.52 , 1.59]**
Total events:	19		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



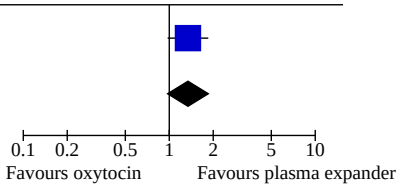
Comparison 4. Oxytocin solution versus plasma expander

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Manual removal of the placenta	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.97, 1.85]
4.2 Severe postpartum haemorrhage (> 1000 mL)	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.34, 2.75]

Analysis 4.1. Comparison 4: Oxytocin solution versus plasma expander, Outcome 1: Manual removal of the placenta

Study or Subgroup	Oxytocin Events	Oxytocin Total	Plasma expander Events	Plasma expander Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Makkonen 1995	49	68	22	41	100.0%	1.34 [0.97 , 1.85]
Total (95% CI)		**68**		**41**	**100.0%**	**1.34 [0.97 , 1.85]**
Total events:	49		22			

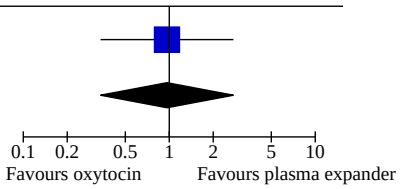
Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Oxytocin solution versus plasma expander, Outcome 2: Severe postpartum haemorrhage (> 1000 mL)

Study or Subgroup	Oxytocin Events	Oxytocin Total	Plasma expander Events	Plasma expander Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Makkonen 1995	8	68	5	41	100.0%	0.96 [0.34 , 2.75]
Total (95% CI)		**68**		**41**	**100.0%**	**0.96 [0.34 , 2.75]**
Total events:	8		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.95)
Test for subgroup differences: Not applicable



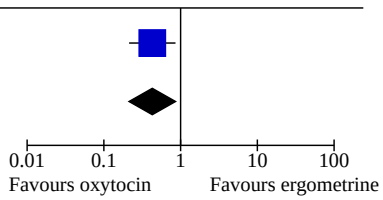
Comparison 5. Oxytocin solution versus ergometrine solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Manual removal of the placenta	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.21, 0.86]
5.2 Time from injection to placental delivery (minutes)	1	53	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.59, 2.79]

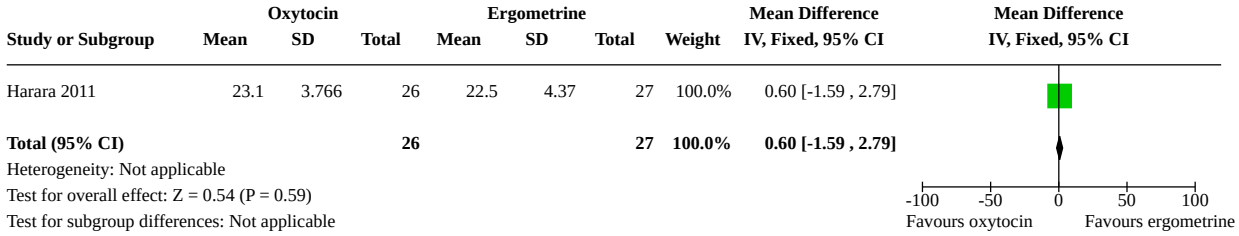
Analysis 5.1. Comparison 5: Oxytocin solution versus ergometrine solution, Outcome 1: Manual removal of the placenta

Study or Subgroup	Oxytocin Events	Oxytocin Total	Ergometrine Events	Ergometrine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harara 2011	7	26	17	27	100.0%	0.43 [0.21 , 0.86]
Total (95% CI)		**26**		**27**	**100.0%**	**0.43 [0.21 , 0.86]**
Total events:	7		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Oxytocin solution versus ergometrine solution, Outcome 2: Time from injection to placental delivery (minutes)



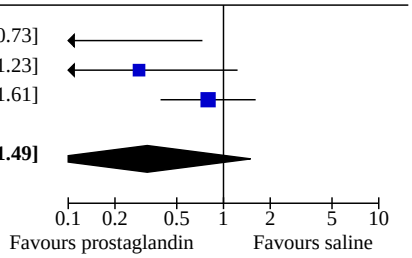
Comparison 6. Prostaglandin solution versus saline solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Manual removal of the placenta	3	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.07, 1.49]
6.2 Additional therapeutic uterotonics	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.46, 2.38]
6.3 Mean blood loss (mL)	2	63	Mean Difference (IV, Random, 95% CI)	-78.56 [-161.94, 4.82]
6.4 Vomiting following injection	1	46	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.5 Shivering following injection	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.02]
6.6 Nausea following injection	1	46	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.7 Headache following injection	1	46	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.8 Maternal pain following injection	1	46	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.9 Abdominal pain	1	17	Risk Ratio (M-H, Fixed, 95% CI)	5.09 [0.30, 85.39]
6.10 Fever	2	63	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.10, 46.92]

Analysis 6.1. Comparison 6: Prostaglandin solution versus saline solution, Outcome 1: Manual removal of the placenta

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Random, 95% CI
Bider 1996	0	10	7	7	19.6%	0.05 [0.00 , 0.73]
Rajab 2014	2	23	7	23	34.7%	0.29 [0.07 , 1.23]
Rogers 2007	9	21	7	13	45.8%	0.80 [0.39 , 1.61]
Total (95% CI)		**54**		**43**	**100.0%**	**0.32 [0.07 , 1.49]**
Total events:	11		21			

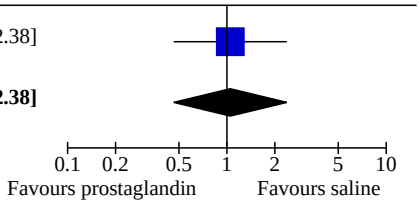
Heterogeneity: Tau² = 1.21; Chi² = 6.53, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Prostaglandin solution versus saline solution, Outcome 2: Additional therapeutic uterotonics

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	6	10	4	7	100.0%	1.05 [0.46 , 2.38]
Total (95% CI)		**10**		**7**	**100.0%**	**1.05 [0.46 , 2.38]**
Total events:	6		4			

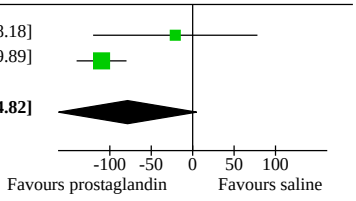
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Prostaglandin solution versus saline solution, Outcome 3: Mean blood loss (mL)

Study or Subgroup	Prostaglandin Mean	Prostaglandin SD	Prostaglandin Total	Saline Mean	Saline SD	Saline Total	Weight	Mean Difference IV, Random, 95% CI
Bider 1996	210	126.5	10	231	82	7	35.3%	-21.00 [-120.18 , 78.18]
Rajab 2014	100	7.5	23	210	73.3	23	64.7%	-110.00 [-140.11 , -79.89]
Total (95% CI)			**33**			**30**	**100.0%**	**-78.56 [-161.94 , 4.82]**

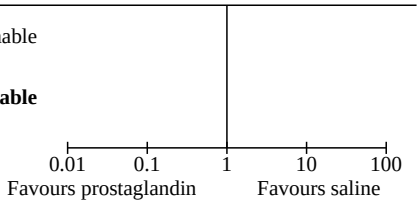
Heterogeneity: Tau² = 2562.08; Chi² = 2.83, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Prostaglandin solution versus saline solution, Outcome 4: Vomiting following injection

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajab 2014	0	23	0	23		Not estimable
Total (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			

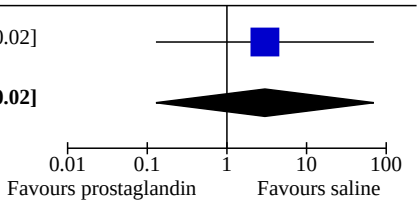
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Prostaglandin solution versus saline solution, Outcome 5: Shivering following injection

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajab 2014	1	23	0	23	100.0%	3.00 [0.13 , 70.02]
Total (95% CI)		**23**		**23**	**100.0%**	**3.00 [0.13 , 70.02]**
Total events:	1		0			

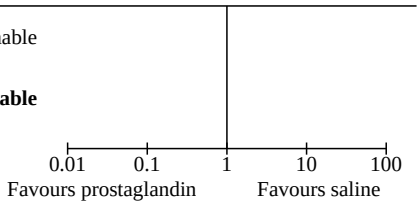
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Prostaglandin solution versus saline solution, Outcome 6: Nausea following injection

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajab 2014	0	23	0	23		Not estimable
Total (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			

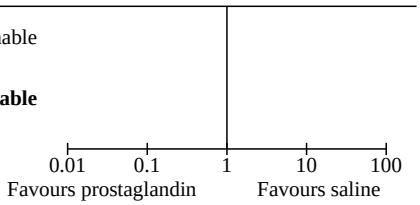
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.7. Comparison 6: Prostaglandin solution versus saline solution, Outcome 7: Headache following injection

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajab 2014	0	23	0	23		Not estimable
Total (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			

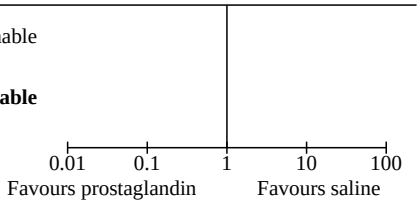
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6: Prostaglandin solution versus saline solution, Outcome 8: Maternal pain following injection

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajab 2014	0	23	0	23		Not estimable
Total (95% CI)		**23**		**23**		**Not estimable**
Total events:	0		0			

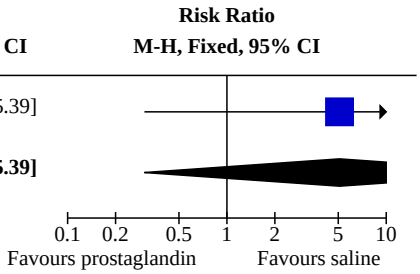
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.9. Comparison 6: Prostaglandin solution versus saline solution, Outcome 9: Abdominal pain

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	3	10	0	7	100.0%	5.09 [0.30 , 85.39]
Total (95% CI)		**10**		**7**	**100.0%**	**5.09 [0.30 , 85.39]**
Total events:	3		0			

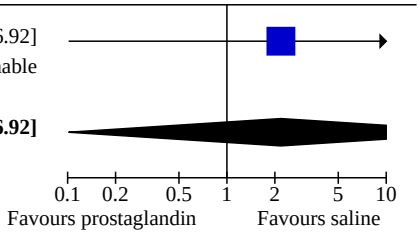
Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Prostaglandin solution versus saline solution, Outcome 10: Fever

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	1	10	0	7	100.0%	2.18 [0.10 , 46.92]
Rajab 2014	0	23	0	23		Not estimable
Total (95% CI)		**33**		**30**	**100.0%**	**2.18 [0.10 , 46.92]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Comparison 7. Prostaglandin solution versus oxytocin solution

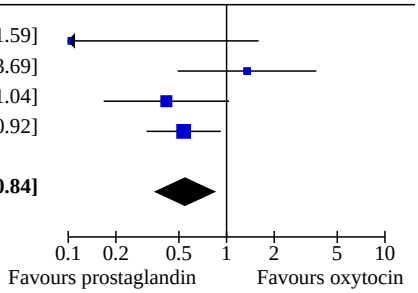
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Manual removal of the placenta	4	173	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.36, 0.84]
7.2 Additional therapeutic uterotonics	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.58, 3.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Mean blood loss (mL)	1	21	Mean Difference (IV, Fixed, 95% CI)	-19.00 [-118.19, 80.19]
7.4 Time from injection to placental delivery (minutes)	3	132	Mean Difference (IV, Random, 95% CI)	-6.70 [-7.58, -5.82]
7.5 Shivering following injection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.83]
7.6 Fever	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.08, 15.36]
7.7 Abdominal pain	1	21	Risk Ratio (M-H, Fixed, 95% CI)	3.30 [0.41, 26.81]

Analysis 7.1. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 1: Manual removal of the placenta

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	0	10	5	11	13.6%	0.10 [0.01 , 1.59]
Harara 2011	7	26	5	25	13.2%	1.35 [0.49 , 3.69]
Nazeer 2016	5	30	12	30	31.0%	0.42 [0.17 , 1.04]
Rogers 2007	9	21	16	20	42.3%	0.54 [0.31 , 0.92]
Total (95% CI)		**87**		**86**	**100.0%**	**0.55 [0.36 , 0.84]**
Total events:	21		38			

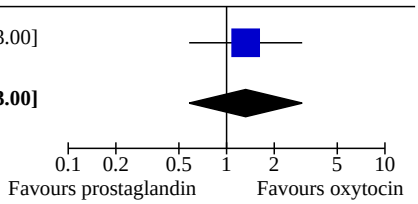
Heterogeneity: Chi² = 4.87, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 2: Additional therapeutic uterotonics

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	6	10	5	11	100.0%	1.32 [0.58 , 3.00]
Total (95% CI)		**10**		**11**	**100.0%**	**1.32 [0.58 , 3.00]**
Total events:	6		5			

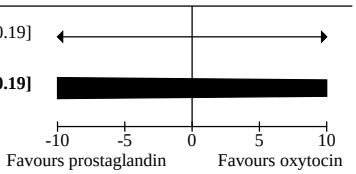
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 3: Mean blood loss (mL)

Study or Subgroup	Prostaglandin Mean	SD	Total	Oxytocin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bider 1996	210	126.5	10	229	102.8	11	100.0%	-19.00 [-118.19 , 80.19]
Total (95% CI)			**10**			**11**	**100.0%**	**-19.00 [-118.19 , 80.19]**

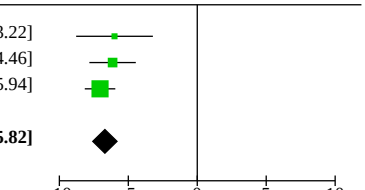
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 4: Time from injection to placental delivery (minutes)

Study or Subgroup	Prostaglandin Mean	SD	Total	Oxytocin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bider 1996	7	3.2	10	13	3.3	11	10.0%	-6.00 [-8.78 , -3.22]
Harara 2011	7	2.2	25	13.14	3.76	26	27.2%	-6.14 [-7.82 , -4.46]
Nazeer 2016	8.5	1.23	30	15.55	2.84	30	62.8%	-7.05 [-8.16 , -5.94]
Total (95% CI)			**65**			**67**	**100.0%**	**-6.70 [-7.58 , -5.82]**

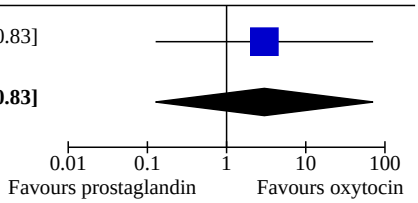
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 14.95 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 5: Shivering following injection

Study or Subgroup	Prostaglandin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nazeer 2016	1	30	0	30	100.0%	3.00 [0.13 , 70.83]
Total (95% CI)		**30**		**30**	**100.0%**	**3.00 [0.13 , 70.83]**
Total events:	1		0			

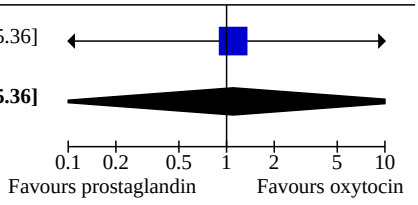
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 6: Fever

Study or Subgroup	Prostaglandin Events	Total	Oxytocin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	1	10	1	11	100.0%	1.10 [0.08 , 15.36]
Total (95% CI)		**10**		**11**	**100.0%**	**1.10 [0.08 , 15.36]**
Total events:	1		1			

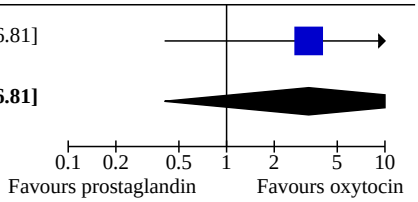
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 7.7. Comparison 7: Prostaglandin solution versus oxytocin solution, Outcome 7: Abdominal pain

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bider 1996	3	10	1	11	100.0%	3.30 [0.41 , 26.81]
Total (95% CI)		**10**		**11**	**100.0%**	**3.30 [0.41 , 26.81]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



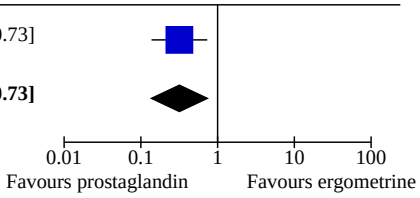
Comparison 8. Prostaglandin solution versus ergometrine solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Manual removal of the placenta	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.14, 0.73]
8.2 Time from injection to placental delivery (minutes)	1	52	Mean Difference (IV, Fixed, 95% CI)	-15.50 [-17.36, -13.64]

Analysis 8.1. Comparison 8: Prostaglandin solution versus ergometrine solution, Outcome 1: Manual removal of the placenta

Study or Subgroup	Prostaglandin Events	Prostaglandin Total	Ergometrine Events	Ergometrine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harara 2011	5	25	17	27	100.0%	0.32 [0.14 , 0.73]
Total (95% CI)		**25**		**27**	**100.0%**	**0.32 [0.14 , 0.73]**
Total events:	5		17			

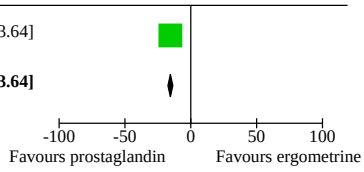
Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Prostaglandin solution versus ergometrine solution, Outcome 2: Time from injection to placental delivery (minutes)

Study or Subgroup	Prostaglandin Mean	Prostaglandin SD	Prostaglandin Total	Ergometrine Mean	Ergometrine SD	Ergometrine Total	Weight	Mean Difference IV, Fixed, 95% CI
Harara 2011	7	2.2	25	22.5	4.37	27	100.0%	-15.50 [-17.36 , -13.64]
Total (95% CI)			**25**			**27**	**100.0%**	**-15.50 [-17.36 , -13.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.33 (P < 0.00001)
Test for subgroup differences: Not applicable



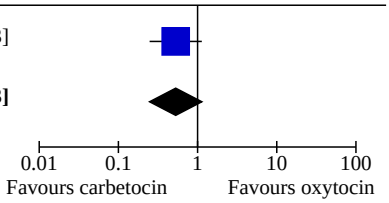
Comparison 9. Carbetocin solution versus oxytocin solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Manual removal of the placenta	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.25, 1.13]
9.2 Blood transfusion	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.14]
9.3 Additional uterotonics	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.17, 0.40]
9.4 Postpartum haemoglobin concentration (g/dL)	1	200	Mean Difference (IV, Fixed, 95% CI)	0.87 [0.08, 1.66]
9.5 Postpartum haemorrhage (> 500 mL)	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.09, 1.06]
9.6 Mean blood loss (mL)	1	200	Mean Difference (IV, Fixed, 95% CI)	-98.00 [-192.47, -3.53]
9.7 Change in haemoglobin concentration (g/dL)	1	200	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.59, -0.51]
9.8 Adherent placenta, piecemeal removal, and uterine curettage	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.01]

Analysis 9.1. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 1: Manual removal of the placenta

Study or Subgroup	Carbetocin Events	Carbetocin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salem 2019	9	100	17	100	100.0%	0.53 [0.25 , 1.13]
Total (95% CI)		**100**		**100**	**100.0%**	**0.53 [0.25 , 1.13]**
Total events:	9		17			

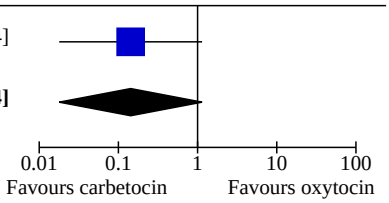
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 2: Blood transfusion

Study or Subgroup	Carbetocin Events	Carbetocin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salem 2019	1	100	7	100	100.0%	0.14 [0.02 , 1.14]
Total (95% CI)		**100**		**100**	**100.0%**	**0.14 [0.02 , 1.14]**
Total events:	1		7			

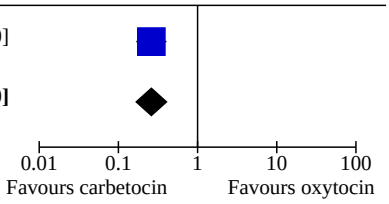
Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 3: Additional uterotonics

Study or Subgroup	Carbetocin Events	Carbetocin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salem 2019	18	100	69	100	100.0%	0.26 [0.17 , 0.40]
Total (95% CI)		**100**		**100**	**100.0%**	**0.26 [0.17 , 0.40]**
Total events:	18		69			

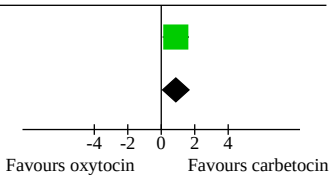
Heterogeneity: Not applicable
Test for overall effect: Z = 6.01 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 4: Postpartum haemoglobin concentration (g/dL)

Study or Subgroup	Carbetocin Mean	Carbetocin SD	Carbetocin Total	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Weight	Mean Difference IV, Fixed, 95% CI
Salem 2019 (1)	10.98	2.74	100	10.11	2.94	100	100.0%	0.87 [0.08 , 1.66]
Total (95% CI)			**100**			**100**	**100.0%**	**0.87 [0.08 , 1.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Not applicable

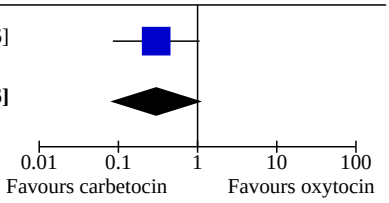


Footnotes
(1) Hb measured 6 hours post delivery

Analysis 9.5. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 5: Postpartum haemorrhage (> 500 mL)

Study or Subgroup	Carbetocin Events	Carbetocin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salem 2019	3	100	10	100	100.0%	0.30 [0.09 , 1.06]
Total (95% CI)		**100**		**100**	**100.0%**	**0.30 [0.09 , 1.06]**
Total events:	3		10			

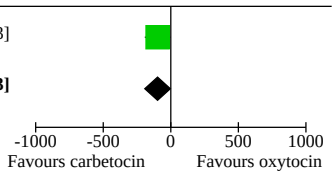
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 9.6. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 6: Mean blood loss (mL)

Study or Subgroup	Carbetocin Mean	Carbetocin SD	Carbetocin Total	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Weight	Mean Difference IV, Fixed, 95% CI
Salem 2019 (1)	435	290	100	533	385	100	100.0%	-98.00 [-192.47 , -3.53]
Total (95% CI)			**100**			**100**	**100.0%**	**-98.00 [-192.47 , -3.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable

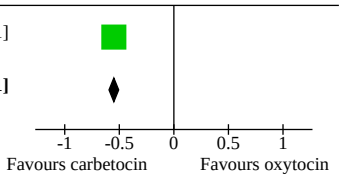


Footnotes
(1) Blood loss in 3rd and 4th stages of labour (until 2 hours post placental delivery)

Analysis 9.7. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 7: Change in haemoglobin concentration (g/dL)

Study or Subgroup	Carbetocin Mean	Carbetocin SD	Carbetocin Total	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Weight	Mean Difference IV, Fixed, 95% CI
Salem 2019 (1)	0.23	0.05	100	0.78	0.22	100	100.0%	-0.55 [-0.59 , -0.51]
Total (95% CI)			**100**			**100**	**100.0%**	**-0.55 [-0.59 , -0.51]**

Heterogeneity: Not applicable
Test for overall effect: Z = 24.38 (P < 0.00001)
Test for subgroup differences: Not applicable

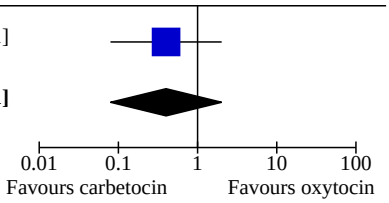


Footnotes
(1) Difference between Hb taken on admission and 6 hours post delivery

Analysis 9.8. Comparison 9: Carbetocin solution versus oxytocin solution, Outcome 8: Adherent placenta, piecemeal removal, and uterine curettage

Study or Subgroup	Carbetocin Events	Carbetocin Total	Oxytocin Events	Oxytocin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Salem 2019	2	100	5	100	100.0%	0.40 [0.08 , 2.01]
Total (95% CI)		**100**		**100**	**100.0%**	**0.40 [0.08 , 2.01]**
Total events:	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search methods for ICTRP and ClinicalTrials.gov

ICTRP

(each line was searched separately with synonyms)

umbilical AND retained AND placenta

intraumbilical AND retained AND placenta

intra-umbilical AND retained AND placenta

ClinicalTrials.gov

Advanced search

Interventional Studies | Retained Placenta | umbilical

Interventional Studies | Retained Placenta | intra-umbilical

umbilical | Interventional Studies | Retained Placenta

WHAT'S NEW

Date	Event	Description
14 June 2020	New citation required but conclusions have not changed	Three new authors joined the team for this update: Nimisha Kumar, Shayesteh Jahanfar, David M Haas. Four new comparisons added: prostaglandin solution versus oxytocin solution; prostaglandin solution versus ergometrine solution; oxytocin solution versus ergometrine solution; carbetocin solution versus oxytocin solution. Four 'Summary of findings' tables incorporated.
14 June 2020	New search has been performed	Search updated and nine new trials included.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 1, 1999

Date	Event	Description
9 March 2011	New citation required and conclusions have changed	The inclusion of high-quality randomised trials show that the use of oxytocin has little or no effect.
9 March 2011	New search has been performed	Search updated. Three new trials included (Rogers 2007; Sivalingam 2001; Weeks 2009).
30 August 2009	New search has been performed	Search updated.
6 November 2008	Amended	Converted to new review format.
6 July 2001	New search has been performed	Search updated.

CONTRIBUTIONS OF AUTHORS

Previous version of the review

GC was responsible for the idea, conception, and preparation of the review. He and E Bergel (an author on the previous version of this review) reviewed the quality of the trials, extracted the data, and wrote the first version of this review.

Updated review

NK and SJ assessed trials for inclusion and risk of bias, and extracted the data.

NK, SJ, and AW interpreted the findings and drafted the text of the review.

DECLARATIONS OF INTEREST

NK: my stipend as the Cochrane Fellow of the US Satellite of the Cochrane Pregnancy & Childbirth Group was funded by a grant from the Indiana Clinical and Translational Sciences Institute (CTSI), but is independent from my work on this review.

SJ: none.

DH: none.

AW: is an inventor of the PPH Butterfly, a device to allow minimally invasive uterine compression to treat postpartum haemorrhage, and one of the inventors of the LifeStart Trolley, a bedside neonatal resuscitation trolley. He is also Chief Investigator for the COPE study, funded by the National Institute for Health Research, that compares oxytocin and carboprost for the first line treatment of postpartum haemorrhage (including retained placenta). He was the Chief Investigator for the Release study, the largest of the studies in this review (Weeks 2009). NK and SJ assessed this trial for risk of bias and extracted data from it.

SOURCES OF SUPPORT

Internal sources

- Centro Rosarino de Estudios Perinatales, Argentina
- School of Reproductive and Developmental Medicine, Division of Perinatal and Reproductive Medicine, The University of Liverpool, UK

External sources

- World Health Organization (WHO) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Switzerland

  This review is supported by funding to Cochrane Pregnancy and Childbirth (University of Liverpool).
- Secretaria de Salud Publica, Municipalidad de Rosario, Argentina
- Grant # UL1TR002529 (A. Shekhar, PI); National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award, USA

  Cochrane Fellow (NK) stipend

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods have been updated to reflect the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The comparison of UVI of oxytocin solution versus saline solution was added to the final GRADE analyses as this was a key comparison to establish the efficacy of oxytocin in comparison to a placebo.

We have added 'fever' to the list of secondary outcomes, as raised temperature is a well-known side effect of misoprostol, and so it is necessary to ensure any data are captured.

INDEX TERMS

Medical Subject Headings (MeSH)

Injections, Intravenous; Oxytocics [*administration & dosage]; Oxytocin [*administration & dosage]; Placenta, Retained [*therapy]; Plasma Substitutes [administration & dosage]; Prostaglandins [administration & dosage]; Randomized Controlled Trials as Topic; Sodium Chloride [administration & dosage]; Umbilical Veins

MeSH check words

Female; Humans; Pregnancy