National Institute for Health and Care Excellence

Draft for consultation

Intrapartum care for healthy women and babies

[K] Active and physiological management of the third stage

NICE guideline CG190 (update)

Evidence review underpinning recommendations 1.10.6 and 1.10.7 in the NICE guideline

April 2023

Draft

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Active and physiological management of the third stage

Review question

What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Introduction

Active management of the third stage of labour involves the administration of a uterotonic, cord clamping (usually in the first 5 minutes after the birth) and delivery of the placenta by controlled cord traction. Physiological management of the third stage involves cord clamping when pulsation has stopped, and spontaneous delivery of the placenta with or without maternal effort.

Active management of the third stage may have benefits for the mother in terms of reduced risk of postpartum haemorrhage but woman may experience side effects of the uterotonics. There is also uncertainty over whether active management reduces the need for additional interventions. This review aims to compare the benefits and the risks associated with active management compared to physiological management.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk postpartum haemorrhage (as defined in recommendation 1.14.29 of CG190)
Intervention	Active management of third stage of labour. This usually involves: • Injection of uterotonic with the delivery of the anterior shoulder, or immediately after the birth of the baby • Clamping and cutting of the umbilical cord, immediately after the birth of the baby, up to 5 minutes after birth • Controlled cord traction
Comparison	Physiological management of third stage of labour (also known as expectant management or natural third stage). This usually involves: • No injection of uterotonic • Clamping of the cord after cord pulsation has ceased (including after the delivery of the placenta) • Placenta is delivered spontaneously or by maternal effort
Outcome	**Critical:** • Maternal death (within 42 days of end of pregnancy) or severe maternal morbidity (cardiac arrest, requirement for ICU admission) • PPH at time of birth and up to 24 hours (PPH ≥ 500 mL) • Maternal postpartum anaemia (requirement for blood transfusion; Hb concentration < 9 g/dL 24 to 48 hours postpartum, or as defined by study authors) **Important:** • Need for further uterotonics during the third stage of labour or within the first 24 hours after birth • Retained placenta beyond 1 hour of birth or need for manual removal of placenta • Side effects (for example, change in blood pressure, headache, nausea/ vomiting, pain, readmission with bleeding) during the third stage or within the first 24 hours after birth • Secondary blood loss/ any vaginal bleeding needing treatment or readmission (after 24 hours and before six weeks) • Women's experience of labour and birth

CG: clinical guideline; Hb: haemoglobin; ICU: intensive care unit; PPH: postpartum haemorrhage

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplement 1).

The definition of active and physiological management in the literature did not always reflect the definitions outlined in the protocol, therefore, the committee were consulted to agree on a possible alternative approach. Following their suggestions we took the approach to only include studies that defined active management or physiological management as per the

protocol. Any studies that used a mixed management approach, or the components of active or physiological management were not entirely clear were excluded from the review.

Post-hoc analysis was performed for the outcome postpartum haemorrhage ≥1000 mL. See appendix L for more details.

During guideline development, the BNF notation for oxytocin dose changed to 'units', so this has been reflected in the evidence report. The evidence tables in appendix D reflect the dose notations as defined by the original study.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Five randomised controlled trials were included for this review (Kashanian 2010; Prendiville 1988; Rogers 1998; Thilaganathan 1993; Yildirim 2016). Studies were from Iran, Turkey and United Kingdom.

All studies compared active management of the third stage of labour to physiological management of the third stage of labour. Two studies (Kashanian 2010; Yildirim 2016) administered oxytocin to the physiological management group after the third stage of labour. Outcomes that may have been measured post placental delivery were analysed in a separate comparison as the oxytocin administered may have influenced the results.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Kashanian 2010 Randomised controlled trial Iran	N=386 women No PPH risk factors No information on oxytocin for augmentation/ induction	Active management • 10 units oxytocin given after birth of the anterior shoulder, before cord clamped • Controlled cord traction	Physiological management • Placenta delivered by maternal effort • 10 units oxytocin infusion was given after delivery of placenta	• Need for further uterotonics
Prendiville 1988	N=1695 women	Active management • 5 units oxytocin and 0.5mg	Physiological management	• Primary postpartum haemorrhage ≥500 mL

Study	Population	Intervention	Comparison	Outcomes
Randomised controlled trial United Kingdom	No PPH risk factors ~75% did not receive oxytocin for augmentation/ induction	ergometrine (or 10 units of synthetic oxytocin if mother has high blood pressure) given after birth of the anterior shoulder, before cord clamped • Controlled cord traction	• Placenta delivered by maternal effort	• Maternal postpartum anaemia: requirement for blood transfusion • Maternal postpartum anaemia: Hb concentration < 9 g/dL • Need for further uterotonics • Retained placenta or need for manual removal of placenta • Side effects
Rogers 1998 Randomised controlled trial United Kingdom	N=1512 women No PPH risk factors No oxytocin for augmentation or induction	<u>Active management</u> • Oxytocin plus ergometrine given after birth of the anterior shoulder, before cord clamped • Controlled cord traction	<u>Physiological management</u> • Placenta delivered by maternal effort	• Primary postpartum haemorrhage ≥500 mL • Maternal postpartum anaemia: requirement for blood transfusion • Need for further uterotonics • Retained placenta of need for manual removal of placenta • Side effects • Antibiotics for bleeding (discharge to 6 weeks) • Women's experience of labour and birth
Thilaganathan 1993 Randomised controlled trial United Kingdom	N=193 women No PPH risk factors No oxytocin for augmentation or induction	<u>Active management</u> • 1 ml syntometrine given as soon as the baby was born, before cord clamped • Controlled cord traction	<u>Physiological management</u> • Placenta delivered by maternal effort	• Maternal postpartum anaemia: requirement for blood transfusion • Maternal postpartum anaemia: Hb concentration < 9 g/dL • Need for further uterotonics • Retained placenta of need for manual

Study	Population	Intervention	Comparison	Outcomes
				removal of placenta
Yildirim 2016 Randomised controlled trial Turkey	N=669 women No PPH risk factors No oxytocin for augmentation or induction	Active management • 10 units of oxytocin given within the first minute after birth, before cord clamped • Controlled cord traction	Physiological management • Placenta delivered by maternal effort • 10 units oxytocin given after placental expulsion	• Maternal postpartum anaemia: requirement for blood transfusion • Need for further uterotonics • Retained placenta of need for manual removal of placenta

Hb: haemoglobin; PPH: postpartum haemorrhage

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Overall, active management had an important benefit over physiological management in terms of primary postpartum haemorrhage and maternal postpartum anaemia. There was an important benefit favouring active management for the need for additional uterotonics. There were no important differences between groups for retained placenta or manual removal of the placenta, antibiotics for bleeding up to 6 weeks post discharge, or women's experience of labour and birth. However, there was an important harm for active management over physiological management in terms of side effects. Post-hoc analysis for postpartum haemorrhage ≥1000 mL showed an important benefit favouring active management.

Active management was also compared to physiological management, where oxytocin was given to the physiological management group after the third stage of labour. Active management had a possible important harm over physiological management in terms of the need for further uterotonics. However, the studies did not describe whether the need for further uterotonics was measured before or after the delivery of the placenta.

The majority of the evidence was low to very low quality, with some evidence at moderate quality. Most outcomes were downgraded for risk of bias due to lack of blinding, and for imprecision.

There was no evidence for maternal death or severe maternal morbidity.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Maternal death or severe maternal morbidity, primary postpartum haemorrhage, and maternal postpartum anaemia were prioritised as critical outcomes by the committee. The committee agreed that one of the main aims of management of the third stage is to prevent postpartum haemorrhage, and this in turn would have an impact on maternal death or severe morbidity and postpartum anaemia.

The committee selected important outcomes for the review. They agreed on outcomes that would enable women to make the best choice, based on the benefits and harms, when deciding on what the best approach for management of the third stage would be. The committee chose the need for further uterotonics as one of the important outcomes of the review, as they agreed it would be necessary to know if a certain approach to management of the third stage increased the likelihood of requiring additional treatment that was associated with side effects. They also agreed that retained placenta or the need for manual removal of the placenta was an important outcome to consider, as it would be useful to consider whether further interventions can be avoided depending on the approach to management of the third stage. In addition, they chose secondary bleeding, or readmission after 24 hours and before 6 weeks as an important outcome and this would reflect the longer-term benefits of a particular approach to management. The committee recognised the great importance of side effects as an outcome for this review. They discussed that although a particular approach may show benefits in terms of postpartum haemorrhage, or the need for further intervention, the side effects associated with that approach would need to be carefully considered for each woman. In addition, the committee chose women's experience of labour and birth as this would also help guide women toward making the best decision for them regarding management of the third stage. The committee recognised the great importance of women's experience of labour and birth, but they were aware that data on this outcome was likely to be sparse and unlikely to inform decision-making in a meaningful way, so they prioritised other outcomes as critical.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as moderate to very low.

All of the evidence was downgraded for risk of bias. Most of the concerns were around unblinding of participants and personnel, leading to deviations from the intended interventions and therefore low adherence to the interventions in most of the studies. Many of the participants allocated to the physiological management arm received active management. There was also lack of clarity over whether the analysis used was intention to treat. There was also bias around the measurement of subjective outcomes due to not blinding. There were also some concerns around selective reporting due to pre-specified protocols not being available. Some of the evidence was also downgraded for imprecision around the effect estimate.

Benefits and harms

The committee discussed the evidence that showed active management of the third stage of labour had important benefits over physiological management in terms of postpartum haemorrhage assessed with blood loss of over 500 mL, need for blood transfusion, low haemoglobin concentration and the need for further uterotonics. The committee discussed that this evidence supported the current recommendations to advise women that they should have active management of the third stage of labour to reduce the risk of postpartum haemorrhage and blood transfusion. The committee noted that some of the evidence was old (dating from pre-2000) and that methods of collecting and measuring the volume of blood

lost during a postpartum haemorrhage have greatly improved since then. They also noted that for the outcome of blood transfusion, transfusion protocols have changed, and the indications for blood transfusion may have been less stringent than they are currently. This is partly supported by the evidence where there appears to be a greater number of blood transfusions in both arms in the pre-2000 evidence compared to the newer evidence. This may have led to the absolute risks of a women experiencing a haemorrhage of more than a 1000 mL which were included in the recommendations being under-estimated, and the absolute risk of a blood transfusion being over-estimated. However, the committee agreed that the absolute risks still showed a relative increase in both these outcomes with physiological management, so although the absolute numbers may not reflect current practice, it was likely that the difference between active management and physiological management still provided women with information on which to base their choice.

The committee discussed the post-hoc analysis of postpartum haemorrhage defined as blood loss over 1000 mL. The committee agreed to look at this post-hoc analysis to understand whether active management also reduced the risk of more severe blood loss. They discussed that the management of someone who had a postpartum haemorrhage of 500 mL would differ compared to someone who had a postpartum haemorrhage of over 1000 mL. They agreed that the evidence supported recommendations for active management to reduce the risk of postpartum haemorrhage over 1000 mL, but noted some heterogeneity in the evidence. The committee discussed that a possible reason for this heterogeneity could be that in one of the studies some of the population received oxytocin for induction of labour. However, as it was not possible to stratify any of the evidence by induction with oxytocin, they agreed that they could not make a recommendation specific to those who had their labour induced. Nonetheless, the committee agreed that the post-hoc analysis reinforced the recommendation to advise women of the benefits of active management on postpartum haemorrhage.

The committee discussed that the evidence also showed an important harm for active management of the third stage in terms of increased number of side effects. They discussed the importance of explaining the side effect profile of the drugs used in active management so that women could make an informed choice about the management of the third stage, taking into account the likely benefits of active management compared to the risk of side effects. The committee agreed that the drugs recommended for management the active management of the third stage of labour to prevent postpartum haemorrhage (oxytocin plus ergometrine, oxytocin alone or carbetocin) (see Evidence review M) had differing side-effect profiles but all were likely to lead to nausea and vomiting as this was reported as a very common or common side-effect for them all, and therefore women should be advised of this. If women wanted more detail on the side-effect profiles of individual uterotonics the committee agreed that staff would refer to the BNF or the summary of product characteristics, as they would when asked about the side-effects of any medication.

The committee discussed the evidence in the comparison where oxytocin had been administered to the physiological management group after the placenta had been delivered. The evidence showed a possible important harm in the active management group in terms of an increase in the need for additional uterotonics.The committee discussed that it was not current practice in the UK to administer oxytocin after delivery of the placenta, and appeared to lead to harms and so did not make any recommendations based on this evidence.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee reasoned that active management was a relatively low-cost intervention with some offsetting savings from a reduction in postpartum haemorrhage and blood transfusions. Given the expected benefits to women's health from a reduction in these outcomes the committee concluded that active management was likely to be cost-effective.

The committee discussed that their recommendations reinforced current practice and so there would not be any significant resource implications. Women choosing active management would receive a uterotonic but the drugs offered had been shown to be cost-effective (see Evidence review M), and the health economic model used to demonstrate this had taken into account factors such as the resources used to administer them and the reduction in postpartum haemorrhage and blood transfusions.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.6 and 1.10.7. Other evidence supporting these recommendations can be found in evidence review M on Uterotonics for the prevention of postpartum haemorrhage.

References – included studies

Effectiveness

Kashanian 2010

Kashanian, Maryam, Fekrat, Mohsen, Masoomi, Zahra et al. (2010) Comparison of active and expectant management on the duration of the third stage of labour and the amount of blood loss during the third and fourth stages of labour: a randomised controlled trial. Midwifery 26(2): 241-5

Prendiville 1988

Prendiville, W. J., Harding, J. E., Elbourne, D. R. et al. (1988) The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ (Clinical research ed.) 297(6659): 1295-300

Rogers 1998

Rogers, J., Wood, J., McCandlish, R. et al. (1998) Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet (London, England) 351(9104): 693-9

Thilaganathan 1993

Thilaganathan, B., Cutner, A., Latimer, J. et al. (1993) Management of the third stage of labour in women at low risk of postpartum haemorrhage. European journal of obstetrics, gynecology, and reproductive biology 48(1): 19-22

Yildirim 2016

Yildirim, Dogukan, Ozyurek, Sefik E., Ekiz, Ali et al. (2016) Comparison of active vs. expectant management of the third stage of labor in women with low risk of postpartum hemorrhage: a randomized controlled trial. Ginekologia polska 87(5): 399-404

Appendices

Appendix A Review protocols

Review protocol for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42022307378
Review title	Active compared with physiological management of the third stage of labour
Review question	What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?
Objective	To update the recommendations in CG190 (2014) for the effectiveness of active management compared with physiological management in the third stage of labour. Surveillance has identified that active management may be associated with additional side effects, such as increased diastolic blood pressure, pain analgesia and readmission with bleeding.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database Searches will be restricted by: • No date limits • English language only • Human studies only

Field	Content
	Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Labour and birth
Population	Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk postpartum haemorrhage (as defined in recommendation 1.14.29 – CG190)
Intervention	Active management of third stage of labour. This usually involves: • Injection of uterotonic with the delivery of the anterior shoulder, or immediately after the birth of the baby • Clamping and cutting of the umbilical cord, immediately after the birth of the baby, up to 5 minutes after birth • Controlled cord traction
Comparator	Physiological management of third stage of labour (also known as expectant management or natural third stage). This usually involves: • No injection of uterotonic • Clamping of the cord after cord pulsation has ceased (including after the delivery of the placenta) • Placenta is delivered spontaneously or by maternal effort
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (cluster, individual) Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.

Field	Content
Other exclusion criteria	None
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Maternal death (within 42 days of end of pregnancy) or severe maternal morbidity (cardiac arrest, requirement for intensive care unit [ICU] admission) • Primary postpartum haemorrhage (PPH) at time of birth and up to 24 hours (PPH ≥ 500 mL) • Maternal postpartum anaemia (requirement for blood transfusion; Hb concentration < 9 g/dL 24 to 48 hours postpartum, or as defined by study authors)
Secondary outcomes (important outcomes)	• Need for further uterotonics during the third stage of labour or within the first 24 hours after birth • Retained placenta beyond 1 hour of birth or need for manual removal of placenta • Side effects (for example, change in blood pressure, headache, nausea/ vomiting, pain, readmission with bleeding) during the third stage or within the first 24 hours after birth • Secondary blood loss/ any vaginal bleeding needing treatment or readmission (after 24 hours and before six weeks) • Women's experience of labour and birth
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the

Field	Content
	interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster randomized trials The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Maternal death or severe morbidity: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes

Field	Content
Analysis of subgroups	Evidence will be stratified by: Timing of injection of uterotonics: • before cord clamping • at, or after, cord clamping • not specified Use of oxytocin to induce or augment labour Women with no intrapartum risk factors for PPH vs women with intrapartum risk factors (as defined in recommendation 1.14.29 – CG190) BMI thresholds on booking: • underweight range: <18.5 kg/m2 • healthy weight range: 18.5 to 24.9 kg/m2 • overweight range: 25 to 29.99 kg/m2 • obesity 1 range: 30 to 34.99 kg/m2 • obesity 2 range: 35 to 39.99 kg/m2 Stratifications will be dealt with in a hierarchy (this is, where possible, stratify first by timing of injection of uterotonics, then by use of oxytocin to induce or augment labour, then by intrapartum risk factors for PPH and then by BMI thresholds on booking) Evidence will be sub grouped by the following only in the event that there is significant heterogeneity in outcomes: Age of woman (<35 vs >/= 35) Ethnicity: • White • Asian/Asian British • Black/African/Caribbean/Black British

Field	Content	
	• Mixed/Multiple ethnic groups • Other ethnic group Women with disability vs not Deprived socioeconomic group vs not Country where the study was conducted: high income countries versus low and middle income countries (as defined by the OECD) Where evidence is stratified or sub grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	28/01/2022	
Anticipated completion date	22/03/2023	

Field	Content
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
Review team members	From the Guideline Development Team NGA: Senior Systematic Reviewer Systematic Reviewer
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE).
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=307378
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication

Field	Content
	publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Active management of labour
Details of existing review of same topic by same authors	Not applicable
Additional information	None
Details of final publication	www.nice.org.uk

BMI: body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; ICU: intensive care unit; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PPH: postpartum haemorrhage; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	LABOR STAGE, THIRD/
2	(third adj3 stage?).ti,ab.
3	or/1-2
4	(active* adj5 manag*).ti,ab.
5	uterotonic?.mp.
6	exp OXYTOCICS/
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp PROSTAGLANDINS/
9	(prostaglandin? or carboprost or sulprostone).mp.
10	UMBILICAL CORD/
11	(cord? adj5 (clamp* or cut* or traction*)).ti,ab.
12	or/4-11
13	3 and 12
14	limit 13 to english language
15	LETTER/
16	EDITORIAL/
17	NEWS/
18	exp HISTORICAL ARTICLE/
19	ANECDOTES AS TOPIC/
20	COMMENT/
21	CASE REPORT/
22	(letter or comment*).ti.
23	or/15-22
24	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
25	23 not 24
26	ANIMALS/ not HUMANS/
27	exp ANIMALS, LABORATORY/
28	exp ANIMAL EXPERIMENTATION/
29	exp MODELS, ANIMAL/
30	exp RODENTIA/
31	(rat or rats or mouse or mice).ti.
32	or/25-31
33	14 not 32
34	META-ANALYSIS/
35	META-ANALYSIS AS TOPIC/
36	(meta analy* or metanaly* or metaanaly*).ti,ab.
37	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
38	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
39	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
40	(search* adj4 literature).ab.
41	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
42	cochrane.jw.
43	or/34-42
44	randomized controlled trial.pt.
45	controlled clinical trial.pt.
46	pragmatic clinical trial.pt.
47	randomi#ed.ab.
48	placebo.ab.
49	randomly.ab.
50	CLINICAL TRIALS AS TOPIC/
51	trial.ti.
52	or/44-51
53	33 and 43

#	Searches
54	33 and 52
55	53 or 54

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	LABOR STAGE 3/
2	(third adj3 stage?).ti,ab.
3	or/1-2
4	(active* adj5 manag*).ti,ab.
5	exp UTEROTONIC AGENT/
6	uterotonic?.mp.
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp *PROSTAGLANDIN/
9	(prostaglandin? or carboprost or sulprostone).mp.
10	UMBILICAL CORD/
11	exp UMBILICAL CORD CLAMPING/
12	(cord? adj5 (clamp* or cut* or traction*)).ti,ab.
13	or/4-12
14	3 and 13
15	limit 14 to english language
16	letter.pt. or LETTER/
17	note.pt.
18	editorial.pt.
19	CASE REPORT/ or CASE STUDY/
20	(letter or comment*).ti.
21	or/16-20
22	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
23	21 not 22
24	ANIMAL/ not HUMAN/
25	NONHUMAN/
26	exp ANIMAL EXPERIMENT/
27	exp EXPERIMENTAL ANIMAL/
28	ANIMAL MODEL/
29	exp RODENT/
30	(rat or rats or mouse or mice).ti.
31	or/23-30
32	15 not 31
33	SYSTEMATIC REVIEW/
34	META-ANALYSIS/
35	(meta analy* or metanaly* or metaanaly*).ti,ab.
36	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41	((pool* or combined) adj2 (data or trials or studies or results)).ab.
42	cochrane.jw.
43	or/33-42
44	random*.ti,ab.
45	factorial*.ti,ab.
46	(crossover* or cross over*).ti,ab.
47	((doubl* or singl*) adj blind*).ti,ab.
48	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49	CROSSOVER PROCEDURE/
50	SINGLE BLIND PROCEDURE/
51	RANDOMIZED CONTROLLED TRIAL/
52	DOUBLE BLIND PROCEDURE/
53	or/44-52
54	32 and 43
55	32 and 53

#	Searches
56	54 or 55

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Labor Stage, Third] this term only
#2	(third near/3 stage*):ti,ab
#3	#1 or #2
#4	(active* near/5 manag*):ti,ab
#5	uterotonic*:ti,ab
#6	MeSH descriptor: [Oxytocics] explode all trees
#7	(oxytocic* or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#8	MeSH descriptor: [Prostaglandins] explode all trees
#9	(prostaglandin* or carboprost or sulprostone):ti,ab
#10	MeSH descriptor: [Umbilical Cord] this term only
#11	(cord* near/5 (clamp* or cut* or traction*)):ti,ab
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	#3 and #12

Database: International Health Technology Assessment

Date of last search: 07/12/2022

#	Searches
	All: (third or 3 or III)
	AND All: (stage or stages)
	AND All: (labor or labour)

Health Economics Search Strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	LABOR STAGE, THIRD/
2	(third adj3 stage?).ti,ab.
3	or/1-2
4	(active* adj5 manag*).ti,ab.
5	uterotonic?.mp.
6	exp OXYTOCICS/
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp PROSTAGLANDINS/
9	(prostaglandin? or carboprost or sulprostone).mp.
10	UMBILICAL CORD/
11	(cord? adj5 (clamp* or cut* or traction*)).ti,ab.
12	or/4-11
13	3 and 12
14	limit 13 to english language
15	LETTER/
16	EDITORIAL/
17	NEWS/
18	exp HISTORICAL ARTICLE/
19	ANECDOTES AS TOPIC/

#	Searches
20	COMMENT/
21	CASE REPORT/
22	(letter or comment*).ti.
23	or/15-22
24	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
25	23 not 24
26	ANIMALS/ not HUMANS/
27	exp ANIMALS, LABORATORY/
28	exp ANIMAL EXPERIMENTATION/
29	exp MODELS, ANIMAL/
30	exp RODENTIA/
31	(rat or rats or mouse or mice).ti.
32	or/25-31
33	14 not 32
34	ECONOMICS/
35	VALUE OF LIFE/
36	exp "COSTS AND COST ANALYSIS"/
37	exp ECONOMICS, HOSPITAL/
38	exp ECONOMICS, MEDICAL/
39	exp RESOURCE ALLOCATION/
40	ECONOMICS, NURSING/
41	ECONOMICS, PHARMACEUTICAL/
42	exp "FEES AND CHARGES"/
43	exp BUDGETS/
44	budget*.ti,ab.
45	cost*.ti,ab.
46	(economic* or pharmaco?economic*).ti,ab.
47	(price* or pricing*).ti,ab.
48	(financ* or fee or fees or expenditure* or saving*).ti,ab.
49	(value adj2 (money or monetary)).ti,ab.
50	resourc* allocat*.ti,ab.
51	(fund or funds or funding* or funded).ti,ab.
52	(ration or rations or rationing* or rationed).ti,ab.
53	ec.fs.
54	or/34-53
55	33 and 54

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	LABOR STAGE 3/
2	(third adj3 stage?).ti,ab.
3	or/1-2
4	(active* adj5 manag*).ti,ab.
5	exp UTEROTONIC AGENT/
6	uterotonic?.mp.
7	(oxytocic? or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
8	exp *PROSTAGLANDIN/
9	(prostaglandin? or carboprost or sulprostone).mp.
10	UMBILICAL CORD/
11	exp UMBILICAL CORD CLAMPING/
12	(cord? adj5 (clamp* or cut* or traction*)).ti,ab.
13	or/4-12
14	3 and 13
15	limit 14 to english language
16	letter.pt. or LETTER/
17	note.pt.
18	editorial.pt.
19	CASE REPORT/ or CASE STUDY/
20	(letter or comment*).ti.
21	or/16-20
22	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
23	21 not 22
24	ANIMAL/ not HUMAN/

#	Searches
25	NONHUMAN/
26	exp ANIMAL EXPERIMENT/
27	exp EXPERIMENTAL ANIMAL/
28	ANIMAL MODEL/
29	exp RODENT/
30	(rat or rats or mouse or mice).ti.
31	or/23-30
32	15 not 31
33	HEALTH ECONOMICS/
34	exp ECONOMIC EVALUATION/
35	exp HEALTH CARE COST/
36	exp FEE/
37	BUDGET/
38	FUNDING/
39	RESOURCE ALLOCATION/
40	budget*.ti,ab.
41	cost*.ti,ab.
42	(economic* or pharmaco?economic*).ti,ab.
43	(price* or pricing*).ti,ab.
44	(financ* or fee or fees or expenditure* or saving*).ti,ab.
45	(value adj2 (money or monetary)).ti,ab.
46	resourc* allocat*.ti,ab.
47	(fund or funds or funding* or funded).ti,ab.
48	(ration or rations or rationing* or rationed).ti,ab.
49	or/33-48
50	32 and 49

Database: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Labor Stage, Third] this term only
#2	(third near/3 stage*):ti,ab
#3	#1 or #2
#4	(active* near/5 manag*):ti,ab
#5	uterotonic*:ti,ab
#6	MeSH descriptor: [Oxytocics] explode all trees
#7	(oxytocic* or carbetocin or ergometrine or ergonovine or methylergonovine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#8	MeSH descriptor: [Prostaglandins] explode all trees
#9	(prostaglandin* or carboprost or sulprostone):ti,ab
#10	MeSH descriptor: [Umbilical Cord] this term only
#11	(cord* near/5 (clamp* or cut* or traction*)):ti,ab
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	#3 and #12
#14	MeSH descriptor: [Economics] this term only
#15	MeSH descriptor: [Value of Life] this term only
#16	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#17	MeSH descriptor: [Economics, Hospital] explode all trees
#18	MeSH descriptor: [Economics, Medical] explode all trees
#19	MeSH descriptor: [Resource Allocation] explode all trees
#20	MeSH descriptor: [Economics, Nursing] this term only
#21	MeSH descriptor: [Economics, Pharmaceutical] this term only
#22	MeSH descriptor: [Fees and Charges] explode all trees
#23	MeSH descriptor: [Budgets] explode all trees
#24	budget*:ti,ab
#25	cost*:ti,ab
#26	(economic* or pharmaco?economic*):ti,ab
#27	(price* or pricing*):ti,ab
#28	(financ* or fee or fees or expenditure* or saving*):ti,ab
#29	(value near/2 (money or monetary)):ti,ab
#30	resourc* allocat*:ti,ab
#31	(fund or funds or funding* or funded):ti,ab
#32	(ration or rations or rationing* or rationed):ti,ab
#33	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32

#	Searches
#34	#13 and #33

Database: International Health Technology Assessment

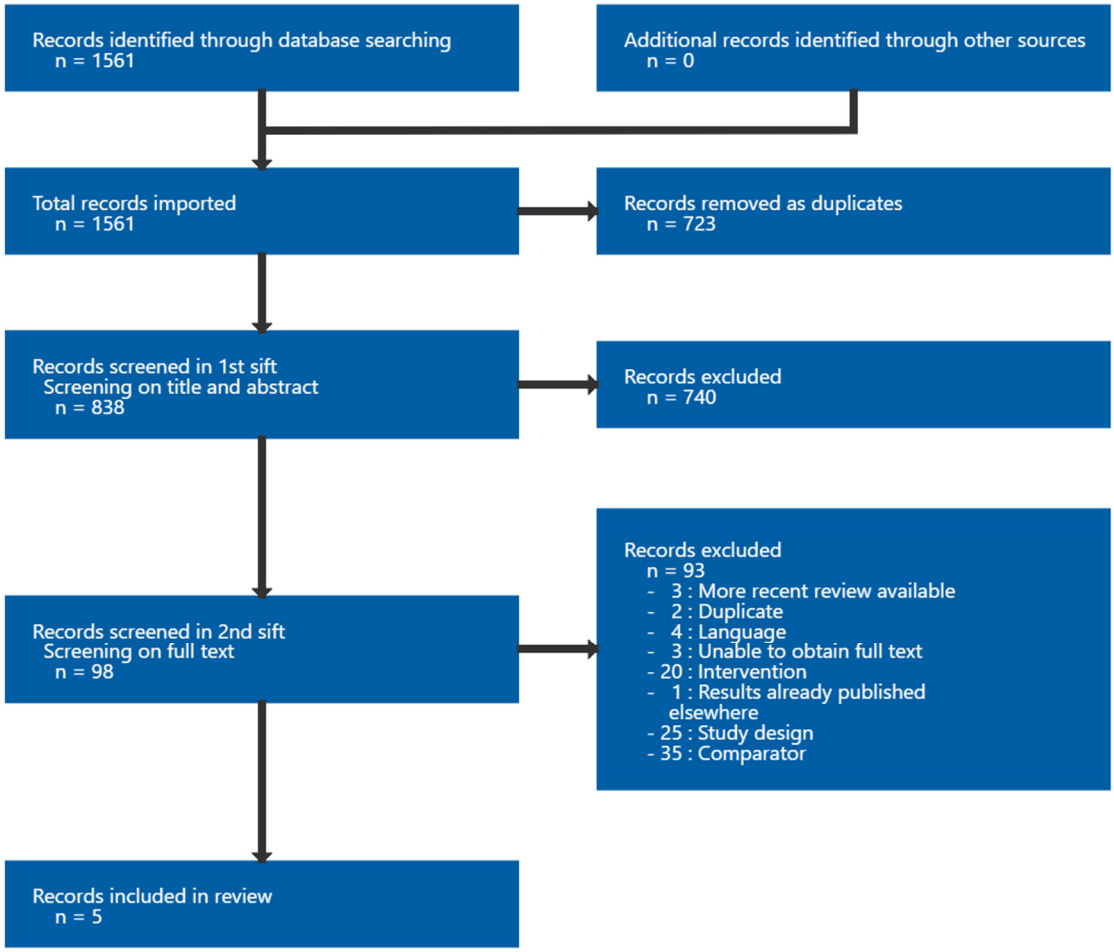
Date of last search: 07/12/2022

#	Searches
	All: (third or 3 or III)
	AND All: (stage or stages)
	AND All: (labor or labour)

Appendix C Effectiveness evidence study selection

Study selection for: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Kashanian, 2010

Bibliographic Reference	Kashanian, Maryam; Fekrat, Mohsen; Masoomi, Zahra; Sheikh Ansari, Narges; Comparison of active and expectant management on the duration of the third stage of labour and the amount of blood loss during the third and fourth stages of labour: a randomised controlled trial; Midwifery; 2010; vol. 26 (no. 2); 241-5

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	April to August 2004
Inclusion criteria	• Gestational age between 37 to 42 weeks • singleton pregnancy • live fetus • cephalic presentation • neonatal birth weight of 2500g to 4000g • parity of 1 to 5 • maternal age <35 • vaginal birth
Exclusion criteria	• blood pressure >=140/90 mmHg • placenta previa • placental abruption • history of bleeding during pregnancy • history of curettage • caesarean section or any uterine scar • history of postpartum haemorrhage • polyhydramnios

	• rhesus-negative blood group • maternal infection • prolonged rupture of membranes • known uterine anomalies; • history of any drug use during labour • abnormal placentation (accreta, inccreta or perccreta) • coagulation defects • instrumental deliveries • analgesia or anaesthesia for birth • haemoglobin concentration <11 g/dL • history of anticoagulant drugs • beta-mimetic medications during pregnancy • first stage of labour >15 hours
Patient characteristics	**Maternal age, years - mean (SD):** Intervention: 22.99 (6.23) Comparison: 23.27 (5.12) **Parity, mean (SD):** Intervention: 1.86 (1.16) Comparison: 2.09 (1.37) **Gestational age, weeks - mean (SD):** Intervention: 39.46 (2.24) Comparison: 39.56 (1.4)
Intervention(s)/control	Intervention - active management: • 10 IU of oxytocin was injected intramuscularly into the mother following birth or the anterior shoulder of the baby • the umbilical cord was clamped and cut • intermittent and controlled cord traction was exerted on the umbilical cord (when uterus is contracted) until placental separation and delivery

	• simultaneous pressure to the uterus applied • women observed for one hour after delivery of the placenta and blood loss measured. Control - expectant management: • After the birth of the baby the placenta was delivered spontaneously by gravity and maternal expulsive forces. • After delivery of the placenta, 10IU of oxytocin in 500 ml of normal saline was infused.
Sources of funding	Not reported
Sample size	N=386 randomised Intervention: n= 194 randomised (n = 100 analysed) Comparison: n= 192 randomised (n = 100 analysed) Intervention: 39 did not received allocated intervention 55 excluded following birth for: vaginal bleeding during labour; caesarean delivery; instrumental delivery; birthweight <2500g; analgesia. Comparison: 47 did not received allocated intervention 45 excluded following birth for: vaginal bleeding during labour; caesarean delivery; instrumental delivery; birthweight <2500g; regional analgesia.
Other information	Information for stratifications • Oxytocin given before cord clamped (immediately after birth of the anterior shoulder)

	• Whether oxytocin was used to induce or augment was not specified • Women with no intrapartum risk factors for PPH • BMI not specified

Outcomes

Outcome	Active management, , N = 100	Physiological management, , N = 100
Uterotonic drugs administered for excessive bleeding Time period not known No of events	n = 40	n = 27

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and concealed. No baseline imbalances.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Participants were likely not blinded and therefore there was potential for them to change group to which they were assigned. Over 40% of participants did not receive their allocated intervention. This could likely reflect what might be seen in practice due to the type of intervention, however there was no information on the analysis used and therefore likely to be bias.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(There were exclusions post-randomisation that were in line with the exclusion criteria set out. These were balanced between arms. No other data was missing therefore low risk of bias.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(High risk of bias for need for additional uterotonic. Measurement of blood loss is subjective, and as outcome assessors were probably not blinded, the need for additional uterotonics based on blood loss is at risk of bias.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(There is not protocol available to compare pre-specified criteria to actual data available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Prendiville, 1988

Bibliographic Reference	Prendiville, W. J.; Harding, J. E.; Elbourne, D. R.; Stirrat, G. M.; The Bristol third stage trial: active versus physiological management of third stage of labour; BMJ (Clinical research ed.); 1988; vol. 297 (no. 6659); 1295-300

Study details

Country/ies where study was carried out	United Kingdom
Study type	Randomised controlled trial (RCT)
Study dates	January 1986
Inclusion criteria	• expected to deliver vaginally
Exclusion criteria	• refusal to participate • cardiac disease • antepartum haemorrhage

	• breech presentation • multiple pregnancy • intrauterine death • if midwives of obstetricians thought there was good reason for exclusion (these were documented) After the first 5 months, exclusions included: • women with ritodrine given 2 h before birth • anticoagulant treatment • any condition needing a particular management of the third stage (for example meconium-stained liquor, dural tap)
Patient characteristics	**Maternal age, years - mean (SD)** Intervention: 27.2 (5.1) Comparison: 27.4 (5.1) **Multiparous - number:** Intervention: 409 Comparison: 372 **Gestational age, weeks - mean (SD):** Intervention: 40.0 (12.2) Comparison: 40.1 (11.5) **Gestational age <37 weeks - number:** Intervention: 21 Comparison: 17
Intervention(s)/control	Intervention - active management:

	• 1 ampoule (5 units oxytocin and 0.5mg ergometrine maleate) (or 10 units synthetic oxytocin if the mother has high blood pressure) - given immediately after delivery of the anterior shoulder • cord clamped 30 seconds after delivery of the baby • when the uterus has contracted, try to deliver the placenta by controlled cord traction, with a hand on the abdomen • no instruction regarding posture. Comparison - expectant management: • no oxytocin given • leave the cord attached to the baby until placenta is delivered • no controlled cord traction or manual interference with the uterus • encourage the mother to concentrate on the feeling of the urge to push • if there is an urge to push, or other signs of placental separation encourage maternal effort • if the placenta does not delivery spontaneously, put the bay on the breast and encourage maternal effort again. If the placenta is retained after one hour: • empty bladder • reattempt by active management • remove placenta manually under general anaesthetic or epidural block.
Sources of funding	Not industry funded
Sample size	N=1695 randomised Intervention: n=846 Comparison: n=849
Other information	Information for stratifications • Oxytocin given before cord clamped (immediately after birth of the anterior shoulder) • Oxytocin was used to induce or augment in <33% of participants • Women with no intrapartum risk factors for PPH

	• BMI not specified

PPH: postpartum haemorrhage; RCT: randomised controlled trial; SD: standard deviation

Outcomes

Outcome	Active management , , N = 846	Expectant management, , N = 849
Postpartum haemorrhage ≥500ml No of events	n = 57	n = 178
Haemoglobin ≤90 g/L (24-48 hours postpartum) No of events	n = 27	n = 51
Blood transfusion No of events	n = 18	n = 48
Need for further uterotonics time period not reported No of events	n = 54	n = 252
Manual removal of placenta No of events	n = 16	n = 22
Side effects vomiting, headache, diastolic blood pressure >100mm Hg in labour ward No of events	n = 132	n = 71

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation not described in detail but authors mention the allocation was random.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(There were deviations from the intended interventions. However there is no information on where analysis was by intention to treat, and other analysis would affect the outcome. Deviations occurred due to a change in protocol half way through the trial, with concerns over the increased risk of postpartum haemorrhage in the physiological arm. Therefore if a woman needed change to active management group during labour this was possible. 403/849 participants from the physiological management group received the allocated intervention. 840/846 of active management group received the allocated intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(There is missing outcome data for haemoglobin levels. Lower levels could indicate further management which meant follow up was not possible. Missing outcome data is similar between arms but there is not enough information to make a clear assessment.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Assessment of postpartum haemorrhage could have been influenced by the knowledge of the intervention, as well as need for additional uterotonics based on this assessment.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No protocol available, however many outcomes reported but not in the methods.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Rogers, 1998

Bibliographic Reference	Rogers, J.; Wood, J.; McCandlish, R.; Ayers, S.; Truesdale, A.; Elbourne, D.; Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial; Lancet (London, England); 1998; vol. 351 (no. 9104); 693-9

Study details

Country/ies where study was carried out	United Kingdom
Study type	Randomised controlled trial (RCT)
Study dates	June 1993 to December 1995
Inclusion criteria	• Low risk of postpartum haemorrhage • giving birth at the study hospital • including water births
Exclusion criteria	• placenta praevia • previous postpartum haemorrhage • antepartum haemorrhage after 20 weeks gestation • Haemoglobin <10 g/dL or mean corpuscular volume <75 fL • non-cephalic presentation • multiple pregnancy • intrauterine death • epidural anaesthesia • parity >5 • uterine fibroid • oxytocin augmentation infusion • anticoagulation therapy • intended instrumental or operative vaginal birth • gestation <32 weeks

	• any other contraindication in clinician's view
Patient characteristics	**Maternal age, years - mean (SD):** Intervention: 28.7 (4.9) Comparison: 28.5 (4.4) **Primiparous - number (%):** Intervention: 295 (39.4) Comparison: 280 (36.6) **Gestational age <37 weeks - number (%):** Intervention: 23 (3.1) Comparison: 15 (2)
Intervention(s)/control	Intervention - active management (2 arms, upright position and supine position): • administration of uterotonic (oxytocin plus ergometrine) as soon as possible after delivery of the anterior shoulder (within 2 minutes of birth) • immediate clamping and cutting of the cord • delivery of the placenta by controlled corn traction or maternal effort Comparison - expectant management (2 arms, upright position and supine position): • no uterotonic • no clamping of the cord until pulsation ceased • delivery of the placenta by maternal effort within 1 hour
Sources of funding	Not industry funded
Sample size	N=1512 randomised

	Intervention: n=748 Comparison: n=764
Other information	Information for stratifications • Oxytocin given before cord clamped (immediately after birth of the anterior shoulder) • Oxytocin infusion excluded: assume therefore oxytocin induce or augment was not included • Women with no intrapartum risk factors for PPH • BMI not specified

Outcomes

Outcome	**Active management, , N = 748**	**Expectant management, , N = 764**
Postpartum haemorrhage ≥500ml on labour ward No of events	n = 51	n = 126
Blood transfusion on labour or postnatal ward No of events	n = 4	n = 20
Need for further uterotonics ≥ 2mins after birth No of events	n = 24	n = 161
Manual removal of placenta No of events	n = 15	n = 13

Outcome	Active management, , N = 748	Expectant management, , N = 764
Side effects nausea, vomiting, headache, diastolic BP >100mmHg, systolic BP >160mmHg, readmitted for bleeding problems No of events	n = 164	n = 74
Antibiotics for bleeding (discharge to 6 weeks) No of events	n = 39	n = 36
Satisfied with third stage management No of events	n = 721	n = 718
Felt in control during third stage No of events	n = 621	n = 667

BP: blood pressure

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and concealed.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(There were deviations from the intended interventions, however the study describes that some happened due to clinical indication. However there were deviations without a reason given, these could have been due to experimental context and knowing the intervention, and not balanced between arms (physiological management received active management). However intention to treat assumed.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for most participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Knowledge of the intervention could have influenced postpartum haemorrhage recording. However, the study mentions that technicians who did antenatal and postnatal blood tests were unaware of allocation - but no particular mention that technicians recorded the blood loss.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No protocol available. Some outcomes reported that were not mentioned in the methods.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Thilaganathan, 1993

Bibliographic Reference	Thilaganathan, B.; Cutner, A.; Latimer, J.; Beard, R.; Management of the third stage of labour in women at low risk of postpartum haemorrhage; European journal of obstetrics, gynecology, and reproductive biology; 1993; vol. 48 (no. 1); 19-22

Study details

Country/ies where study was carried out	United Kingdom

Study type	Randomised controlled trial (RCT)
Study dates	January 1988 to February 1990
Inclusion criteria	• women at low risk of postpartum haemorrhage • term 37-42 weeks
Exclusion criteria	• grand multiparity • malpresentation • multiple pregnancy • previous caesarean section or post partum haemorrhage • antepartum haemorrhage • pregnancy induced hypertension • intrauterine fetal death • augmentation of labour • instrumental or operative delivery • third degree tears and cervical lacerations
Patient characteristics	Not reported in detail, however there were no significant differences in maternal age, birthweight or parity between groups.
Intervention(s)/control	Intervention - active management: • 1ml syntometrine (no information if intravenous or intramuscular) as soon as baby was born • cord clamped immediately • placenta delivered by controlled cord traction Comparison - expectant management: • no oxytocics or placebo • cord not cut or clamped until after pulsation ceased • when there were signs of placenta separation, mother encourage to adopt upright position and bear down • when the placenta was in the vagina, the midwife could then assist delivery Retained placenta - if placenta not delivered in 30 minutes:

	• empty bladder • medical assistance south • if delivery not imminent, manual removal performed.
Sources of funding	Not reported
Sample size	N=193 randomised Intervention: n=103 Comparison: n=90
Other information	Information for stratifications • Oxytocin given before cord clamped (immediately after birth) • Augmentation not included • Women with no intrapartum risk factors for PPH • BMI not specified

Outcomes

Outcome	**Active management, , N = 103**	**Expectant management, , N = 90**
Haemoglobin <9g/dl postpartum day postpartum not specified No of events	n = 1	n = 5
Blood transfusion No of events	n = 1	n = 0
Need for further oxytocics	n = 1	n = 7

Outcome	Active management, , N = 103	Expectant management, , N = 90
Time period not known No of events		
Retained placenta (30 minutes) No of events	n = 1	n = 0

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and concealed. Baseline characteristics not given in detail, but study states there were no significant differences between maternal age, birthweight or parity.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and study personnel were aware of assigned intervention. No information on analysis, or whether there were deviations. Study states number of participants that received their allocated intervention on entry, but no information on how many were randomised at the start.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Study states 193 women completed the study and all results available, however it is not clear if this was the same number randomised, although it is assumed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Outcome assessors were not blinded. This is low risk for non-subjective outcomes, however, need for additional uterotonics may be based on blood loss judgement which is subjective.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No pre-specified protocol available)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High risk of bias for need for further oxytocics. Some concerns for other outcomes.

Yildirim, 2016

Bibliographic Reference	Yildirim, Dogukan; Ozyurek, Sefik E.; Ekiz, Ali; Eren, Elif C.; Hendem, Derya Uyan; Bafali, Olgu; Seckin, Kerem D.; Comparison of active vs. expectant management of the third stage of labor in women with low risk of postpartum hemorrhage: a randomized controlled trial; Ginekologia polska; 2016; vol. 87 (no. 5); 399-404

Study details

Country/ies where study was carried out	Turkey
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• Absence of risk factors for postpartum haemorrhage • gestational age of 36-42 weeks • singleton pregnancy • live fetus • cephalic presentation

	• expected fetal birth weight of 2500-45000gm • maternal age <40 years • parity 0-3
Exclusion criteria	• acute fetal distress • conversion to abdominal delivery during labour • need for labour augmentation • persistent high blood pressure (>140/90 mmHg) • placenta previa • ablatio placenta or uterine bleeding of any other cause encountered during pregnancy or labour • previous caesarean • uterine scare • postpartum haemorrhage in previous pregnancy • hydramnios • symptoms of maternal infection • drug use in labour • abnormal placentation (accreta, increta or percreta) • coagulation defects • forceps or vacuum extraction • haemoglobin concentration of <8 g/dL • use of anticoagulants and tocolytics during pregnancy • multiple gestations • known uterine malformations • keep vaginal lacerations
Patient characteristics	**Maternal age, years - mean (SD):** Expectant: 25.92 (5.13) Active: 25.98 (5.25) **BMI, kg/m2 - mean (SD):** Expectant: 27.94 (3.8) Active: 27.55 (3.39)

	Gestational age, weeks - mean (SD): Expectant: 39.84 (1.81) Active: 38.74 (1.66) **Nulliparous, n (%):** Expectant: 131 (40.06) Active: 129 (39.45) **Multiparous, n (%):** Expectant: 196 (59.94) Active: 198 (60.55)
Intervention(s)/control	Active management: • 10 IU of oxytocin intramuscular injection given within the first minute after delivery • early umbilical cord clamping • application of controlled cord traction with uterine massage Expectant management: • umbilical cord clamping after cord pulsation had slowed down • placental separation signs were expected (gush of blood from vagina) • placenta was allowed to fall by maternal effort and gravity • a 10 IU oxytocin intramuscular injection administered after placental expulsion The placenta was removed manually if it did not fall after 30 minutes. In both groups uterine massage was performed every 15 minutes until leaving the delivery room.
Sources of funding	Not reported
Sample size	N= 669 randomised

	Active management: n=333 (327 analysed) Expectant management: n= 336 (327 analysed)
Other information	Information for stratifications • Oxytocin given before cord clamped (within a minute of birth) • Augmentation excluded • Women with no intrapartum risk factors for PPH • BMI overweight range, but not specified that this is BMI at booking

Outcomes

Outcome	**Active management, , N = 327**	**Expectant management, , N = 327**
Blood transfusion No of events	n = 3	n = 4
Additional Uterotonics Time period not known No of events	n = 27	n = 30
Manual removal of placenta 30 minutes No of events	n = 2	n = 3

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and concealed. No baseline differences to suggest imbalances.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and personnel were not blinded, however there were no deviations from the intended intervention and all received their allocation intervention. There was no information on analysis, but intention to treat was assumed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Personnel were not blinded. The study reports the outcome analyser being blinded, but it is not clear whether this was the outcome assessor. The need for additional uterotonics could be influences by the subjective measuring of blood loss, which is likely to have been assessed by the performer of the intervention who was not blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No protocol available)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Some concerns for need for additional uterotonics. Low risk for other non-subjective outcomes.

BMI: body mass index; PPH: postpartum haemorrhage; RCT: randomised controlled trial; SD: standard deviation

Appendix E Forest plots

Forest plots for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 1: Active versus physiological management

Figure 2: Primary postpartum haemorrhage ≥ 500 mL

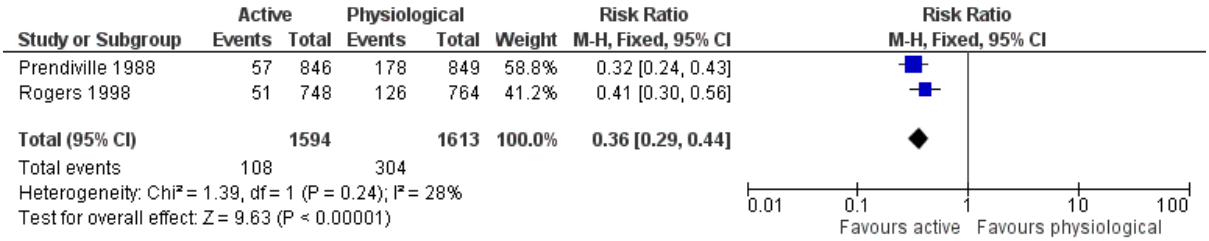


Figure 3: Maternal postpartum anaemia: requirement for blood transfusion

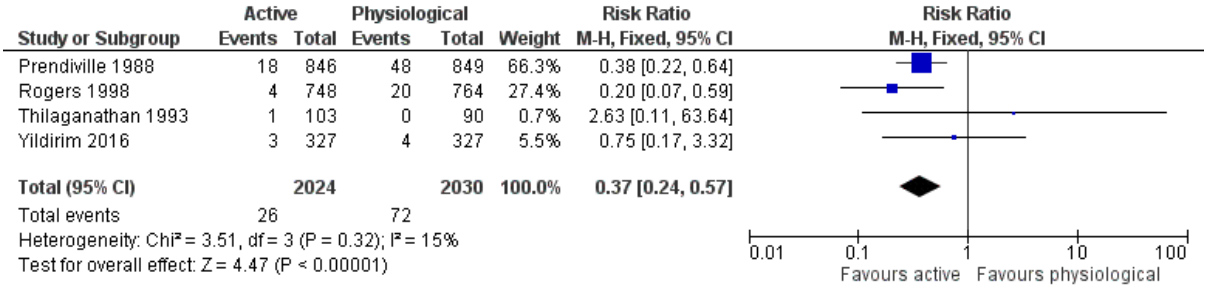


Figure 4: Maternal postpartum anaemia: Hb concentration < 9g/dL

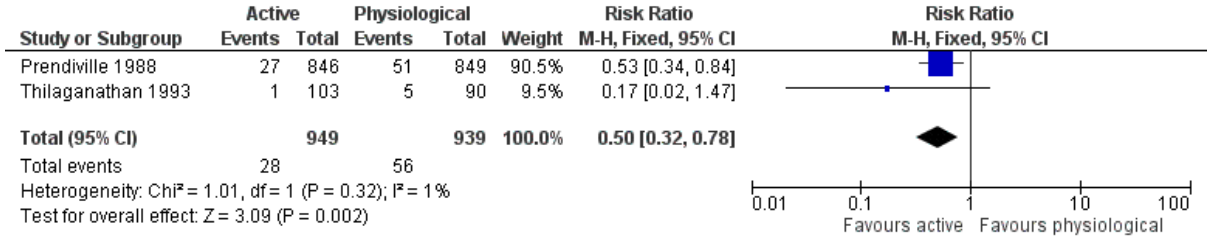


Figure 5: Need for further uterotonics – high income setting

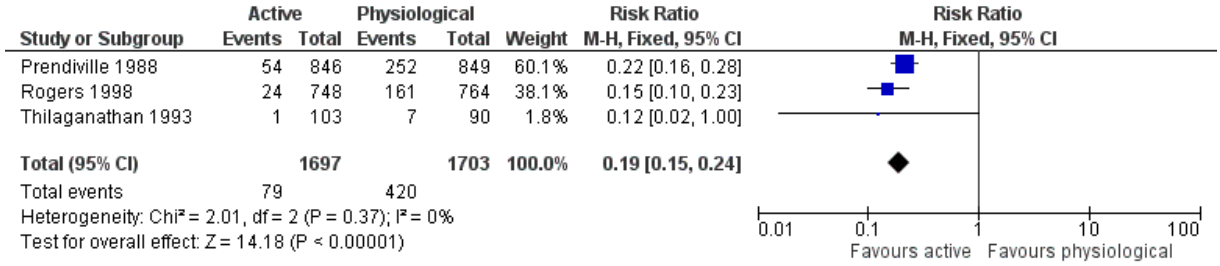


Figure 6: Retained placenta or need for manual removal of placenta

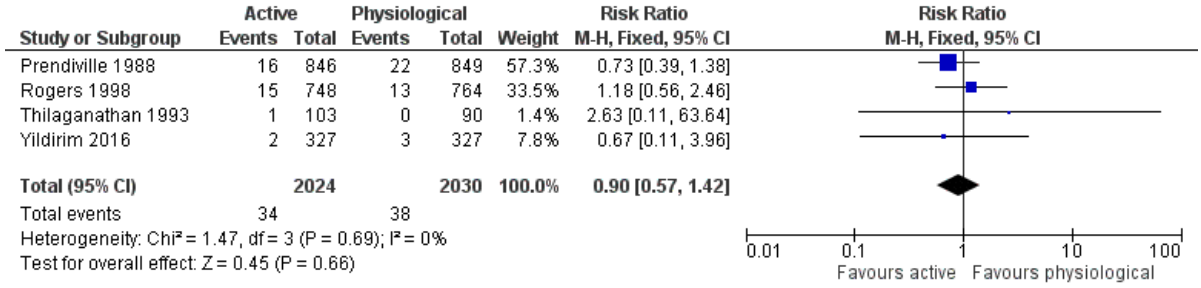
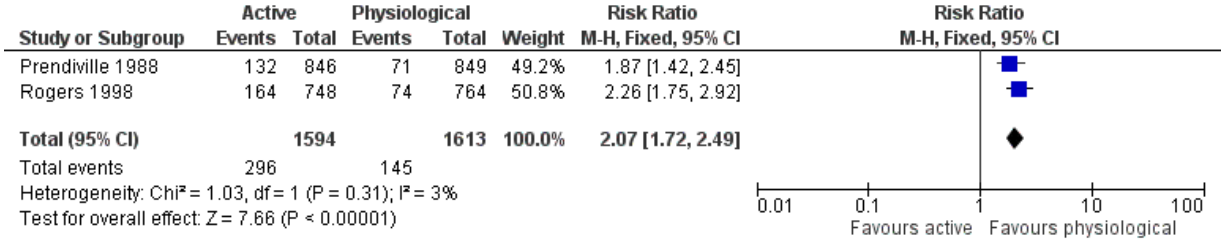
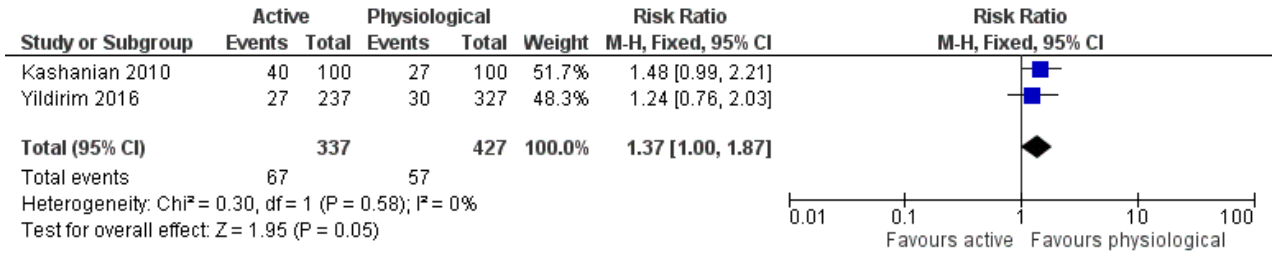


Figure 7: Side effects



Comparison 2: Active versus physiological management (with oxytocin post placental delivery)

Figure 8: Need for further uterotonics



Appendix F GRADE tables

GRADE tables for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Table 4: Evidence profile for comparison 1: Active versus physiological management

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Physiological	Relative (95% CI)	Absolute		
Primary postpartum haemorrhage (assessed with: ≥500ml)												
2 (Prendiville 1988; Rogers 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/1594 (6.8%)	304/1613 (18.8%)	RR 0.36 (0.29 to 0.44)	121 fewer per 1000 (from 106 fewer to 134 fewer)	LOW	CRITICAL
Maternal postpartum anaemia (assessed with: number needing blood transfusion)												
4 (Prendiville 1988; Rogers 1998; Thilaganathan 1993; Yildirim 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/2024 (1.3%)	72/2030 (3.5%)	RR 0.37 (0.24 to 0.57)	22 fewer per 1000 (from 15 fewer to 27 fewer)	LOW	CRITICAL
Maternal postpartum anaemia (assessed with: Hb concentration <9g/dL)												
2 (Prendiville 1988; Thilaganathan 1993)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/949 (3%)	56/939 (6%)	RR 0.5 (0.32 to 0.78)	30 fewer per 1000 (from 13 fewer to 41 fewer)	LOW	CRITICAL
Need for further uterotonics												
3 (Prendiville 1988; Rogers 1998; Thilaganathan 1993)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/1697 (4.7%)	420/1703 (24.7%)	RR 0.19 (0.15 to 0.24)	200 fewer per 1000 (from 187 fewer to 210 fewer)	LOW	IMPORTANT
Retained placenta beyond 1 hour or need for manual removal												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Physiological	Relative (95% CI)	Absolute		
4 (Prendiville 1988; Rogers 1998; Thilaganathan 1993; Yildirim 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	34/2024 (1.7%)	38/2030 (1.9%)	RR 0.9 (0.57 to 1.42)	2 fewer per 1000 (from 8 fewer to 8 more)	VERY LOW	IMPORTANT
Side effects (assessed with: nausea, vomiting, headache, diastolic BP >100mmHg, systolic BP >160mmHg, readmitted for bleeding problems)												
2 (Prendiville 1988; Rogers 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	296/1594 (18.6%)	145/1613 (9%)	RR 2.07 (1.72 to 2.49)	96 more per 1000 (from 65 more to 134 more)	LOW	IMPORTANT
Antibiotics for bleeding (discharge to 6 weeks)												
1 (Rogers 1998)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	39/748 (5.2%)	36/764 (4.7%)	RR 1.11 (0.71 to 1.72)	5 more per 1000 (from 14 fewer to 34 more)	LOW	IMPORTANT
Satisfied with third stage management												
1 (Rogers 1998)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	721/748 (96.4%)	718/764 (94%)	RR 1.03 (1 to 1.05)	28 more per 1000 (from 0 more to 47 more)	MODERATE	IMPORTANT
Felt in control during third stage												
1 (Rogers 1998)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	621/748 (83%)	667/764 (87.3%)	RR 0.95 (0.91 to 0.99)	44 fewer per 1000 (from 9 fewer to 79 fewer)	MODERATE	IMPORTANT

BP: blood pressure; CI: confidence interval; Hb: haemoglobin; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs [3] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 5: Evidence profile for comparison 2: Active versus physiological management (with oxytocin post placental delivery)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Physiological (with oxytocin post placental delivery)	Relative (95% CI)	Absolute		
Need for further uterotonics												
1 (Kashanian 2010; Yildirim 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	67/337 (19.9%)	57/427 (13.3%)	RR 1.37 (1.00 to 1.87)	49 more per 1000 (from 0 more to 116 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

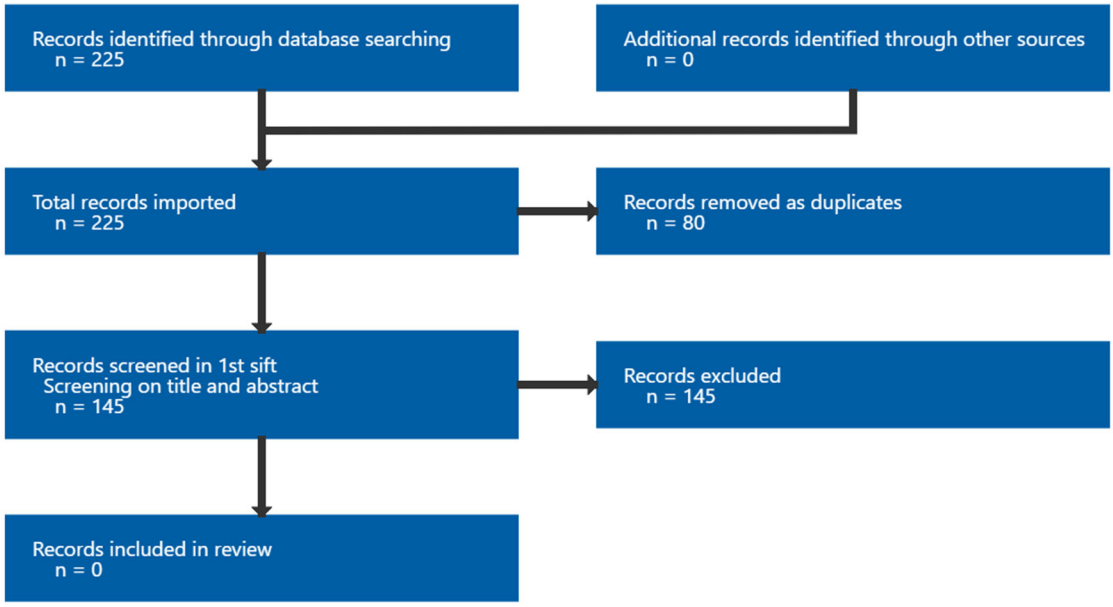
[2] 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

No economic evidence was identified which was applicable to this review question.

Figure 9: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason
Actrn (2007) A double-blind randomised controlled trial of oxytocin bolus plus placebo infusion versus oxytocin bolus plus oxytocin infusion at elective caesarean section. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12607000631404	- Comparator *Trial protocol only, however both arms received oxytocin after birth so full results not located*
Adnan, Nita; Boland, Fiona; Murphy, Deirdre J. (2017) Intramuscular oxytocin versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery (LabOR trial): study protocol for a randomised controlled trial. Trials 18(1): 541	- Comparator *Oxytocin provided in both arms. Study protocol only but full results not located as protocol does not meet the criteria*
Althabe, F., Bergel, E., Buekens, P. et al. (2006) Controlled cord traction in the third stage of labor. Systematic review. International Journal of Gynecology and Obstetrics 94(suppl2): S126-S127	- Study design *Summary only of systematic review. Included references checked but do not meet the protocol as they both have controlled cord traction*
Amorim, M., Katz, L., Coutinho, I. et al. (2015) Placental cord drainage in the third stage of labor. International Journal of Gynecology and Obstetrics 131(suppl5): e226	- Study design *Conference abstract only*
Anjaneyulu, R., Pk, Devi, Jain, S. et al. (1988) PROPHYLACTIC USE OF 15(S)15 METHYL PGF2alpha , BY INTRAMUSCULAR ROUTE - A CONTROLLED CLINICAL TRIAL. Acta obstetricia et gynecologica Scandinavica 67(s145): 9-11	- Comparator *Active management for both arms*
Anorlu, Rose I.; Maholwana, Babalwa; Hofmeyr, G. Justus (2008) Methods of delivering the placenta at caesarean section. The Cochrane database of systematic reviews: cd004737	- Comparator *Comparison group does not meet physiological*

Study	Reason
	management criteria specified in the protocol
Asicioglu, Osman, Unal, Canan, Asicioglu, Berhan Besimoglu et al. (2015) Influence of placental cord drainage in management of the third stage of labor: a multicenter randomized controlled study. American journal of perinatology 32(4): 343-50	- Intervention *Both groups received uterotonic injections*
Athavale, R. D., Nerurkar, N. M., Dalvi, S. A. et al. (1991) Umbilical vein oxytocin in the management of third stage of labour. Journal of postgraduate medicine 37(4): 219-220	- Comparator *Not enough information on the other components of management*
Begley, C. M. (1990) A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 6(1): 3-17	- Comparator *Comparison arms includes 'gentle cord traction' which is considered mixed management*
Begley, C. M., Gyte, G. M. L., Devane, D. et al. (2019) Active versus expectant management for women in the third stage of labour. Cochrane Database of Systematic Reviews 2019(2): cd007412	- Comparator *Some included studies used a mixed management approach. Relevant studies were included and extracted separately*
Bider, D., Ben-Rafael, Z., Dulitzky, M. et al. (1992) Effect of intraumbilical prostaglandin F2 alpha injection on the third stage of labor. The Journal of reproductive medicine 37(4): 317-9	- Comparator *Both groups received cord traction*
Bider, D., Zolti, M., Menashe, Y. et al. (1991) Oxytocin or saline injected intra-umbilically did not influence the third stage of labor. Acta obstetricia et gynecologica Scandinavica 70(45): 321-3	- Intervention *Both arms received controlled cord traction*
Carroli, G., Belizan, J. M., Grant, A. et al. (1998) Intra-umbilical vein injection and retained placenta: evidence from a collaborative large randomised controlled trial. Grupo Argentino de Estudio de Placenta Retenida. British journal of obstetrics and gynaecology 105(2): 179-85	- Intervention *Injection of uterotonic was more than 30 minutes after birth (not with the delivery of the anterior shoulder, or immediately after birth)*

Study	Reason
Chelmow, D. (2011) Postpartum haemorrhage: prevention. BMJ clinical evidence 2011	- Unable to obtain full text
Chestnut, D. H. and Wilcox, L. L. (1987) Influence of umbilical vein administration of oxytocin on the third stage of labor: a randomized, double-blind, placebo-controlled study. American journal of obstetrics and gynecology 157(1): 160-2	- Intervention *Cord traction was a possibility in both arms, and no information on how many received it*
Chukudebelu, W. O.; Marshall, A. T.; Chalmers, J. A. (1963) Use of 'syntometrine' in the third stage of labour. BMJ (Clinical research ed.) 1: 1390-1391	- Study design *Not a randomised controlled trial*
Dagli, A. C. (1998) Management of the third stage of labor. The Journal of family practice 46(6): 452-453	- Study design *Editorial review*
Dehbashi, S.; Honarvar, M.; Fardi, F. H. (2004) Manual removal or spontaneous placental delivery and postcesarean endometritis and bleeding. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 86(1): 12-5	- Comparator *Definition of physiological management in the study does not match the criteria in the protocol*
Deneux-Tharaux, C., Sentilhes, L., Maillard, F. et al. (2012) Effect of controlled traction of the cord during the third stage of labour on the incidence of postpartum haemorrhage (Tracor study): A multicentre randomised controlled trial. Journal of Maternal-Fetal and Neonatal Medicine 25(suppl2): 94	- Intervention *Abstract only. Full results located but not included because both arms received uterotonic injection after birth*
Elbourne, D. R., Prendiville, W. J., Carroli, G. et al. (2001) Prophylactic use of oxytocin in the third stage of labour. Cochrane database of systematic reviews (Online): cd001808	- More recent review available *Relevance assessed under 2019 version*
Elbourne, D. and Harding, J. (1991) Routine management for the third stage of labour: evidence from two random controlled trials. Journal of Obstetrics and Gynaecology 11(suppl1): S23-S27	- Study design *Not a systematic review, however included references checked and they have been identified in the search and their relevance assessed individually*

Study	Reason
Ergen, E. B., Kilicci, C., Kumru, P. et al. (2019) Placental drainage versus no placental drainage after vaginal delivery in the management of third stage of labour: A randomized study. Zeynep Kamil Tip Bulteni 50(1): 26-29	- Intervention *Both groups received uterotonic injection*
Erickson, Elise N.; Lee, Christopher S.; Emeis, Cathy L. (2017) Role of Prophylactic Oxytocin in the Third Stage of Labor: Physiologic Versus Pharmacologically Influenced Labor and Birth. Journal of midwifery & women's health 62(4): 418-424	- Study design *Not a systematic review or randomised controlled trial, however included studies checked and all have been identified by the search and assessed for relevance individually*
Gallos, I., Williams, H., Price, M. et al. (2019) Uterotonic drugs to prevent postpartum haemorrhage: A network meta-analysis. Health Technology Assessment 23(9): 1-356	- Study design *Network meta-analysis. Included studies checked for relevance, and suitable ones already identified by the search. Other studies not relevant because the intervention was just looking at oxytocin administration, and not any other components of active management, and comparator arms were not looking at the components of physiological management*
Gazvani, M. R., Luckas, M. J., Drakeley, A. J. et al. (1998) Intraumbilical oxytocin for the management of retained placenta: a randomized controlled trial. Obstetrics and gynecology 91(2): 203-7	- Comparator *Active management in both arms*
Ghulmiyyah, L. M., Wehbe, S. A., Saltzman, S. L. et al. (2005) Effects of intraumbilical vein injection of saline versus oxytocin plus saline on duration of the third stage of labor: a randomized double-blind placebo trial. American journal of obstetrics and gynecology 193(6suppl): 18	- Study design *Study abstract only*
Ghulmiyyah, Labib M., Wehbe, Salim A., Saltzman, Steven L. et al. (2007) Intraumbilical vein injection of oxytocin and the third stage of labor: randomized double-blind placebo trial. American journal of perinatology 24(6): 347-52	- Comparator *Both arms received active management components*

Study	Reason
Giacalone, P. L., Vignal, J., Daures, J. P. et al. (2000) A randomised evaluation of two techniques of management of the third stage of labour in women at low risk of postpartum haemorrhage. British Journal of Obstetrics and Gynaecology 107(3): 396-400	- Comparator *Controlled cord traction provided in both arms*
Gulmezoglu, A. Metin, Lumbiganon, Pisake, Landoulsi, Sihem et al. (2012) Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet (London, England) 379(9827): 1721-7	- Comparator *Comparator was active management without cord traction (not physiological management)*
Gutarra-Vilchez, R.; Campos, T.; Samalvides, F. (2012) Third stage of labor assisted with intraumbilical oxytocin: expectant and routinary. Revista peruana de ginecología y obstetricia 58(4): 285-290	- Language *Article in Spanish*
Hamdy, Amr, Azmy, Osama, Lotfy, Rehab et al. (2019) Multicenter randomized controlled trial assessing the impact of a cervical traction maneuver (Amr's maneuver) on the incidence of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 144(1): 56-61	- Comparator *Active management in both groups*
Hoffman, M.; Castagnola, D.; Naqvi, F. (2006) A randomized trial of active versus expectant management of the third stage of labor. American journal of obstetrics and gynecology 195(6suppl1): 107	- Study design *Study abstract only*
Hoffman, M.; Naqvi, F.; Sciscione, A. (2004) A randomized trial of active versus expectant management of the third stage of labor. American journal of obstetrics and gynecology 191(6suppl1): 82	- Study design *Study abstract only*
Hofmeyr, G. Justus; Mshweshwe, Nolundi T.; Gulmezoglu, A. Metin (2015) Controlled cord traction for the third stage of labour. The Cochrane database of systematic reviews 1: cd008020	- Comparator *Women in both arms received uterotonics in all included studies*
Irct201206182204N (2012) Active management of third stage of labor. https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT201206182204N3	- Study design *Trial protocol only. Unable to locate any published results*
Irct2017052810340N (2017) The effect of Oxytocin on the duration of third stage of labor. https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT2017052810340N15	- Study design *Trial protocol only. Unable to locate any published results*

Study	Reason
Isrctn (2004) Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN63422923	- Study design *Trial protocol only. Results assessed under Rogers 1998. Unable to locate more recent results*
Jangsten, E., Bergh, I., Mattsson, L. A. et al. (2011) Afterpains: a comparison between active and expectant management of the third stage of labor. Birth (Berkeley, Calif.) 38(4): 294-301	- Results already published elsewhere *Study results published in British Journal of Obstetrics and Gynaecology (Jangsten 2011). However not included as comparison arm was mixed management (cord was clamped immediately in expectant arm)*
Jangsten, E., Mattsson, L. A., Lyckestam, I. et al. (2011) A comparison of active management and expectant management of the third stage of labour: a Swedish randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 118(3): 362-9	- Comparator *Comparison arm was mixed management (cord was clamped immediately in expectant arm)*
Jerbi, M., Hidar, S., Elmoueddeb, S. et al. (2007) Oxytocin in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 96(3): 198-9	- Comparator *Comparison arm not expectant management as defined in the protocol (mixed management)*
Jongkolsiri, Piphat and Manotaya, Saknan (2009) Placental cord drainage and the effect on the duration of third stage labour, a randomized controlled trial. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92(4): 457-60	- Intervention *Not enough information provided on whether the two groups had active or physiological management of the third stage*
Kemp, J. (1963) Clinical trial of "syntometrine" in the third stage of labour. British medical journal 1(5342): 1391-2	- Comparator *Syntometrine compared with ergometrine - there is no physiological management*

Study	Reason
Kerekes, L. and Domokos, N. (1979) The effect of prostaglandin F2 alpha on third stage labor. Prostaglandins 18(1): 161-6	- Intervention *Not enough information on the components of active or physiological management*
Khan, G. Q., John, I. S., Wani, S. et al. (1997) Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. American journal of obstetrics and gynecology 177(4): 770-4	- Comparator *Comparison arm used mixed management (expectant arm clamped the cord immediately)*
Kovavisarach, E. and Rojsangruang, S. (1998) Effect of umbilical vein oxytocin injection on the third stage of labor: a randomized controlled study. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 81(9): 693-7	- Comparator *Not enough information on the other components of management*
Kresch, Mitchell J. (2017) Management of the Third Stage of Labor: How Delayed Umbilical Cord Clamping Can Affect Neonatal Outcome. American journal of perinatology 34(14): 1375-1381	- Study design *Not a randomised controlled trial or a systematic review*
Liabsuetrakul, T., Choobun, T., Peeyananjarassri, K. et al. (2018) Prophylactic use of ergot alkaloids in the third stage of labour. Cochrane Database of Systematic Reviews 2018(6): cd005456	- Intervention *Intervention focused on different components of active management only*
Luamprapas, A. (1994) A study of umbilical vein administration of oxytocin to shorten the third stage of labor. Chon buri hospital journal 19(2): 14-25	- Unable to obtain full text
Makvandi, S.; Shoushtari, S. Z.; Hosseini, V. Z. (2013) Management of third stage of labor: a comparison of intraumbilical oxytocin and placental cord drainage. Shiraz e medical journal 14(2)	- Comparator *All groups received controlled cord traction*
Martínez, M. M., López Farfán, J. A., Ramos Alvarez, G. et al. (2006) Oxitocin trough umbilical vein to shorten the third stage of labor. Ginecologia y obstetricia de Mexico 74(2): 89-94	- Language *Article in Spanish*
Masuzawa, Yuko, Kataoka, Yaeko, Fujii, Kana et al. (2018) Prophylactic management of postpartum haemorrhage in the third stage of labour: an overview of systematic reviews. Systematic reviews 7(1): 156	- Intervention *Most of the included studies did not match the intervention or*

Study	Reason
	comparator from the protocol. References checked for relevant studies. Any relevant studies have already been identified in the search
Mori, Rintaro, Nardin, Juan Manuel, Yamamoto, Naoko et al. (2012) Umbilical vein injection for the routine management of third stage of labour. The Cochrane database of systematic reviews: cd006176	- Intervention *Systematic review. Included studies already identified by the search but do not meet the criteria specified in the protocol due to mixed management approaches*
Nct (2007) Active Versus Expectant Management of the Third Stage of Labor. https://clinicaltrials.gov/show/NCT00473707	- Study design *Trial protocol only, published results not found*
Nct (2018) Placental Drainage Versus no Placental Drainage After Vaginal Delivery in the Management of Third Stage of Labour. https://clinicaltrials.gov/show/NCT03542292	- Study design *Trial protocol only. Results not located as both groups received oxytocin after birth*
Nct (2018) Intraumbilical Oxytocin Versus Placental Cord Drainage in the Management of 3rd Stage of Labor. https://clinicaltrials.gov/show/NCT03395730	- Study design *Trial protocol only. Full results not located as cord clamped before 5 minutes in all arms*
Nct (2010) Third Stage of Labor a Swedish Randomized Controlled Trial. https://clinicaltrials.gov/show/NCT01221051	- Study design *Trial protocol only. Full results identified in the search and assessed for relevance*
Nct (2010) Prevention of Post-partum Haemorrhage. https://clinicaltrials.gov/show/NCT01044082	- Study design *Trial protocol only. Full results not included as both arms received uterotonic injection after birth*

Study	Reason
Nct (2010) Effect of Prophylactic Administration of Oxytocin in Uniject™ on Postpartum Hemorrhage at Home Births in Ghana. https://clinicaltrials.gov/show/NCT01108289	- Intervention *Not enough information on the other components of management*
Nct (2010) Effectiveness, Safety and Feasibility of Auxiliary Nurse Midwives' (ANM) Use of Oxytocin in Uniject™ to Prevent Postpartum Hemorrhage in India. https://clinicaltrials.gov/show/NCT01108302	- Intervention *Not enough information on the other components of management*
Nct (2012) Effectiveness of Placental Drainage in the Third Stage of Labor: a Randomized Clinical Trial. https://clinicaltrials.gov/show/NCT01655576	- Intervention *Women in both arms received oxytocin*
Nordstrom, L., Fogelstam, K., Fridman, G. et al. (1997) Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. British journal of obstetrics and gynaecology 104(7): 781-6	- Intervention *Controlled cord traction not part of active management group*
Odent, M. (1998) Active versus expectant management of third stage of labour. Lancet 351(9116)	- Study design *Correspondence letter*
Ozcan, T.; Sahin, G.; Senoz, S. (1996) The effect of intraumbilical oxytocin on the third stage of labour. The Australian & New Zealand journal of obstetrics & gynaecology 36(1): 9-11	- Comparator *Cord traction in both arms*
Pactr (2019) The effect of cranial uterine traction on the incidence of postpartum hemorrhage: A randomized clinical trial. https://trialsearch.who.int/Trial2.aspx?TrialID=PACTR202001882345033	- Study design *Trial protocol only, unable to locate any published results*
Pactr (2017) Management of third stage of labour. https://trialsearch.who.int/Trial2.aspx?TrialID=PACTR201707002372422	- Study design *Trial protocol only, unable to locate any published results*
Pantoja, Tomas, Abalos, Edgardo, Chapman, Evelina et al. (2016) Oxytocin for preventing postpartum haemorrhage (PPH) in non-facility birth settings. The Cochrane database of systematic reviews 4: cd011491	- Intervention *Systematic review. Study included did not specify other components of active or*

Study	Reason
	physiological management
Peters, Nina C. J. and Duvekot, Johannes J. (2009) Carbetocin for the prevention of postpartum hemorrhage: a systematic review. Obstetrical & gynecological survey 64(2): 129-35	- Comparator *Systematic review. Included studies administered uterotonics to both groups*
Pierre, F.; Mesnard, L.; Body, G. (1992) For a systematic policy of i.v. oxytocin inducted placenta deliveries in a unit where a fairly active management of third stage of labour is yet applied: results of a controlled trial. European journal of obstetrics, gynecology, and reproductive biology 43(2): 131-5	- Comparator *All groups received controlled cord traction*
Poeschmann, R. P.; Doesburg, W. H.; Eskes, T. K. (1991) A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. British journal of obstetrics and gynaecology 98(6): 528-30	- Intervention *Controlled cord traction not part of active management*
Prendiville, W. J. (1996) The prevention of post partum haemorrhage: optimising routine management of the third stage of labour. European journal of obstetrics, gynecology, and reproductive biology 69(1): 19-24	- Study design *Not a systematic review or a randomised controlled trial. However references were checked and all relevant trials have already been identified by the search*
Prendiville, W. J., Harding, J. E., Elbourne, D. R. et al. (1988) The Bristol third stage trial: active vs physiological management of third stage of labour. BMJ (Clinical research ed.) 297: 1295-1300	- Duplicate
Ramirez, O., Benito, V., Jimenez, R. et al. (2001) Third stage of labour: active or expectant management? preliminary results. Journal of perinatal medicine suppl1(pt2): 364	- Study design *Study abstract only*
Rogers, M. S.; Yuen, P. M.; Wong, S. (2007) Avoiding manual removal of placenta: Evaluation of intra-umbilical injection of uterotonics using the Pipingas technique for management of adherent placenta. Acta Obstetricia et Gynecologica Scandinavica 86(1): 48-54	- Intervention *Active management components in all arms*
Salati, J. A., Leathersich, S. J., Williams, M. J. et al. (2019) Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database of Systematic Reviews 2019(4): cd001808	- Comparator *Most included studies did not meet the physiological management for the*

Study	Reason
	comparison. Potential relevant studies assessed separately for inclusion
Sharma, J. B., Pundir, P., Malhotra, M. et al. (2005) Evaluation of placental drainage as a method of placental delivery in vaginal deliveries. Archives of gynecology and obstetrics 271(4): 343-5	- Comparator *Both arms received uterotonic injection*
Sharma, J. B., Sharman, W. A., Newman, M. R. B. et al. (1995) Evaluation of placental drainage at caesarean section as a method of placental delivery. Journal of Obstetrics and Gynaecology 15(4): 237-239	- Comparator *All women received oxytocin following the birth*
Sheldon, W., Blum, J., Durocher, J. et al. (2011) How effective are the components of active management of the third stage of labor?. Contraception 84(3): 336	- Study design *Study abstract only*
Siriwarakul, W. (1991) A study of umbilical vein administration of oxytocin to shorten the third stage of labor. Chon buri hospital journal 16(1): 40-51	- Unable to obtain full text
Soltani, H.; Dickinson, F.; Symonds, I. M. (2009) Placental cord drainage after spontaneous vaginal delivery as part of the management of the third stage of labour. Cochrane Database of Systematic Reviews: cd004665	- More recent review available *Relevance assessed under the 2011 version*
Soltani, Hora; Poulose, Thomas A.; Hutchon, David R. (2011) Placental cord drainage after vaginal delivery as part of the management of the third stage of labour. The Cochrane database of systematic reviews: cd004665	- Comparator *Included studies did not meet the criteria for physiological management*
Su, L. L.; Chong, Y. S.; Samuel, M. (2007) Oxytocin agonists for preventing postpartum haemorrhage. The Cochrane database of systematic reviews: cd005457	- More recent review available *Relevance assessed under 2012 version*
Su, Lin-Lin; Chong, Yap-Seng; Samuel, Miny (2012) Carbetocin for preventing postpartum haemorrhage. The Cochrane database of systematic reviews: cd005457	- Comparator *References checked but none of the included studies met the criteria in the protocol as comparison arms include administration of a uterotonic*

Study	Reason
Sujatha, M. S.; Chatterjee, A.; Roy, P. (2015) Placental blood drainage as a part of active management of third stage of labour after spontaneous vaginal delivery. International Journal of Gynecology and Obstetrics 131(suppl5): E491-E492	- Comparator *Active management of labour in both arms*
Tehseen, Fehmida; Anwar, Ambreen; Arfat, Yasir (2008) Intraumbilical veinous injection oxytocin in the active management of third stage of labour. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 18(9): 551-4	- Comparator *Both groups received active management*
Vasconcelos, Fernanda Barros, Katz, Leila, Coutinho, Isabela et al. (2018) Placental cord drainage in the third stage of labor: Randomized clinical trial. PloS one 13(5): e0195650	- Comparator *All women received oxytocin after birth of the baby*
Vasegh, F. R., Bahiraie, A., Mahmoudi, M. et al. (2005) Comparison of active and physiologic management of third stage of labor. HAYAT: the journal of tehran faculty of nursing & midwifery 10(23): 102	- Language *Study not in English*
Waqar, Fareesa; Nasar, Razia; Fawad, Anisa (2008) The comparison of placental removal methods on operative blood loss. Journal of Ayub Medical College, Abbottabad : JAMC 20(3): 3-5	- Intervention *Active management compared to mixed management*
Wu, H. L., Chen, X. W., Wang, P. et al. (2017) Effects of placental cord drainage in the third stage of labour: A meta-analysis. Scientific reports 7(1): 7067	- Comparator *Systematic review. Included studies did not compare different components of active to physiological management*
Wu, Yu, Wang, Huan, Wu, Qi-Yan et al. (2020) A meta-analysis of the effects of intramuscular and intravenous injection of oxytocin on the third stage of labor. Archives of gynecology and obstetrics 301(3): 643-653	- Comparator *Included studies compared oxytocin route of administration*
Young, S. B., Martelly, P. D., Greb, L. et al. (1988) The effect of intraumbilical oxytocin on the third stage of labor. Obstetrics and gynecology 71(5): 736-8	- Duplicate
Young, S. B., Martelly, P. D., Greb, L. et al. (1988) The effect of intraumbilical oxytocin on the third stage of labor. Obstetrics and Gynecology 71(5): 736-738	- Comparator *Likely other components of active management were present in both groups, but it is unclear*

Study	Reason
Zhao, Y., Lu, H., Zang, Y. et al. (2020) A systematic review of clinical practice guidelines on uncomplicated birth. BJOG : an international journal of obstetrics and gynaecology 127(7): 789-797	- Intervention *Systematic review does not meet the criteria of the protocol so references not checked*
Zhou, H. L. and Zhang, L. (1994) Study on the effect of third stage of labor through different channels of injection of oxytocin. Chinese journal of nursing 29(8): 453-455	- Language *Study not in English*

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the benefits and risks associated with active management compared to physiological management in the third stage of labour?

No research recommendations were made for this review question.

Appendix L – Post-hoc analysis

Although this post-hoc analysis was not specifically described in the review protocol, the committee further wished to explore what proportion of women had a postpartum haemorrhage ≥1000mL, as the clinical consequences are different to women experiencing a postpartum haemorrhage closer to 500 mL. The forest plot is presented below.

Post-hoc analyses – comparison 1: Active versus physiological management

Figure 10: Postpartum haemorrhage ≥1000 mL