National Institute for Health and Care Excellence

Final

Twin and triplet pregnancy

[I] Evidence reviews for interventions to prevent postpartum haemorrhage in the third stage of labour

NICE guideline NG137

Evidence review

September 2019

Final

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

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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.

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ISBN: 978-1-4731-3513-0

Contents

Managing the third stage of labour to reduce postpartum haemorrhage

Review question

What is the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Introduction

Excessive uncontrolled postpartum haemorrhage (PPH) can lead to an increased risk of hysterectomy, multi-organ failure and maternal mortality. Twin and triplet pregnancy is associated with an increased risk of PPH. Prevention of PPH would reduce the need for emergency interventions. This review aims to address the uncertainty around the optimal management of the third stage of labour in twin and triplet pregnancy to reduce the risk of PPH.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO Table)

Population	All women confirmed as having a twin or triplet pregnancy by the 11–13-week ultrasound scan and carried to ≥24 weeks of pregnancy and all fetuses confirmed alive and who are in the third stage of labour. Setting: any setting
Intervention	**Vaginal birth:** • physiological management of the third stage of labour • active management plus additional uterotonics, for example, further oxytocin (by infusion), longer-acting oxytocin, carboprost, misoprostol, ergometrine (as defined in studies) **Caesarean section:** • active management plus additional uterotonics, for example, further oxytocin (by infusion), longer acting oxytocin, carboprost, misoprostol, ergometrine (as defined in studies)
Comparison	**Vaginal birth:** • active management of the third stage of labour: o administration of 10 IU of oxytocin by intramuscular injection with the birth of the anterior shoulder or immediately after the birth of the baby and before the cord is clamped and cut **Caesarean section:** • active management of the third stage of labour o administration of 10 IU of oxytocin by IV injection with the birth of the anterior shoulder or immediately after the birth of the baby and before the cord is clamped and cut
Outcomes	**Critical** For the woman: • mortality • PPH (blood loss > 1000ml) • hysterectomy **Important:**

	For the woman: • side effects of drugs (for example, change in blood pressure, headache, nausea/vomiting) • need for further intervention (for example, additional uterotonics, manual removal of placenta, blood transfusion, balloon tamponade) • need for intensive care unit or high dependency unit • women's satisfaction/experience of labour and birth

IU: international unit; IV: intravenous; ml: millilitres; PPH: postpartum haemorrhage

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from March 2017 until March 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Three studies were identified that met the inclusion criteria for this review (Demetz 2013, Fahmy 2016 and Sotillo 2018). One randomised controlled trial (RCT) (Fahmy 2016), 1 prospective cohort study (Sotillo 2018), and 1 retrospective cohort study (Demetz 2013).

All looked at the effectiveness of one particular uterotonic (carbetocin compared to oxytocin) to prevent or reduce the risk of PPH for women with twin pregnancy during planned or emergency caesarean section (active management in caesarean section). The RCT compared carbetocin (N=30) and oxytocin (N=30) administered slowly over 1 minute, immediately after birth whilst women were under general anaesthetic for planned caesarean section. The prospective cohort study compared a standard protocol of oxytocin within 10-15 minutes of birth (N=86), to the study intervention treatment of carbetocin (N=80) administered in the first minute after birth, for the prevention of PPH in twin pregnancies undergoing caesarean section. The retrospective cohort study compared a standard protocol of oxytocin delivered during the birth of the second baby (N=24) to the same protocol using carbetocin instead (N=39), in women undergoing either planned or emergency caesarean section.

No evidence was found assessing physiological or active management for vaginal birth.

The clinical studies included in this evidence review are summarised in Table 2.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, and GRADE profiles in appendix F.

Excluded studies

Studies not included in this review with reasons for their exclusion are listed in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies for twin pregnancy

Study	Population	Intervention	Comparator	Outcomes
Demetz 2013 Retrospective cohort France	Women with twin or triplet pregnancy undergoing caesarean section (planned or emergency) • Before group (oxytocin): N=24 (0% triplets), • After group (carbetocin) N=39 (10.3% triplets) *(twins and triplets)*	"Active management": Carbetocin: 100 microgram in IV injection • continued to receive oxytocin by slow perfusion 3 hours after birth	"Active management": • oxytocin as uterotonic • 10 units by IV injection	• Blood loss (PPH) • Blood transfusion • Emergency surgery required
Fahmy 2016 RCT Egypt	Women with twin pregnancy undergoing planned caesarean section • N=60 twin pregnancies: • Control group (oxytocin): N=30 • Intervention (carbetocin): N=30	"Active management": Carbetocin: 100 microgram carbetocin in 10 ml saline solution was injected slowly IV over one minute after birth of babies	"Active management" • oxytocin as uterotonic • 20 IU of oxytocin in 10 ml saline solution was injected slowly IV over one minute after birth of babies	• Blood transfusion • Side effect of the drugs - change in blood mean arterial blood pressure (measured in 5 minute intervals) • Need for further intervention - additional uterotonics agents (methergine)
Sotillo 2018 Prospective cohort Spain	Women with twin pregnancy undergoing caesarean section • N=166 twin pregnancies: • Control group (oxytocin): N=80 • Intervention (carbetocin): N=86	"Active management": Carbetocin • 100 mg IV in bolus in the 1 minute after birth	"Active management" • oxytocin as uterotonic • 20 IU of oxytocin in Ringer lactate 500 ml in 10–15 minutes	• Need for further treatment • Need for additional uterotonics agents • Blood transfusion

IV: intravenous; min: minute; mg: milligrams; ml: millilitres; N: number of women; PPH: postpartum haemorrhage; RCT: randomised controlled trial

Meta-analysis was not conducted due to the different study designs (RCT, retrospective cohort, prospective cohort), and due to the different timings of drug administration (during or after birth).

See appendix D for the full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for the 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.

See the appendix B for the economic search strategy and appendix G for the economic evidence selection flow chart for further information.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Summary of studies included in the economic evidence review

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.

Evidence statements

Carbetocin versus oxytocin (control) for active management of women with twin pregnancy undergoing caesarean section

Outcomes for the woman

PPH (blood loss, ml)

Very low quality evidence from 1 cohort study (N=63) showed no clinically important difference in blood loss between the intervention (carbetocin) and control (oxytocin) groups.

Side effects from the drugs – change in mean arterial blood pressure over time (0, 5, 10 minutes after injection of uterotonic drug)

Moderate quality evidence from 1 RCT (N=60) showed no clinically important difference in mean arterial blood pressure between the intervention (carbetocin) and control (oxytocin) groups.

Side effects from the drugs – change in mean arterial blood pressure over time (15, 20, 25, 30 minutes after injection of uterotonic drug)

High quality evidence from 1 RCT (N=60) showed a clinically important difference in favour of the intervention (carbetocin) group as mean arterial blood pressure remained stable and the oxytocin (control) group's blood pressure fell (hypotensive).

Side effects from the drugs – change in mean arterial blood pressure over time (35 minutes after injection of uterotonic drug)

Moderate quality evidence from 1 RCT (N=60) showed a clinically important difference in favour of the intervention (carbetocin) group as mean arterial blood pressure remained stable and the oxytocin (control) group's blood pressure was lower (hypotensive).

Side effects from the drugs – change in mean arterial blood pressure over time (40, 50, 60 minutes after injection of uterotonic drug)

High quality evidence from 1 RCT (N=60) showed a clinically important difference in favour of the intervention (carbetocin) group as mean arterial blood pressure remained stable and the oxytocin (control) group's blood pressure was lower (hypotensive).

Need for further treatment (any - anaemia treatment and/or additional uterotonics agents)

Low quality evidence from 1 cohort study (N=166) showed a clinically important difference between groups for the need for any further treatment (anaemia treatment and/or additional uterotonics agents) with a higher incidence in the oxytocin (control) group.

Need for additional uterotonic agents

Very low quality evidence from 1 cohort study (N=166) showed no clinically important difference between groups for the need for additional uterotonics agents.

High quality evidence from 1 RCT (N=60) showed a clinically important difference in the need for additional uterotonic agents in favour of the intervention (carbetocin) group compared to the control (oxytocin) group.

Blood transfusion

Very low quality evidence from 1 cohort study (N=166) showed a clinically important difference between groups for the incidence of blood transfusions with a higher incidence in the oxytocin (control) group.

Very low quality evidence from 1 cohort study (N=63) showed no clinically important difference in the need for blood transfusion between the intervention (carbetocin) and control (oxytocin) groups.

Low quality evidence from 1 RCT (N=60) showed no clinically important difference in the need for blood transfusion between the intervention (carbetocin) and control (oxytocin) group.

Additional treatment required – emergency surgery

Very low quality evidence from 1 cohort study (N=63) showed no clinically important difference between the intervention (carbetocin) and the control (oxytocin) groups.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised PPH as a critical outcome for twin and triplet birth. Prevention of PPH would reduce the need for further interventions. This would improve the woman's experience in labour and enhance recovery time postpartum. Excessive uncontrolled PPH can lead to an increased risk of hysterectomy, multi-organ failure and maternal mortality. The committee agreed that these were critical outcomes as many women would be well prior to birth. Hysterectomy and multi-organ failure could have long term consequences on the woman's physical and mental health. PPH was reported as an outcome in 1 study and other studies reported 'need for additional treatments' as an outcome.

Admission to the intensive care unit or high dependency unit were prioritised as important outcomes as they reflect the severe sequelae of PPH. Although, admission into intensive care or high dependency units following birth is relatively rare, PPH remains the leading cause of postnatal admissions (the Intensive Care National Audit and Research Centre, 2013). Not all birth settings will have an onsite intensive care or high dependency unit, which could potentially delay lifesaving treatment. The committee therefore agreed it was important to choose admission to an intensive care or high dependency unit as an important outcome. Women admitted to intensive care or high dependency units have longer recovery times and may require separation from their babies. This may have long term effects on the woman's health and bonding with babies. Need for admission to the intensive care unit was not an outcome that was reported.

The committee agreed that the side effects of uterotonics were important outcomes as they could result in unwanted effects on the woman such as diarrhoea and vomiting. This could affect the overall woman's experience in labour. However, the committee agreed that the risk of PPH outweighed the potential adverse effects of uterotonics and therefore it was important that uterotonics were administered appropriately. The data on side effects were related only to blood pressure changes which was not considered to be a determining factor in the decision making of the committee.

Need for blood transfusion was also considered important since it would indicate how much blood loss could be prevented by each strategy. This would therefore have an impact on other outcomes for the woman, such as anaemia and fatigue.

The quality of the evidence

The quality of the evidence from the included studies was assessed with GRADE. Ratings for evidence from the observational cohort studies were very low, and evidence from the RCT was rated as low to high quality. Study design and risk of bias in the studies were the main factors that lowered the confidence in the evidence. The studies were also relatively small which meant that there was a lot of uncertainty around the estimates which led to evidence being downgraded for imprecision.

Benefits and harms

Planning birth: information and support

The committee decided, based on their experience and knowledge, that discussions about birth plans are important and that such discussions should enable the woman to make an informed decision about childbirth. At such a life changing time her wishes and preferences should be explored and information should be tailored to each woman. She can then feel better prepared which may ease some of her concerns and anxieties. Such discussions (including managing the third stage of labour) should be conducted at the latest by week 28 of her pregnancy because of the high risk of preterm birth. The committee emphasised that these discussions should be revisited as often as required or desired by the woman, to provide opportunity for her to receive further information and be part of the ongoing decision making process. The committee also acknowledged that the best practice on how to provide information and how to communicate with adults is described in NICE's guideline on patient experience in adult NHS services and cross referred to it.

Healthcare professionals providing intrapartum care

The committee recognised that the core multidisciplinary team recommended by the previous guideline (see recommendation 1.3.1) provides care during the antenatal period and would not be the same team providing intrapartum care. Because intrapartum care was added to the guideline update, based on their knowledge and experience they made a

recommendation to clarify that healthcare professionals supporting women when they are giving birth should also have knowledge and experience in multiple pregnancy.

Assessing risk

Based on their expertise and current practice (which is in turn informed by NICE guidance on managing PPH prior to this update), the committee acknowledged that the risk of PPH in women with twin and triplet pregnancy could lead to an increased risk of maternal morbidity, death, multiorgan failure, hysterectomy and blood transfusion and that it is therefore critical to have clear guidance to prevent such serious events. The committee noted that the list of risk factors highlighted in NICE's guideline on intrapartum care for healthy women and babies already includes multiple pregnancy (because of over-distension of the uterus and enlarged placenta or placentas) as one of the factors. However, there are many other risk factors that should also be taken into consideration when assessing risk and hence this guideline has been cross-referenced. In this way risk can be stratified according to the individual circumstances of each woman. Assessing the woman's risks of PPH and having conversations with her about this and all possible management options is a critical aspect of care to identify any particular factors that may raise concerns and to enable the woman to make an informed choice. The process of risk stratification should remain dynamic throughout the intrapartum stage as the woman's individual risks could change due to events in the intrapartum period.

Management

Based on their expertise and experience the committee noted that a physiological approach to care in the third stage is practised in the UK mostly in midwife-led units and at home births and would therefore be only appropriate for women identified as being at low risk of PPH. They agreed, that twin and triplet pregnancy is a risk factor for PPH and that physiological management of third stage labour is inappropriate and should not be offered. All women should be offered active management of the third stage since it would decrease this risk and / or the need for blood transfusion.

The committee specifically reviewed evidence from the 3 identified studies on the effectiveness of carbetocin for the management of the third stage of labour in multiple pregnancies. They discussed and agreed to discount the evidence from the prospective cohort study (Sotillo 2018) as it does not compare carbetocin with UK standard recommended active third stage therapy (10 IU oxytocin intramuscular [IM] or 5 IU IV slow bolus). The comparator in this study was high dose and rapid IV infusion and repeated high doses of oxytocin as indicated clinically. Based on expertise and experience, the committee noted that a high dose and rapid infusion of oxytocin are associated with an increased risk of maternal serious adverse effects such as cardiovascular collapse. The committee based this on knowledge of the report of the Confidential Enquiries into Maternal Deaths in the UK. Prolonged infusion of high-dose oxytocin may also be associated with water intoxication. Therefore a high dose of oxytocin is contraindicated in clinical practice and the committee agreed that it was an inappropriate control intervention to compare with carbetocin.

The committee also reviewed the evidence available from the only included RCT (Fahmy 2016). They were concerned by a number of limitations of this study which compared the use of IV carbetocin to 20 IU of oxytocin for the prevention of primary PPH in twin pregnancies delivered by caesarean section. The limitations were the small sample size (N=60) of twin pregnancies, the use of general anaesthetic for all births, the high and rapid IV dose of oxytocin used within the control group and the lack of accurate assessment of blood loss. The retrospective cohort study (Demetz 2013) was also small (N=63), and showed no significant differences between groups. The committee therefore agreed that none of these studies offered conclusive or convincing evidence to support any recommendation for the use of carbetocin in the active management of the third stage of labour in multiple pregnancies.

All of the identified evidence related to the use of uterotonics in active management of the third stage of labour of women with twin and triplet pregnancies, and more specifically looked at the use of carbetocin compared to oxytocin (control). The committee reviewed this evidence and were also aware of a recently published Cochrane network meta-analysis (NMA) (Gallos 2018), examining multiple uterotonics, including both carbetocin and oxytocin alongside others, to reduce the risk of PPH in the third stage of labour in a mixed population of both singleton and multiple pregnancies (the Cochrane NMA [Gallos 2018] could not be included in this review due to the mixed population of women with singleton or twin pregnancy). However, the findings of the Cochrane NMA (Gallos 2018) remain important due to the size and depth of the analysis. On the basis of the evidence presented in this guideline evidence review, the committee concluded that oxytocin should remain the first-line treatment for the prevention of PPH. This is consistent with the findings of the mixed-population Cochrane review (Gallos 2018) which concluded that no other studied agent is significantly more effective when compared with the reference uterotonic agent oxytocin.

Due to the limited evidence available specific to women with twin or triplet pregnancy, the committee based the recommendations related to the additional uterotonics on their clinical experience and expertise and decided to make a weaker recommendation for this. They concluded that there was insufficient information to favour one uterotonic over another. The committee agreed based on their experience, where women were identified to have an additional risk factor for PPH over and above that generated by multiple pregnancy, units should refer to local protocols to advise safe choice of additional uterotonics. The committee clarified that local protocols would already be in place for the management of the third stage of labour. The committee also recognised that the side effect profile and contraindications differ amongst individual uterotonics. For this reason, the committee agreed that further uterotonics should be individualised to the woman. The committee concluded that whilst there were side effects to certain uterotonics (for example nausea and vomiting), the benefits of uterotonics outweighed the risks.

Blood transfusion

The committee reiterated the importance of discussions with the woman about what may happen in the event of heavy blood loss, to ensure that all expectant mothers are well informed. As described above, this discussion should include the risks of PPH and management plans, but it should also cover the possible need for blood transfusions. Therefore the potential need for blood products and the transfusion process, in the event of excessive blood loss, should be discussed and documented prior to the intrapartum period.

The committee concurred that women with twin or triplet pregnancy should have intravenous access sited early in labour with full blood count and group and save. The benefits of having intravenous access in the event of an obstetric emergency are that it allows prompt fluid/blood product resuscitation in the event of a PPH, outweighing potential risks of pain and infection.

In case of emergency related to PPH, the committee decided, based on their experience, that it would be critical to make sure that the appropriate blood transfusion is readily available.

Despite the limited evidence, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research recommendations.

Cost effectiveness and resource use

In the absence of any economic evidence or original analysis, the committee made a qualitative assessment about the cost effectiveness of recommendations for managing the third stage of labour to reduce the risk of PPH in twin and triplet pregnancy.

The committee noted that interventions to prevent PPH are relatively inexpensive and that effective treatment would offset future costs by reducing the need for further intervention, including blood transfusions and admission to intensive care. Furthermore, effective treatment reduces the risk of serious adverse outcomes. The committee concluded that active management would be more cost effective than physiological management because it reduces the risk of PPH in twin and triplet pregnancies, which are at an increased risk of this outcome.

The committee agreed that, because of the risks to health-related quality of life arising from PPH, the benefits of uterotonics outweighed any potential side effects. No evidence was found to suggest any uterotonic agent is significantly more effective than the reference agent oxytocin and therefore considered that oxytocin should remain the first-line treatment for PPH, in line with current practice. In cases where additional uterotonics may be considered for the active management of the third stage of labour, the committee did not think a clear cost-effectiveness case could be made for one uterotonic over another. This reflected both the clinical evidence and the fact that the side effect profile and contraindications of uterotonics differ, which means that the cost-effective choice is often highly individualised.

References

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Gallos, ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, Williams MJ, Diaz V, Pasquale J, Chamillard M, Widmer M, Tunçalp Ö, Hofmeyr GJ, Althabe F, Gülmezoglu AM, Vogel JP, Oladapo OT, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis, Cochrane Database of Systematic Reviews, 2018

Sotillo 2018

Sotillo, L., De la Calle, M., Magdaleno, F., Bartha, J. L., Efficacy of carbetocin for preventing postpartum bleeding after cesarean section in twin pregnancy, Journal of Maternal and Fetal Neonatal Medicine, 1-5, 2018

Appendices

Appendix A – Review protocol

Review protocol – What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Table 3: Review protocol for managing the third stage of labour to reduce the risk of PPH

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?
II	Type of review question	Intervention
III	Objective of the review	Twin and triplet pregnancy is associated with an increased risk of PPH. This review aims to address the uncertainty around the optimal management of the third stage of labour in twin and triplet pregnancy to prevent PPH
IV	Eligibility criteria – population/disease/condition/issue/domain	All women confirmed as having a twin or triplet pregnancy by the 11–13-week ultrasound scan and carried to ≥24 weeks of pregnancy and all fetuses confirmed alive and who are in the third stage of labour **Setting**: any setting
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Vaginal birth:** • physiological management of third stage • active management plus additional uterotonics, e.g. further oxytocin (by infusion), longer acting oxytocin, carboprost, misoprostol, ergometrine (as defined in studies) **Caesarean section:** • active management plus additional uterotonics, e.g. further oxytocin (by infusion), longer acting oxytocin, carboprost, misoprostol, ergometrine (as defined in studies)
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Vaginal birth:** • active management of third stage: ○ administration of 10 IU of oxytocin by intramuscular injection with the birth of the anterior shoulder or immediately after the birth of the baby and before the cord is clamped and cut **Caesarean section:** • active management of third stage: ○ administration of 10 IU of oxytocin by IV injection with the birth of the anterior shoulder or immediately after the birth of the baby and before the cord is clamped and cut
VII	Outcomes and prioritisation	**Critical** For the woman: • mortality • PPH (blood loss > 1000ml) • hysterectomy **Important** For the woman:

ID	Field (based on PRISMA-P)	Content
		• side effects of drugs (e.g. change in blood pressure, headache, nausea/vomiting) • need for further intervention (e.g. additional uterotonics, manual removal of placenta, blood transfusion, balloon tamponade) • need for intensive care unit or high dependency unit • women's satisfaction/experience of labour and birth
VIII	Eligibility criteria – study design	Systematic reviews of randomised controlled trials (RCTs) for twin and triplet pregnancy Randomised controlled trials If insufficient trial evidence is available for each comparison: Cohort studies for triplets (prospective cohort studies will be prioritised over retrospective) Conference abstracts will not be considered
IX	Other inclusion exclusion criteria	Exclusions: • women with a quadruplet or higher-order pregnancy as per scope • women with known serious fetal anomaly • studies that do not report results specifically for twin and/or triplet pregnancies • studies that include <5 pregnancies • women with placenta praevia or morbidly adherent placenta (accreta, increta, percreta) • women with medical bleeding disorders • women with fibroids
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • Twin pregnancy • Triplet pregnancy • Vaginal birth • Caesarean section The following groups will used to explore any significant heterogeneity identified: • parity • previous caesarean section • previous PPH
XI	Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question (as it has not been prioritised for economic analysis), although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair
XII	Data management (software)	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists. Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5).

ID	Field (based on PRISMA-P)	Content
		'GRADEpro' will be used to assess the quality of evidence for each outcome. A full description of this is provided in the methods in supplementary material C.
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Search limits: • Limit to English language • Limit to human-only studies No limit on study design No limit year of publication Limit to randomised controlled trials (RCTs) and systematic reviews in first instance but download all results.
XIV	Identify if an update	This is a new area in the guideline.
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014 For details please see appendix B.
XVII	Search strategy – for one database	For details please see appendix B.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables)
XX	Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews, • Cochrane risk of bias for RCTs • Newcastle-Ottawa scale for cohort studies For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence was 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/
XXI	Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
XXII	Methods for analysis – combining studies and exploring (in)consistency	A full description of this is provided in the methods in supplementary material C.

ID	Field (based on PRISMA-P)	Content
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Anthony Pearson in line with section 3 of Developing NICE guidelines: the manual 2014 Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. A full description of this is provided in the methods in supplementary material C.
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register for Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IU: international unit; IV: intravenous; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence

Appendix B – Literature search strategies

Literature search for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Clinical Searches

Date of initial search: 26/03/2018

Database(s): Embase Classic+Embase 1947 to 2018 March 23, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 11/09/2018

Database(s): Embase Classic+Embase 1947 to 2018 September 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emczd
3	((dizygotic or monozygotic or multiple or triplet* or trizygotic or twin) adj3 (birth* or f?etus* or f?etal or gestation* or pregnan*)).tw.
4	(chorionicity or dichorionic or monochorionic or trichorionic).tw.
5	or/1-4
6	((active management or expectant management or physiological management or natural) adj3 ("3rd stage" or "stage 3" or third stage)).tw.
7	(EMTSL or AMTSL).tw.
8	((placenta* or afterbirth) adj3 (separat* or expulsion or expel* or extract* or remov* or push* or pull* or maternal effort)).tw.
9	Oxytocics/ use ppez or Oxytocin/ use ppez or oxytocic agent/ use emczd
10	exp Uterotonic agent/ use emczd
11	exp ergot alkaloids/ppez or ergonovine/ use ppez or ergot alkaloid/ use emczd
12	Misoprostol/ use ppez or Carboprost/ use ppez or carboprost/ use emczd or misoprostol/ use emczd
13	(carboprost* or ergometrin* or ergonovin* or ergot alkaloid* or misoprostol* or oxytoci* or uterotonic*).tw.
14	(cord clamping or cord-clamping or cordclamping or cord traction or cord cutting).tw.
15	Postpartum Hemorrhage/pc use ppez or postpartum hemorrhage/pc use emczd
16	((postpartu* or post partu* or excessive or high or severe) adj3 (blood* or bleed* or haemorrhag* or hemorrhag*) adj3 prevent*).tw.
17	or/6-16
18	5 and 17
19	Letter/ use ppez
20	letter.pt. or letter/ use emczd
21	note.pt.
22	editorial.pt.
23	Editorial/ use ppez
24	News/ use ppez
25	exp Historical Article/ use ppez
26	Anecdotes as Topic/ use ppez
27	Comment/ use ppez
28	Case Report/ use ppez
29	case report/ or case study/ use emczd
30	(letter or comment*).ti.
31	or/19-30
32	randomized controlled trial/ use ppez
33	randomized controlled trial/ use emczd
34	random*.ti,ab.
35	or/32-34
36	31 not 35
37	animals/ not humans/ use ppez
38	animal/ not human/ use emczd
39	nonhuman/ use emczd
40	exp Animals, Laboratory/ use ppez
41	exp Animal Experimentation/ use ppez

#	Searches
42	exp Animal Experiment/ use emczd
43	exp Experimental Animal/ use emczd
44	exp Models, Animal/ use ppez
45	animal model/ use emczd
46	exp Rodentia/ use ppez
47	exp Rodent/ use emczd
48	(rat or rats or mouse or mice).ti.
49	or/36-48
50	18 not 49
51	limit 50 to english language
52	remove duplicates from 51

Date of initial search: 26/03/2018

Database(s): The Cochrane Library, issue 3 of 12, March 2018

Date of updated search: 11/09/2018

Database(s): The Cochrane Library, issue 9 of 12, September 2018

ID	Search
#1	MeSH descriptor: [Pregnancy, Multiple] explode all trees
#2	((dizygotic or monozygotic or multiple or triplet* or trizygotic or twin) near/3 (birth* or foetus* or foetal or fetus* or fetal or gestation* or pregnan*))
#3	(monochorionic* or dichorionic* or trichorionic*)
#4	{or #1-#3}
#5	((active management or expectant management or physiological management or natural) near/3 ("3rd stage" or "stage 3" or third stage))
#6	(EMTSL or AMTSL)
#7	((placenta* or afterbirth) near/3 (separat* or expulsion or expel* or extract* or push* or pull* or remov* or maternal effort))
#8	MeSH descriptor: [Oxytocics] this term only
#9	MeSH descriptor: [Oxytocin] this term only
#10	MeSH descriptor: [Ergot Alkaloids] explode all trees
#11	MeSH descriptor: [Misoprostol] this term only
#12	MeSH descriptor: [Carboprost] this term only
#13	(carboprost* or ergometrine* or ergonovine* or ergot alkaloids or misoprostol* or oxytoci* or uterotonic*)
#14	(cord clamping or cord-clamping or cordclamping or cord traction or cord cutting) .tw.
#15	MeSH descriptor: [Postpartum Hemorrhage] this term only and with qualifier(s): [Prevention & control - PC]
#16	((postpartu* or post partu* or excessive or high or severe) near/3 (blood* or bleed* or haemorrhag* or hemorrhag*) near/3 prevent*)
#17	{or #5-#16}
#18	#4 and #17

Health economics searches

For the Cochrane Library, see above

Date of initial search: 26/03/2018

Database(s): Embase Classic+Embase 1947 to 2018 March 23, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 11/09/2018

Database(s): Embase Classic+Embase 1947 to 2018 September 11, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

	Searches
1	exp Pregnancy, Multiple/ use ppez
2	exp multiple pregnancy/ use emczd

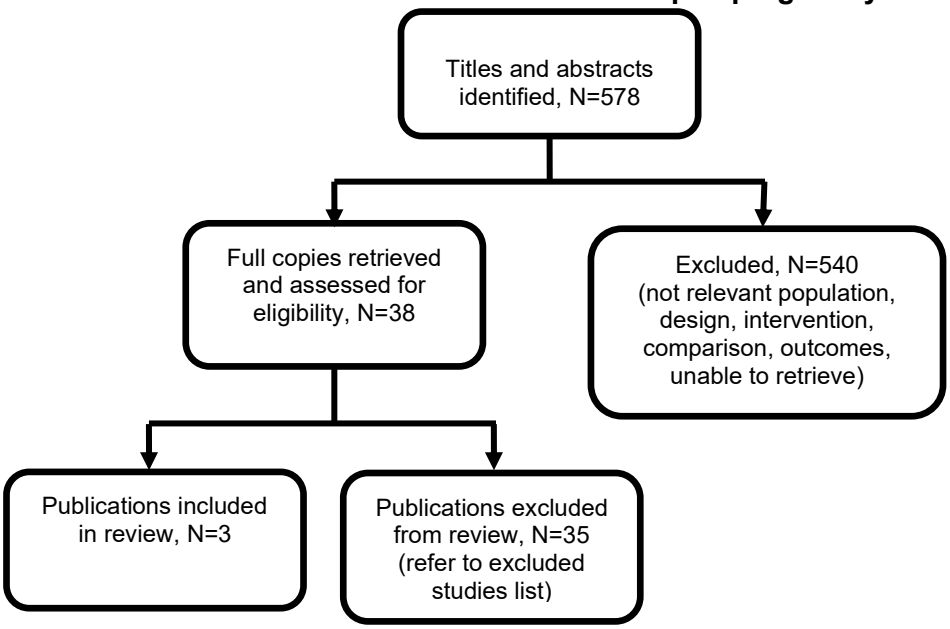
	Searches
3	((dizygotic or monozygotic or multiple or triplet* or trizygotic or twin) adj3 (birth* or f?etus* or f?etal or gestation* or pregnan*)).tw.
4	(chorionicity or dichorionic or monochorionic or trichorionic).tw.
5	or/1-4
6	((active management or expectant management or physiological management or natural) adj3 ("3rd stage" or "stage 3" or third stage)).tw.
7	(EMTSL or AMTSL).tw.
8	((placenta* or afterbirth) adj3 (separat* or expulsion or expel* or extract* or remov* or push* or pull* or maternal effort)).tw.
9	Oxytocics/ use ppez or Oxytocin/ use ppez or oxytocic agent/ use emczd
10	exp Uterotonic agent/ use emczd
11	exp ergot alkaloids/ppez or ergonovine/ use ppez or ergot alkaloid/ use emczd
12	Misoprostol/ use ppez or Carboprost/ use ppez or carboprost/ use emczd or misoprostol/ use emczd
13	(carboprost* or ergometrin* or ergonovin* or ergot alkaloid* or misoprostol* or oxytoci* or uterotonic*).tw.
14	(cord clamping or cord-clamping or cordclamping or cord traction or cord cutting).tw.
15	Postpartum Hemorrhage/pc use ppez or postpartum hemorrhage/pc use emczd
16	((postpartu* or post partu* or excessive or high or severe) adj3 (blood* or bleed* or haemorrhag* or hemorrhag*) adj3 prevent*).tw.
17	or/6-16
18	5 and 17
19	Letter/ use ppez
20	letter.pt. or letter/ use emczd
21	note.pt.
22	editorial.pt.
23	Editorial/ use ppez
24	News/ use ppez
25	exp Historical Article/ use ppez
26	Anecdotes as Topic/ use ppez
27	Comment/ use ppez
28	Case Report/ use ppez
29	case report/ or case study/ use emczd
30	(letter or comment*).ti.
31	or/19-30
32	randomized controlled trial/ use ppez
33	randomized controlled trial/ use emczd
34	random*.ti,ab.
35	or/32-34
36	31 not 35
37	animals/ not humans/ use ppez
38	animal/ not human/ use emczd
39	nonhuman/ use emczd
40	exp Animals, Laboratory/ use ppez
41	exp Animal Experimentation/ use ppez
42	exp Animal Experiment/ use emczd
43	exp Experimental Animal/ use emczd
44	exp Models, Animal/ use ppez
45	animal model/ use emczd
46	exp Rodentia/ use ppez
47	exp Rodent/ use emczd
48	(rat or rats or mouse or mice).ti.
49	or/36-48
50	18 not 49
51	limit 50 to english language
52	Economics/
53	Value of life/
54	exp "Costs and Cost Analysis"/
55	exp Economics, Hospital/
56	exp Economics, Medical/
57	Economics, Nursing/
58	Economics, Pharmaceutical/
59	exp "Fees and Charges"/
60	exp Budgets/
61	(or/52-60) use ppez
62	health economics/
63	exp economic evaluation/
64	exp health care cost/
65	exp fee/
66	budget/
67	funding/

	Searches
68	(or/62-67) use emczd
69	budget*.ti,ab.
70	cost*.ti.
71	(economic* or pharmaco?economic*).ti.
72	(price* or pricing*).ti,ab.
73	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
74	(financ* or fee or fees).ti,ab.
75	(value adj2 (money or monetary)).ti,ab.
76	or/69-74
77	61 or 68 or 76
78	51 and 77
79	remove duplicates from 78

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Figure 1: Flow diagram of clinical article selection for management of the third stage of labour to reduce PPH risk in twin and triplet pregnancy



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Demetz J, Clouqueur E , D'Haveloose A, Staelen P, Ducloy AS, Subtil ., Systematic use of carbetocin during cesarean delivery of multiple pregnancies: A before-and-after study, Archives of Gynecology and Obstetrics, 287, 875-880, 2013 **Ref Id** 932656 **Country/ies where the study was carried out** France	**Sample size** • Oxytocin (before group) n=24 (1 lost to follow up) • Carbetocin (after group) n=39 (of which n=27 treated as allocated; 0 lost to follow up) **Characteristics** • Using intention to treat (before: n=24, after n=39) • Maternal age: before: 31.6±4.3 years; after: 31.1±5.8 years • GA at birth: before: 35.3±2.5 weeks; after: 34.3±3.1 weeks • Triplet pregnancy: before n=0/48; after n=4/82 newborns (ITT 10.3% triplets) **Inclusion criteria**	**Interventions** **Oxytocin (before group):** at the delivery of the second child, a bolus of 10 units of oxytocin was administered by direct intravenous injection. In case of PPH, French national guidelines were applied and sulprostone administered in a maximal delay of 30 min, at an initial dosage of 250 microgram during first 20 minutes, then 250 microgram during 40 minutes, finally 500 lg during each successive 12 hours. Three hours after birth, according to hospital protocol, 10 units of oxytocin were systematically perfused for 12 hours **Carbetocin (after group):** patients received an ampoule of 100 microgram carbetocin (Pabal, Ferring, Kiel, Germany) by direct intravenous injection,	**Details** The analysis was conducted on an ''ITT'' basis, that is, patients who did not receive the planned treatment were nonetheless analysed in their group, according to period. The data collected during the two periods were recorded and analysed with Epi-info 6.4 software (Epi Info Software, Atlanta, GA, USA). In view of the number of study subjects, the comparisons used nonparametric tests: Fisher's test to compare percentages, Kruskal–Wallis test to compare means.	**Results** According to the protocol, 100% of the women during the before period received oxytocin (n = 24), but only 69% of the patients in the after period received carbetocin (n = 27); the others received oxytocin (31%). Results presented for ITT analysis and (PP) per protocol (received carbetocin as allocated). PPH: Blood loss (ml) Before: 800±790; after (ITT): 720±680; after (PP) 660±430	**Limitations** Quality assessment was done using the Newcastle Ottawa scale for cohort studies **SELECTION (4/4)** 1. Representativeness of exposed cohort (twin pregnancy undergoing C-section) somewhat representative (one group includes triplets) (1-star) 2. Selection of the non-exposed cohort (oxytocin/control) draw n from the same community (1-star) 3. Ascertainment of exposure secure record (1-star) 4. Demonstration that outcome of interest was not present at start of study yes (1-star)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Retrospective cohort (before and after protocol change) **Aim of the study** To evaluate the efficacy of carbetocin administered systematically during caesarean deliveries of multiple pregnancies **Study dates** Before: 6 months to 1 Feb 2010 (1 Aug 2009 - 31 Jan 2010) After: 6 months from 1 Feb 2010 (1 Feb 2010 - 31 July 2010) **Source of funding** Not reported	• Women with multiple pregnancy undergoing C-section (planned or emergency) at ≥22 weeks **Exclusion criteria** • Medical terminations	instead of oxytocin. The Protocol continued to call for injection of oxytocin by slow perfusion beginning 3 hours after delivery		<u>Blood transfusion required</u> Before: n-1/24; After (ITT) n=2/39; After (PP) n=1/27 <u>Emergency surgery required</u> Before: n=1/24; After (ITT) n=3/39; After (PP) n=1/27	**COMPARABILITY (1/2)** 1. Comparability of cohorts on the basis of the design or analysis controlled for confounders study compared baseline characteristics: age, nulliparity, use of assisted reproductive techniques, GA at birth; unequal regarding inclusion of triplet pregnancy in one group (1-star) **OUTCOME (3/3)** 1. Assessment of outcome record linkage (1-star) 2. Was follow up long enough for outcome to occur? Yes (1-star) 3. Adequacy of follow-up of cohorts n=1 woman lost to follow up in one (before) group ; less than 20%, unlikely to introduce bias (1-star) **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
One conflict: D. Subtil (author) is a member of the board of directors of the FERRING laboratory, which markets carbetocin in France (PABAL).					
Full citation Fahmy, NG, Yousef, HM, Zaki, HV. Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section, Egyptian Journal of Anaesthesia, 32 (1): 117-121, 2016	**Sample size** N=60 twin pregnancies • Control group (oxytocin): N=30 • Intervention (carbetocin): N=30 **Characteristics** • Maternal age: carbetocin: 25.4±4 years: oxytocin: 24.5±3 years • Previous C-section: carbetocin: median 2 IQR 1-3; oxytocin: 2 (2-2) • Birthweight: carbetocin: 2.4±0.34 kg; oxytocin: 3±0.3 kg **Inclusion criteria**	**Interventions** Intervention: (N=30) received 100 microgram carbetocin in 10 ml saline Control: (N=30) received 20 IU oxytocin in 10 ml of saline solution Whichever uterotonic drug was allocated, was injected slowly IV over one minute after delivery of babies. If uterine contraction score was less than 3 after 5 minutes, isoflurane concentration was decreased from 1 to 0.5. If still unsatisfactory additional uterotonics were administered as necessary (methylergometrine 100 IU). Patients who lost more than 1200 ml of	**Details** Pre-operative investigations in the form of ECG, complete blood picture, coagulation profile, liver and kidney functions were performed. A venous cannula 18G size was inserted and basic monitoring (ECG, pulse oximeter, NIBP) was applied. All patients underwent general anaesthesia; pre-oxygenation with 100% oxygen for 4 min then induction with intravenous thiopentone sodium 4–7 mg/kg, cisatracurium 0.5 mg/kg to facilitate endotracheal intubation (as all patients underwent elective C-section. and were fasting for at least 8 hours) and anaesthesia was maintained with oxygen (FiO2 0.4), isoflurane (MAC 1) and intermittent doses of cisatracurium. Lactated Ringer's	**Results** Carbetocin N=30 twin pregnancies; Oxytocin (control) N=30 twin pregnancies **Need for further intervention (blood transfusion)**: Carbetocin: N=1/30; Oxytocin: N=4/30; p<0.001 **Need for further intervention (additional uterotonics - methergine)**: Carbetocin; N=4/30; Oxytocin: N=15/30 (1 dose); N=10/30 (2 doses);	**Limitations** Quality assessment was done using the Cochrane Risk of Bias tool for RCTs **Selection bias: LOW** • **Random sequence generation** *Randomisation was performed using a computer-generated program (**LOW**)* • **Allocation concealment** *Both drugs were prepared preoperatively and coded so the working investigator and obstetrician were blinded to the drug injected (**LOW**)* **Performance bias: LOW**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Ref Id
743775
Country/ies where the study was carried out
Egypt
Study type
RCT
Aim of the study
To compare the effect of carbetocin and oxytocin on uterine contraction and though the use of other uterotonic drugs postoperative in multiple pregnancy patients undergoing elective C-section
Study dates
November 2012 – June 2013</td>
<td>• Acetylsalicyclic Acid (ASA) physical status I
• Aged 28–36 years
• Scheduled for elective C-section in study hospital
Exclusion criteria
• Women with hypertension, pre-eclampsia, cardiac, respiratory, renal or liver disease, pre-existing bleeding disorder such as haemophilia
• Women taking therapeutic anticoagulants, hypersensitivity to carbetocin or oxytocin.
• Women with preoperative haemoglobin less than 9.5 gm%
• Women pregnant with more than two babies</td>
<td>blood were prepared for blood transfusion to maintain hemodynamic and good tissue perfusion</td>
<td>solution was infused at a rate of 10–15 ml/kg.
Whichever uterotonic drug was allocated, was injected slowly IV over one minute after delivery of babies.
If uterine contraction score was less than 3 after 5 minutes, isoflurane concentration was decreased from 1 to 0.5. If still unsatisfactory additional uterotonics were administered as necessary (methylergometrine 100 IU). Patients who lost more than 1200 ml of blood were prepared for blood transfusion to maintain hemodynamic and good tissue perfusion</td>
<td>p<0.001
Side effect of drugs - change in blood pressure (mean arterial blood pressure): p<0.05 from 20 to 50 mins inclusive (fall in BP is not beneficial, stable BP is preferable)
<table>
<tr><th>Time</th><th>MABP (mmHg) carbetocin</th><th>MABP (mmHg) oxytocin</th></tr>
<tr><td>Baseline</td><td>71 ± 6.3</td><td>72.1 ± 4.8</td></tr>
<tr><td>5 min</td><td>69.6 ± 3.6</td><td>70 ± 3.4</td></tr>
<tr><td>10 min</td><td>75.8 ± 2.7</td><td>74.3 ± 4</td></tr>
<tr><td>15 min</td><td>75.2 ± 2.8</td><td>71 ± 2.3</td></tr>
</table>
</td>
<td>• Blinding of participants: no information – unlikely to be told if hospital staff did not know. Under general anaesthetic throughout procedure (LOW)
• Blinding of personnel: Both drugs were prepared preoperatively and coded so the working investigator and obstetrician were blinded to the drug injected (LOW)
Detection bias - Blinding of outcome assessment: information noted during procedure (LOW)
Attrition bias - Incomplete outcome data: Data presented for all women recruited, all treatment as allocated (LOW)
Reporting bias - Selective reporting: Protocol not available (UNCLEAR)
Other information
None</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported				20 min: 75 ± 2.6; 70 ± 3.8 25 min: 74 ± 2.4; 68.7 ± 3 30 min: 73.6 ± 2.4; 68.8 ± 2.3 35 min: 73 ± 2.4; 69.4 ± 5 40 min: 74 ± 1.8; 69.3 ± 4.8 50 min: 75 ± 4.7; 70.5 ± 3.7 60 min: 74.4 ± 5; 70.6 ± 2.2	
Full citation Sotillo, L., De la Calle, M., Magdaleno, F., Bartha, J. L., Efficacy of carbetocin for preventing postpartum bleeding after cesarean	**Sample size** N=166 twin pregnancies • Control group (oxytocin): N=80 • Intervention (carbetocin): N=86 **Characteristics** • Maternal age: carbetocin group	**Interventions** Intervention: carbetocin 100 mg IV in bolus during 1min after birth. If adequate uterine tone was not achieved, misoprostol or Methylergometrine was administered. Control: "C-section active management" oxytocin as uterotonic for the	**Details** Main variables were: • Intraoperative bleeding (estimated by the anaesthetist from the amount of blood collected in the aspirator and the number of compresses used during the intervention), • Surgical time (from the skin incision to the skin closure),	**Results** Carbetocin N=86 twin pregnancies*; oxytocin (control) N=80 twin pregnancies* **Need for further intervention** (any treatment - anaemia treatment and/or additional	**Limitations** Quality assessment was done using the Newcastle Ottawa scale for cohort studies **SELECTION (4/4)** • Representativeness of exposed cohort (twin pregnancy undergoing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
section in twin pregnancy, Journal of Maternal and Fetal Neonatal Medicine, 1-5, 2018 **Ref Id** 888911 **Country/ies where the study was carried out** Spain **Study type** Prospective observational (cohort) study **Aim of the study** To compare the effectiveness of carbetocin and oxytocin for prevention of PPH in twin pregnancies undergoing caesarean section **Study dates**	34.45±5.8 years; oxytocin group (control) 35.15±5.56 years • GA at birth: carbetocin 35.4±2.7 weeks; oxytocin 34.56±3.3 weeks • Chorionicity (n per subtype DCDA: MCDA: MCMA): carbetocin 63:15:1 twin pregnancies; oxytocin (control) 63:19:4 twin pregnancies • Elective C-section: carbetocin N=44 (55%); oxytocin N=40 (46.5%) **Inclusion criteria** • Patients older than 18 years, • Elective or nonelective C-section performed in twin gestations over 24 weeks • C-section performed through low segment hysterotomy,	prevention of PPH (standard protocol at the hospital included the administration, after birth, of 20 IU of oxytocin in Ringer lactate 500 ml in 10–15 minutes. If inadequate uterine tone, then either an extra dose of 10–20 IU of oxytocin or a maintaining oxytocin serum with 20 IU during the first hour were given)	• Haemoglobin fall, • Haematocrit drop, • Additional uterotonic use (methylergometrine and/or isoprostol), • Need for blood transfusion, • IV iron therapy. Composite variable (to assess the possible differences in efficacy between oxytocin and carbetocin): • The proportion of patients who needed additional treatments during the postpartum period, • Understanding as such the need for additional uterotonic (methylergometrine and/or misoprostol) • The need for treatment for anaemia (IV iron therapy and/or blood transfusion	uterotonics agents): Carbetocin N=6/86 (7.5%); Oxytocin N=17/80 (19.8%); p=0.02 • **Additional uterotonics: carbetocin** N=3/86 (3.8%); oxytocin N=7/80 (8.1%); p=0.23 • **Blood transfusion**: carbetocin N=1/86 (1.3%); oxytocin N=8/80 (9.3%); p=0.03 *All results here as presented in the study paper - though calculations suggest that participant number may have been reported the wrong way around (N=86 in oxytocin group and not the carbetocin group as reported; and N=80 in the carbetocin group	C-section) truly representative (1-star) • Selection of the non-exposed cohort (oxytocin/control) drawn from the same community (1 star) • Ascertainment of exposure secure record (1 star) • Demonstration that outcome of interest was not present at start of study? Yes (1 star) **COMPARABILITY (2/2)** Comparability of cohorts on the basis of the design or analysis controlled for confounders study compared baseline characteristics: age, parity, chorionicity, GA at birth (2-stars) **OUTCOME (3/3)** • Assessment of outcome record linkage (1-star) • Was follow up long enough for outcome to occur? Yes (1-star) • Adequacy of follow-up of cohorts complete follow up - all subjects

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 2010 - December 2013 **Source of funding** Not reported	• Absence of maternal contraindications for the use of carbetocin (serious cardiovascular disorders, liver or kidney failure, and/or eclampsia) • C-section under epidural or spinal anaesthesia **Exclusion criteria** • Treatment with blood products prior to the end of pregnancy, • Severe fetal malformations, • Fetoscopy during the course of pregnancy, • HELLP syndrome or eclampsia, • Transverse incision of the uterine isthmus with an inverted T-extension and general anaesthesia			and not oxytocin as reported)	accounted for, though reporting of data seems confused* (1-star) **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** *All results here as presented in the study paper - though calculations suggest that participant number may have been reported the wrong way around (N=86 in oxytocin group and not the carbetocin group as reported; and N=80 in the carbetocin group and not oxytocin as reported) **Other information** None

ASA: acetylsalicylic; C-section: Caesarean section; DCDA; dichorionic diamniotic; ECG: electrocardiogram; GA: gestational age; HELLP: hemolysis, elevated liver enzymes, and a low platelet count; IQR: interquartile range; ITT: intention to treat; IU: international units; IV: intravenous; MCDA: monochorionic diamniotic; MCMA: monochorionic monoamniotic; NIBP: non-invasive measurement of blood pressure; PP: per protocol; RCT: randomised controlled trial

Appendix E – Forest plots

Forest plots for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

No meta-analysis was undertaken for this review and so there are no forest plots.

Appendix F – GRADE tables

Grade profile for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Table 4: Comparison: carbetocin versus oxytocin for active management of twin pregnancy in women undergoing caesarean section, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CAR (IG)	OXY (CG)	Relative (95% CI)	Absolute	Quality	Importance
Postpartum haemorrhage (blood loss, ml)												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	39	24	-	MD 140 less (484 less to 204 more)	VERY LOW ⨁⊖⊖⊖	CRITICAL
Side effects of drugs – change in mean arterial blood pressure over time (fall in BP is not beneficial: stable or higher BP is preferable to lower BP)												
1 Baseline (0 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	30	30	-	MD 1.10 lower (3.93 lower to 1.73 higher)	⨁⨁⨁⊖ MODERATE	IMPORTANT
1 (5 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	30	30	-	MD 0.40 lower (2.17 lower to 1.37 higher)	⨁⨁⨁⊖ MODERATE	IMPORTANT
1 (10 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	30	30	-	MD 1.50 higher (0.23 lower to 3.23 higher)	⨁⨁⨁⊖ MODERATE	IMPORTANT

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CAR (IG)	OXY (CG)	Relative (95% CI)	Absolute		
1 (15 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 4.20 higher (2.90 to 5.50 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
1 (20 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 5.00 higher (3.35 to 6.65 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
1 (25 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 5.30 higher (3.93 to 6.67 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
1 (30 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 4.8 higher (3.61 to 5.99 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
1 (35 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	30	30	-	MD 3.60 higher (1.62 to 5.58 higher)	⨁⨁⨁⊖ MODERATE	IMPORTANT
1 (40 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 4.70 higher (2.87 to 6.53 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CAR (IG)**	**OXY (CG)**	**Relative (95% CI)**	**Absolute**		
1 (50 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 4.50 higher (2.36 to 6.64 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
1 (60 mins)	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30	30	-	MD 3.80 higher (1.85 to 5.75 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Need for further treatment (any: anaemia treatment and/or additional uterotonic agents)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[4]	None	6/86 (7%)	17/80 (21.3%)	RR 0.33 (0.14 to 0.79)	142 fewer per 1000 (from 45 fewer to 183 fewer)	⨁⨁⨀⨀ LOW	IMPORTANT
Need for additional uterotonic agents												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4,5]	None	3/86 (3.5%)	7/80 (8.8%)	RR 0.4 (0.11 to 1.49)	52 fewer per 1000 (from 78 fewer to 43 more)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/30 (13.3%)	15/30 (50%)[6]	RR 0.27 (0.10 to 0.71)	365 fewer per 1000 (from 145 fewer to 450 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CAR (IG)	OXY (CG)	Relative (95% CI)	Absolute	Quality	Importance
Blood transfusion												
1	Observational studies	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	Serious[7]	None	1/86 (1.2%)	8/80 (10%)	RR 0.12 (0.01 to 0.91)	88 fewer per 1000 (from 9 fewer to 99 fewer)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious[1]	Very serious[5]	None	2/39 (5.1%)	1/24 (4.2%)	RR 1.23 (0.12 to 12.85)	10 more per 1000 (37 fewer to 494 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/30 (3.3%)	4/30 (13.3%)	RR 0.25 (0.03 to 2.11)	100 fewer per 1000 (from 129 fewer to 148 more)	⨁⨁⊖⊖ LOW	IMPORTANT
Additional treatments required - emergency surgery												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious[1]	Very serious[5]	None	3/39 (7.7%)	1/24 (4.2%)	RR 1.85 (0.20 to 16.25)	35 more per 1000 (33 fewer to 656 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CAR: carbetocin; CG: control group; CI: confidence interval; IG: intervention group; MID: minimal important difference; Mins: minutes; OXY: oxytocin; PPH: postpartum haemorrhage; RCT: randomised controlled trial; RR: risk ratio

1 The quality of the evidence was downgraded by 1 level for indirectness as one group included 10% triplets (as reported in the study)

2 The quality of the evidence was downgraded by 1 level because the 95% CI crosses the lower MID threshold as calculated for continuous variables

3 The quality of the evidence was downgraded by 1 level because the 95% CI crosses the upper MID threshold as calculated for continuous variables

4 All results here as presented in the study paper - though calculations suggest that N may have been reported the wrong way around (N=86 in oxytocin group and not the carbetocin group as reported; and N=80 in the carbetocin group and not oxytocin as reported)

5 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)

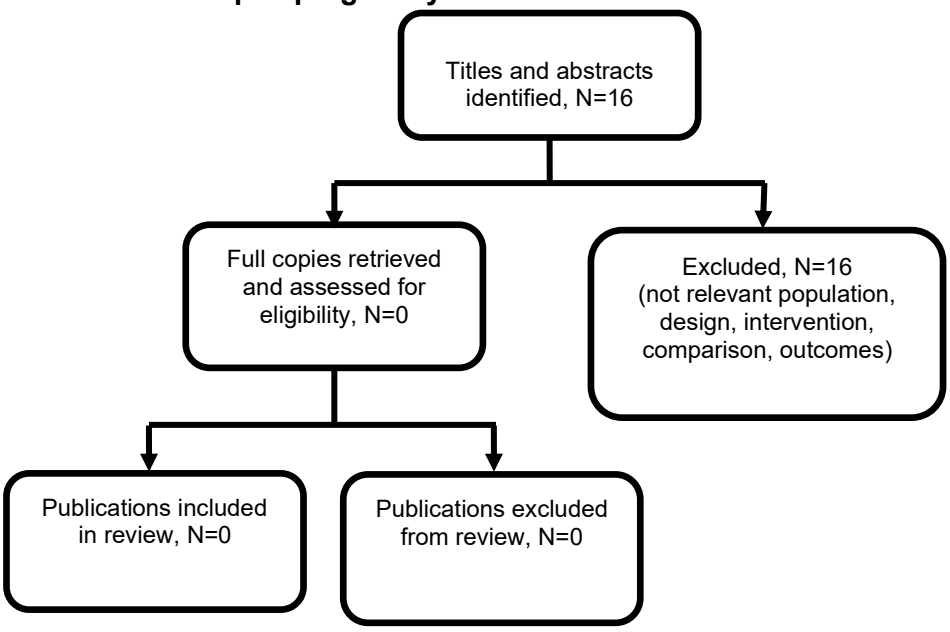
6 Data for number of women requiring one dose of methergine. Data also available for those requiring 2 doses of oxytocin: N=10/30 (33.3%)

7 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Figure 2: Flow diagram of economic article selection for the optimal managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

No economic analysis was identified for this review.

Appendix K – Excluded studies

Excluded studies for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

Clinical studies

Study	Reason for Exclusion
Amaya, S., Mattox, J., Tussey, C., Kang, P., Evaluating severity of postpartum hemorrhage retrospectively based on risk factors, Obstetrics and Gynecology, 129, 113S-114S, 2017	Abstract only
Anorlu, Rose I, Maholwana, Babalwa, Hofmeyr, G Justus, Methods of delivering the placenta at caesarean section, Cochrane Database of Systematic Reviews, 2008	Comparison is not relevant to the protocol
Bayoumeu,F., Baka,N.E., Fresson,J., Monnier-Barbarino,P., Do prophylactic prostaglandins reduce the transfusion rate at cesarean section in high-order multiple pregnancies?, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 111, 38-42, 2003	Comparison is not relevant to the protocol
Begley, Cecily M, Gyte, Gillian Ml, Devane, Declan, McGuire, William, Weeks, Andrew, Active versus expectant management for women in the third stage of labour, Cochrane Database of Systematic Reviews, 2015	Results are not presented for twin or triplet pregnancies
Bombelli, F. M., Cavoretto, P., di Piazza, L., Valentini, G., Convenient use of carbetocin during 70 elective cae- sarean deliveries, Italian Journal of Gynaecology and Obstetrics, 23, 83-89, 2011	Article in Italian
Bullough, C. H, Msuku, R. S, Karonde, L., Early suckling and postpartum haemorrhage: controlled trial in deliveries by traditional birth attendants, Lancet, 2, 522-5, 1989	Comparison is not relevant to the protocol
Campbell, D., A review of maternal complications of multiple pregnancy, Twin ResearchTwin Res, 4, 146-9, 2001	Narrative review
Dahlke, J. D., Mendez-Figueroa, H., Maggio, L., Hauspurg, A. K., Sperling, J. D., Chauhan, S. P., Rouse, D. J., Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines, American Journal of Obstetrics & Gynecology, 213, 76.e1-10, 2015	No relevant results are presented for twin or triplet pregnancies
de Groot, A. N., Prevention of postpartum haemorrhage, Baillieres Clinical Obstetrics & Gynaecology, 9, 619-31, 1995	Narrative review
Demetz,J, Clouqueur,E, D'Haveloose,A, Staelen,P, Ducloy,A.S, Subtil,D., Systematic use of carbetocin during cesarean delivery of multiple pregnancies: a before-and-after study.[Erratum appears in Arch Gynecol Obstet. 2013 Jul;288(1):235 Note: Julie, Demetz [corrected to Demetz, Julie]; Elodie, Clouqueur [corrected to Clouqueur, Elodie]; Anne, D'Haveloose [corrected to D'Haveloose, Anne];	Comparison is not relevant to the protocol

Study	Reason for Exclusion
Pauline, Staelen [corrected to Staelen, Pauline]; Anne-sophie, Ducloy [corrected to Ducloy, Anne-Sophie]; Damien, Subtil [corrected to Subtil, Damien]], Archives of Gynecology and Obstetrics, 287, 875-880, 2013	
Foley, A., Gunter, A., Nunes, K. J., Shahul, S., Scavone, B. M., Patients Undergoing Cesarean Delivery After Exposure to Oxytocin During Labor Require Higher Postpartum Oxytocin Doses, Anesthesia & AnalgesiaAnesth Analg, 126, 920-924, 2018	Non relevant population
Gallos, ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, Williams MJ, Diaz V, Pasquale J, Chamillard M, Widmer M, Tunçalp Ö, Hofmeyr GJ, Althabe F, Gülmezoglu AM, Vogel JP, Oladapo OT, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis, Cochrane Database of Systematic Reviews, 2018	Systematic review. Includes singletons and twins, does not present data separately. Included one study of twins only, assessed for inclusion
Hofmeyr, G Justus, Gülmezoglu, A Metin, Novikova, Natalia, Lawrie, Theresa A, Postpartum misoprostol for preventing maternal mortality and morbidity, Cochrane Database of Systematic Reviews, 2013	Results are not presented for twin or triplet pregnancies
Hofmeyr, G Justus, Mshweshwe, Nolundi T, Gülmezoglu, A Metin, Controlled cord traction for the third stage of labour, Cochrane Database of Systematic Reviews, 2015	Results are not presented for twin or triplet pregnancies
Liabsuetrakul, Tippawan, Choobun, Thanapan, Peeyananjarassri, Krantarat, Islam, Q Monir, Prophylactic use of ergot alkaloids in the third stage of labour, Cochrane Database of Systematic Reviews, 2007	Results are not presented for twin or triplet pregnancies
Liabsuetrakul, Tippawan, Choobun, Thanapan, Peeyananjarassri, Krantarat, Islam, Q Monir, Prophylactic use of ergot alkaloids in the third stage of labour, Cochrane Database of Systematic Reviews, 2018	Includes any pregnancy expecting vaginal birth - no information on singleton/multiple pregnancies. Only one study listed mentions multiple gestation (as an exclusion criteria)
McDonald, Susan J, Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour, Cochrane Database of Systematic Reviews, 2004	Results are not presented for twin or triplet pregnancies
McDonald, Susan J, Middleton, Philippa, Dowswell, Therese, Morris, Peter S, Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes, Cochrane Database of Systematic Reviews, 2013	RCTs including women with multiple pregnancies excluded from review
Mikhailov, A., Shman, V., Kuznetsov, A., Romanovsky, A., Shlykova, A., Prevention and management of pph in multiple pregnancy, Twin Research and Human Genetics, 20 (6), 636, 2017	Abstract only
Mori, Rintaro, Nardin, Juan Manuel, Yamamoto, Naoko, Carroli, Guillermo, Weeks, Andrew, Umbilical vein injection for the routine	Results are not presented separately for twin or triplet pregnancy

Study	Reason for Exclusion
management of third stage of labour, Cochrane Database of Systematic Reviews, 2012	
Munn, M. B., Owen, J., Vincent, R., Wakefield, M., Chestnut, D. H., Hauth, J. C., Hofmeyr, G. J., Gulmezoglu, A. M., A higher dose of oxytocin was more effective than a standard dose, when infused over 30 min, in preventing uterine atony after cesarean delivery, Evidence-based Obstetrics and Gynecology, 4, 120-121, 2002	Only 6% were multiple pregnancies
Neimand,K.M, Gibstein,A, Rosenthal,A.H., Oxytocin in twin gestation, American Journal of Obstetrics and Gynecology, 99, 533-538, 1967	Comparison is not relevant to the protocol
Novikova, Natalia, Hofmeyr, G Justus, Cluver, Catherine, Tranexamic acid for preventing postpartum haemorrhage, Cochrane Database of Systematic Reviews, 2015	RCTs including women with multiple pregnancies excluded from review
Pearson, G. A., Pepper, W., Russell, R., MacKenzie, I. Z., Retrospective study to investigate the possible relationship between excess blood loss at caesarean section and reduced intra-operative oxytocin dose, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 196, 31-7, 2016	No relevant results are presented for twin or triplet pregnancies
Rabe, Heike, Diaz-Rossello, Jose Luis, Duley, Lelia, Dowswell, Therese, Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes, Cochrane Database of Systematic Reviews, 2012	Results are not presented separately for twin or triplet pregnancy
Rossen,J., Okland,I., Nilsen,O.B., Eggebo,T.M., Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions?, Acta Obstetricia et Gynecologica Scandinavica, 89, 1248-1255, 2010	No relevant results are presented for twin or triplet pregnancies
Ruangkit, C., Leon, M., Hassen, K., Baker, K., Poeltler, D., Katheria, A., Maternal bleeding complications following early versus delayed umbilical cord clamping in multiple pregnancies, BMC Pregnancy and Childbirth, 18 (1) (no pagination), 2018	Early versus delayed cord clamping - timing of clamping is not included in the protocol
Ruangkit, C., Moroney, V., Viswanathan, S., Bhola, M., Safety and efficacy of delayed umbilical cord clamping in multiple and singleton premature infants - A quality improvement study, Journal of Neonatal-Perinatal Medicine, 8, 393-402, 2015	No relevant results are presented for twin or triplet pregnancies
Saviron-Cornudella, R., Esteban, L. M., Laborda-Gotor, R., Rodriguez-Solanilla, B., De Mucio, B., Sanz, G., Castan-Mateo, S., Maternal morbidity after implementation of a postpartum hemorrhage protocol including use of misoprostol, International Journal of Gynecology and Obstetrics, 140, 198-204, 2018	Cannot separate data for singleton and multiple pregnancies - only outcome available for multiples is haemoglobin(Hb) (not in protocol)
Sayed, W. E., Shirol, V., Kirkpatrick, A., Audit on the use of carbetocin for prevention of	Poster abstract - cost effectiveness analysis of carbetocin in UK

Study	Reason for Exclusion
postpartum haemorrhage, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 24-25, 2014	
Sheldon,W.R., Durocher,J., Winikoff,B., Blum,J., Trussell,J., How effective are the components of active management of the third stage of labor?, BMC Pregnancy and Childbirth, 13, 46-, 2013	No relevant results are presented for twin or triplet pregnancies
Su, Lin-Lin, Chong, Yap-Seng, Samuel, Miny, Carbetocin for preventing postpartum haemorrhage, Cochrane Database of Systematic Reviews, 2012	Results are not presented for twin and triplet pregnancies
Tunçalp, Özge, Hofmeyr, G Justus, Gülmezoglu, A Metin, Prostaglandins for preventing postpartum haemorrhage, Cochrane Database of Systematic Reviews, 2012	No relevant results are presented for twin or triplet pregnancies
Westhoff, Gina, Cotter, Amanda M, Tolosa, Jorge E, Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage, Cochrane Database of Systematic Reviews, 2013	No relevant results are presented for twin or triplet pregnancies
Wu, Lf, Liu, Y, Ruan, Y, Clinical study on prevention of postpartum hemorrhage of cesarean section using hemabat in high risk pregnant women, Zhonghua fu chan ke za zhi, 42, 577-581, 2007	File sent from British Library inaccessible (a full-text copy of the article could not be obtained)

Economic studies

No health economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is for the optimal method of managing the third stage of labour to reduce the risk of postpartum haemorrhage (PPH) in twin and triplet pregnancy?

No research recommendation was made for this review.