National Institute for Health and Care Excellence

Final

Twin and triplet pregnancy

[H] Evidence review for the optimal method of analgesia and anaesthesia during labour and birth

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3513-0

Contents

Intrapartum care: analgesia and anaesthesia

Review question

What is the optimal method of analgesia and anaesthesia during labour and birth in twin and triplet pregnancy?

Introduction

This review compares the use of analgesic techniques, during attempted vaginal birth in twin and triplet pregnancy. This information can be used to address the uncertainty around different methods of analgesia for labour in these pregnancies and to enhance woman- and family-centred decision-making.

Summary of the protocol

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

Table 1: Summary of the protocol (Population, Intervention, Comparison and Outcome [PICO])

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 with all fetuses confirmed alive. All women planning a vaginal birth and in established labour. Setting: hospital
Intervention	• Analgesic techniques: ○ central/regional neuraxial analgesia/anaesthesia (spinal, epidural, combined spinal epidural) • Inhalational analgesia (Entonox® [medical nitrous oxide and oxygen mixture]; referred to as Entonox® hereafter) • Intravenous and intramuscular opioids (pethidine, morphine, diamorphine and remifentanil) • Non-pharmacological analgesic techniques (Transcutaneous Electrical Nerve Stimulation, birthing pools, hypnobirthing)
Comparison	• No intervention versus each of the above classes • Any of the above classes versus another class

Outcomes	<u>Critical outcomes:</u>
	• For the woman:
	  ○ pain (validated scales)
	  ○ conversion to general anaesthesia for any operative intervention
	• For the baby:
	  ○ major neonatal morbidities (hypoxic ischaemic encephalopathy, cerebral palsy/ neurodevelopmental disability / developmental delay, neonatal seizures, meconium aspiration syndrome, fetal trauma, respiratory depression)
	<u>Important outcomes:</u>
	• For the woman:

	○ mode of birth ○ women's satisfaction/experience of labour and birth ○ mortality • For the baby: ○ Mortality

For full 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 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 retrospective cohort studies (Ogbonna 1986; Weekes 1977; Williams 2003) concerning twin pregnancy were included in this review.

Evidence was identified for the comparisons of analgesia versus no analgesia, continuous lumbar epidural analgesia versus parenteral analgesia and epidural analgesia versus pethidine or nitrous oxide. There was no evidence identified for the non-pharmacological analgesic technique (TENS, birthing pools, hypnobirthing) interventions.

Evidence was identified for 2 important outcomes. One was maternal, mode of birth, and the other was neonatal, perinatal mortality.

No evidence was available for the critical maternal outcomes of pain and conversion to general anaesthesia for any operative intervention, nor for the critical neonatal outcomes of major morbidities (including hypoxic ischaemic encephalopathy, cerebral palsy, neurodevelopmental disability, developmental delay, neonatal seizures, meconium aspiration syndrome, fetal trauma, respiratory depression). Neither was evidence found for the important maternal outcomes of women's satisfaction/experience of labour and birth and mortality.

No evidence was identified for triplet pregnancy.

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 tables in appendix F.

Excluded studies

Studies not included in this review with reasons for their exclusions 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/ Comparison	Outcomes	Comments
Ogbonna 1986 Retrospective cohort UK	N=64 women with twin pregnancy who had VB. n=34/64 (53%) received epidural analgesia, n=30/64 (47%) received other analgesia	Epidural analgesia versus pethidine or nitrous oxide	For the woman: • mode of birth	Epidural analgesia defined as bupivacaine hydrochloride, without adrenaline, 0.25%, 0.5% or 0.375%; n=25 mothers received between 4 and 8 ml of 0.5%, n=2 mothers received between 8 and 14 ml of 0.375%, and n=7 mothers received between 8 and 15 ml of 0.25% bupivacaine. Pethidine or nitrous oxide defined as either pethidine in doses of 100 or 150 mg not more often than 4-hourly, or nitrous oxide and oxygen by face mask, as Entonox®
Weekes 1977 Retrospective cohort UK	N=142 women with twin pregnancy eligible for VB. n=50/142 (35%) received lumbar epidural analgesia, n=92/142 (65%) received parenteral analgesia	Continuous lumbar epidural analgesia versus pethidine and promethazine as required and supplementary Entonox® (parenteral analgesia)	For the woman: • mode of birth For the baby: • perinatal mortality (not defined)	Epidural analgesia defined as bupivacaine 0.5% with adrenaline 1/400 000. An initial test dose of 2 ml was given, and incremental doses of 4 ml were then given as required; 6 ml was administered in the sitting position when the cervix was fully dilated and the presenting part visible. Parenteral analgesia defined as analgesia provided during labour by pethidine 150 mg and promethazine hydrochloride 25 mg as required, supplemented by nitrous oxide and oxygen (Entonox®). N=10 women in this group required a general anaesthetic to expedite the birth of the second twin
Williams 2003 Retrospective cohort USA	N=927 women with twin pregnancy eligible for VB. n=689/927 (74%) had epidural analgesia, n=238/927 (26%) had no epidural analgesia	Epidural analgesia versus no epidural analgesia	For the woman: • mode of birth	No definition of epidural analgesia was given

VB: vaginal birth

See appendix D for the full evidence tables.

Quality assessment of clinical studies included in the evidence review

The evidence for this review question is presented in Table 3 and Table 4, and in appendix F. All studies were observational.

The quality of the evidence regarding the mode of birth outcome from studies by Weekes 1977 and Ogbona 1986 was assessed using risk of bias. This was done because no data was presented that showed the numbers of women who gave birth via vaginal birth or caesarean section for both twins, for example vaginal birth for the first twin and caesarean section for the second twin which would be needed to calculate a risk ratio.

The mode of birth outcome using data from the Williams 2003 studies was evaluated and presented using GRADE. The evidence regarding neonatal/perinatal mortality was also evaluated and presented using GRADE.

See appendix F for the GRADE tables.

Table 3: Comparison: continuous lumbar epidural analgesia versus parenteral analgesia for mode of birth for twin pregnancy, outcomes for the woman

Outcome	No of women (studies)	% of women		RoB
		Continuous lumbar epidural analgesia	Parenteral analgesia	
First twin				
Spontaneous vertex (Weekes 1977)	142 (1)	40%	48.9%	Very serious[1]
Forceps (Weekes 1977)	142 (1)	40%	35.9%	Very serious[1]
Assisted breech (Weekes 1977)	142 (1)	18%	14.1%	Very serious[1]
Breech extraction (Weekes 1977)	142 (1)	2%	1.1%	Very serious[1]
Internal version and breech extraction (Weekes 1977)	142 (1)	0%	0%	Very serious[1]
Second twin				
Spontaneous vertex (Weekes 1977)	142 (1)	28%	19.6%	Very serious[1]
Forceps (Weekes 1977)	142 (1)	18%	34.8%	Very serious[1]
Assisted breech (Weekes 1977)	142 (1)	28%	26.1%	Very serious[1]
Breech extraction (Weekes 1977)	142 (1)	24%	8.7%	Very serious[1]
Internal version and breech extraction (Weekes 1977)	142 (1)	2%	10.9%	Very serious[1]

RoB: risk of bias
1 Unclear risk of selection bias; unclear risk of outcome bias; high risk of comparability bias as the study does not control for any factor

Table 4: Comparison: epidural analgesia versus Pethidine or nitrous oxide for mode of birth for twin pregnancy, outcomes for the woman

Outcome	No of women (studies)	% of women		RoB
		Epidural analgesia	Pethidine or nitrous oxide	
First twin				
Normal vaginal birth (Ogbonna 1986)	64 (1)	52.9%	90%	Very serious[1]
Forceps (Ogbonna 1986)	64 (1)	38.2%	3.3%	Very serious[1]
Breech (Ogbonna 1986)	64 (1)	8.8%	6.7%	Very serious[1]
Second twin				
Normal vaginal birth (Ogbonna 1986)	64 (1)	29.4%	56.7%	Very serious[1]
Forceps (Ogbonna 1986)	64 (1)	32.4%	3.3%	Very serious[1]
Ventouse (Ogbonna 1986)	64 (1)	5.9%	Not reported	Very serious[1]
Caesarean section (for transverse lie) (Ogbonna 1986)	64 (1)	2.9%	Not reported	Very serious[1]
Breech (Ogbonna 1986)	64 (1)	29.4%	40%	Very serious[1]

RoB: risk of bias
1 Unclear risk of selection bias; unclear risk of outcome bias; high risk of comparability bias as the study does not control for any factor

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

Comparison 1: analgesia versus no analgesia

Outcomes for the woman

Mode of birth

Caesarean section for both twins

Very low quality evidence from 1 study in women with twin pregnancy (N=927) showed a clinically important difference in the mode of birth with the incidence of caesarean section for both twins being higher in women who had no analgesia (control).

Vaginal birth for first twin and caesarean section for second twin

Very low quality evidence from 1 study in women with twin pregnancy (N=927) showed a clinically important difference in the mode of birth with the incidence of vaginal birth for the first twin and caesarean section for the second twin being higher in women who had no analgesia(control) .

Comparison 2: continuous lumbar epidural analgesia versus parenteral analgesia

Outcomes for the woman

Mode of birth

This section contains only descriptive information on the outcome mode of birth as there were no data reported in the paper to calculate relative risks.

One study with high risk of bias of women with twin pregnancy who were eligible for vaginal birth (N=142) reported that in women who received parenteral analgesia during labour (N=92), the birth of the first twin was:

- spontaneous vertex in 48.9%;
- forceps used in 35.9%;
- assisted breech in 14.1%;
- breech extraction in 1.1%;
- internal version and breech extraction in 0%.

The birth of the second twin was:

- spontaneous vertex in 19.6%;
- forceps used in 34.8%;
- assisted breech in 26.1%;
- breech extraction in 8.7%
- internal version and breech extraction in 10.9%.

In women who received continuous lumbar epidural analgesia (N=50), the birth of the first twin was:

- spontaneous vertex in 40%;
- forceps used in 40%;
- assisted breech in 18%;
- breech extraction in 2%;
- internal version and breech extraction in 0%.

The birth of the second twin was:

- spontaneous vertex in 28%;
- forceps in used 18%;
- assisted breech in 28%;
- breech extraction in 24%;
- internal version and breech extraction in 2%.

Outcomes for the baby

Perinatal mortality

Very low quality evidence from 1 study in women with twin pregnancy (N=142) showed no clinically important difference in the incidence of perinatal mortality between women who had continuous lumbar epidural analgesia or parenteral analgesia.

Comparison 3: epidural analgesia versus pethidine or nitrous oxide

Outcomes for the woman

Mode of birth

This section contains only descriptive information on the outcome mode of birth as there were no data reported to calculate relative risks.

One study with high risk of bias in women with twin pregnancy (N=64) reported that in women who received pethidine or Entonox® during labour (n=30), the first twins' birth was:

- a normal vaginal birth in 90%;
- forceps used in 3.3%;
- breech in 6.7%.

The second twins' birth was:

- normal vaginal birth in 56.7%;
- forceps used in 3.3%;
- breech in 40%.

In women who received epidural analgesia during labour (n=34), the birth of the first twin was:

- normal vaginal birth in 52.9%;
- forceps used in 38.2%;
- breech in 8.8%.

The birth of the second twin was:

- normal vaginal birth in 29.4%;
- forceps used in 32.4%;
- ventouse used in 5.9%;
- caesarean section (for a transverse lie) in 2.9%;
- breech in 29.4%.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised pain as a critical outcome for women in labour with twin and triplet pregnancies. This was because pain was considered to be a discriminating factor in a woman's perception of her experience in labour. This could potentially have a long term psychological effect on the woman's health.

The committee thought that conversion to general anaesthesia was an important outcome for the woman due to the increased risk of morbidity and mortality associated with general anaesthesia in obstetrics.

Perinatal or neonatal mortality and morbidity were prioritised as critical outcomes for the baby by the committee. Perinatal or neonatal death was prioritised as a critical outcome because of the long-term psychological impact that this may have on women and their families. The majority of women and babies would have been healthy prior to birth and so these outcomes were critical in determining the significance of intrapartum events. Neurodevelopmental disorders due to cerebral palsy, brain injury, nerve palsy, learning disability or cognitive impairment were also chosen as critical outcomes again due to the emotional and physical impact of these disorders on the children themselves and caring for them by their families.

The committee agreed that the mode of birth was an important outcome in twin and triplet pregnancy when considering the method of analgesia and anaesthesia.

The quality of the evidence

The quality of the evidence for mode of birth reported in Williams 2003 and for neonatal mortality was assessed with GRADE, and was rated as very low. The quality of the evidence from other included studies (Ogbonna 1986 and Weekes 1977) was based on the risk of bias only and was assessed as having high risk of bias. Overall, study design, risk of bias and imprecision were the main factors that lowered the confidence in the evidence. Furthermore it was unclear in the Williams 2003 study which type of epidural analgesia was used.

Benefits and harms

Information to support the planning of birth

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 informed choices 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 and this may ease some of her concerns and anxieties. Due to the high risk of preterm birth in women with twin or triplet pregnancy such discussions (including analgesia or anaesthesia) should be initiated by week 24 and conducted at the latest by week 28 of the pregnancy. 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.

The committee agreed based on their experience, that it would be important to discuss options for analgesia and anaesthesia with the woman to enable shared decision making. It is important that this discussion takes place as soon as possible, but given the risk of preterm birth in twin and triplet pregnancies, it should take place no later than 28 weeks gestation for women with twin pregnancy and by 24 weeks gestation for women with triplet

pregnancy (because of the higher risk of preterm birth associated with triplet compared to twin pregnancy).

Analgesia

The committee discussed and agreed to discount the evidence from 2 studies (Ogbonna 1986 and Weekes 1977) as the concentrations of analgesics/anaesthetics used in these studies are obsolete and are therefore not relevant to current practice. The committee had also little confidence in the Williams 2003 study since all outcomes were of very low quality and the particular analgesic treatment was not clearly defined. The committee therefore used their expertise and experience to make recommendations.

The committee agreed based that having effective regional anaesthesia would facilitate quicker labour and birth of the babies in an emergency situation reducing the risk of major neonatal morbidities and mortality. The committee discussed the established fact that women with twin or triplet pregnancy have an increased risk of intervention in labour, including the increased likelihood of an assisted birth or caesarean section for one or more of the babies, and additional internal manoeuvres. The committee agreed, based on their experience and the limited evidence, that having an epidural in place also reduces the need for emergency caesarean section for the second twin after vaginal birth of the first twin, possibly by allowing more effective internal manoeuvres to allow the second twin to be born vaginally. Even though there was no evidence for this, the committee acknowledged the necessity of pain relief when women have a caesarean section. This is currently done by using regional anaesthesia (which can be epidural or spinal) and the committee agreed that no change in practice is warranted. They also discussed that there are no recent comparative studies that assess how long it takes to top-up an epidural for the provision of de-novo spinal anaesthesia for operative birth, but there are many non-comparative studies examining the intervals between decision and birth with these top-up techniques. The committee agreed that it is widely recognised in obstetric anaesthesia that an effective epidural in place in a woman who is in established labour, confers a degree of safety because it can be converted rapidly from analgesia to anaesthesia if operative birth is required.

As there was no evidence available for many of the interventions specified in the protocol, the committee chose not to make any recommendations about other strategies of analgesia in labour (for example, those that are recommended for singleton pregnancies in the NICE guideline on intrapartum care for healthy women and babies). This was due to the lack of scientific certainty as to how generalisable and transferrable the singleton evidence would be to twin or triplet pregnancy.

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 methods of analgesia and anaesthesia during labour and birth in twin and triplet pregnancy.

Whilst the committee noted that epidurals are expensive, they were aware of evidence that having an epidural in place can reduce the need for an emergency caesarean section for the second twin after the vaginal birth of the first twin. The committee also reasoned that having an epidural in place can reduce the need for emergency general anaesthesia. Therefore, the committee considered that offering an epidural to women with a twin or triplet pregnancy who choose to have a vaginal birth was likely to be cost effective. Whilst recognising that current practice is varied they considered that their recommendations would reinforce current best practice and would not have a significant resource impact for the NHS.

References

Ogbonna 1986

Ogbonna B & Daw E. Epidural analgesia and the length of labour for vaginal twin delivery. J Obstet Gynaecol, 6:166-68, 1986

Weekes 1977

Weekes AR, Cheridjian VE, Mwanje DK. Lumbar epidural analgesia in labour in twin pregnancy. Br Med J, 2(6089):730-2, 1977

Williams 2003

Williams KP & Galerneau F. Intrapartum influences on cesarean delivery in multiple gestation. Acta Obstet Gynecol Scand, 82(3):241-5, 2003

1 Appendix A – Review protocols

2 Review protocol – What is the optimal method of analgesia and anaesthesia during
3 labour and birth in twin and triplet pregnancy?

4 **Table 5: Review protocol for analgesia and anaesthesia**

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal method of analgesia and anaesthesia during labour and birth in twin and triplet pregnancy?
II	Type of review question	Intervention
III	Objective of the review	There is uncertainty around the optimal method of analgesia during labour and birth in twin and triplet pregnancy. This review aims to address this issue.
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. All women planning a vaginal birth and in established labour. Setting: hospitals
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Vaginal birth: • analgesic techniques: ○ central/regional neuraxial analgesia/anaesthesia (spinal, epidural, combined spinal epidural) • inhalational analgesia (Entonox® [medical nitrous oxide and oxygen mixture]; hereafter referred to as Entonox®) • intravenous and intramuscular opioids (pethidine, morphine, diamorphine and remifentanil) • non-pharmacological analgesic techniques (Transcutaneous Electrical Nerve Stimulation, birthing pools, hypnobirthing)
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	Vaginal birth: • no intervention versus each of the above classes • any of the above classes versus another class Studies examining combinations of analgesic techniques will be included. Studies examining within class comparisons will be excluded
VII	Outcomes and prioritisation	**Critical** For the woman: • pain (validated scales) • conversion to general anaesthesia for any operative intervention For the baby: • major neonatal morbidities (hypoxic ischaemic encephalopathy, cerebral palsy/ neurodevelopmental disability / developmental delay, neonatal seizures, meconium aspiration syndrome, fetal trauma, respiratory depression)

ID	Field (based on PRISMA-P)	Content
		Important For the woman: • mode of birth • women's satisfaction/experience of labour and birth • mortality For the baby: • mortality
VIII	Eligibility criteria – study design	Systematic reviews of randomised controlled trials. Randomised controlled trials. If insufficient trials evidence is available for each comparison: • Cohort studies (prospective cohort studies will be prioritised over retrospective) • Conference abstracts will be considered if there is no other evidence available and if published within the last two years, for critical outcomes only
IX	Other inclusion exclusion criteria	Exclude: • women with a quadruplet or higher-order pregnancy as per scope • women with known serious fetal anomaly • contraindication to labour or vaginal birth (for example cervical fibroids, >1 previous CS and specific indications for CS such as breech presentation, placenta praevia and morbidly adherent placenta) • women that have an elective CS • studies that do not report results specifically for twin and/or triplet pregnancies
X	Proposed sensitivity/sub-group analysis, or meta-regression	No subgroup analyses are planned. The following groups will used to explore any significant heterogeneity identified: • parity • previous CS • comorbidities such as obesity (BMI ≥30) • pre-existing medical conditions
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 and data extraction and recording quality assessment using checklists

ID	Field (based on PRISMA-P)	Content
		Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion. 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
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 G (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 G (clinical evidence tables) or H (economic evidence tables) of the full guideline
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 and 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 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/
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
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

ID	Field (based on PRISMA-P)	Content
XX VI	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
XX VII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XX VIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXI X	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
XX X	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; CS: caesarean section; BMI: body mass index; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence

Appendix B – Literature search strategies

Literature search for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

Clinical Searches

Date of initial search: 07/02/2018

Database(s): Embase Classic+Embase 1947 to 2018 February 06, 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	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic or dichorionic or trichorionic).tw.
5	or/1-4
6	Labor Pain/
7	exp Delivery, Obstetric/ or exp Labor, Obstetric/ or exp Parturition/
8	or/6-7 use ppez
9	labor pain/
10	exp obstetric delivery/ or exp labor/ or birth/
11	or/9-10 use emczd
12	(deliver* or childbirth or birth* or labo?r* or c?esar* or c-section* or VBAC or forceps or vacuum or ventouse).tw.
13	8 or 11 or 12
14	Pain/pc
15	exp Analgesia/
16	Anesthesia, Obstetrical/
17	exp Anesthesia, Epidural/
18	Analgesics, Opioid/
19	Nitrous Oxide/
20	Bupivacaine/
21	Meperidine/
22	Morphine/
23	Heroin/
24	Transcutaneous Electric Nerve Stimulation/
25	Baths/
26	Water/
27	Immersion/
28	exp Hypnosis/
29	or/14-28 use ppez
30	exp analgesia/
31	anesthesia/
32	anesthetic agent/

#	Searches
33	obstetric anesthesia/
34	epidural anesthesia/
35	narcotic analgesic agent/
36	nitrous oxide/
37	bupivacaine/
38	pethidine/
39	morphine/
40	diamorphine/
41	transcutaneous electrical nerve stimulation/
42	water immersion labor pool/
43	water birth/
44	hypnosis/
45	or/30-44 use emczd
46	(analges* or anaesthe* or anesthe* or pain control* or pain relief or pain relieving or epidural* or spinal or "gas and air" or nitrous oxide or entonox or bupivacain* or meperidin* or morphine or diamorphine or pethidin* or remifentanil).tw.
47	(TENS or electroanalgesi* or ((transcutaneous or cutaneous or percutaneous or transdermal or electric nerve) adj2 stimulation)).tw.
48	(hypnobirth* or hypno-birth* or (hypnoti* adj birth*) or hypnotherap*).tw.
49	(birthing pool* or (birth* adj pool*) or (water adj birth*)).tw.
50	or/46-49
51	29 or 45 or 50
52	5 and 13 and 51
53	limit 52 to english language
54	Letter/ use ppez
55	letter.pt. or letter/ use emczd
56	note.pt.
57	editorial.pt.
58	Editorial/ use ppez
59	News/ use ppez
60	exp Historical Article/ use ppez
61	Anecdotes as Topic/ use ppez
62	Comment/ use ppez
63	Case Report/ use ppez
64	case report/ or case study/ use emczd
65	(letter or comment*).ti.
66	or/54-65
67	randomized controlled trial/ use ppez
68	randomized controlled trial/ use emczd
69	random*.ti,ab.
70	or/67-69
71	66 not 70
72	animals/ not humans/ use ppez
73	animal/ not human/ use emczd
74	nonhuman/ use emczd
75	exp Animals, Laboratory/ use ppez
76	exp Animal Experimentation/ use ppez
77	exp Animal Experiment/ use emczd
78	exp Experimental Animal/ use emczd
79	exp Models, Animal/ use ppez
80	animal model/ use emczd
81	exp Rodentia/ use ppez
82	exp Rodent/ use emczd

#	Searches
83	(rat or rats or mouse or mice).ti.
84	or/71-83
85	53 not 84
86	remove duplicates from 85

Date of initial search: 07/02/2018

Database(s): The Cochrane Library, issue 2 of 12, February 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	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) near/3 (birth* or pregnan* or gestation* or foetus* or foetal or fetus* or fetal))
#3	(chorionicity or monochorionic or dichorionic or trichorionic)
#4	{or #1-#3}
#5	MeSH descriptor: [Labor Pain] this term only
#6	MeSH descriptor: [Delivery, Obstetric] explode all trees
#7	MeSH descriptor: [Labor, Obstetric] explode all trees
#8	MeSH descriptor: [Parturition] explode all trees
#9	{or #5-#8}
#10	MeSH descriptor: [Pain] this term only and with qualifier(s): [Prevention & control - PC]
#11	MeSH descriptor: [Analgesia] explode all trees
#12	MeSH descriptor: [Anesthesia, Obstetrical] this term only
#13	MeSH descriptor: [Anesthesia, Epidural] explode all trees
#14	MeSH descriptor: [Analgesics, Opioid] this term only
#15	MeSH descriptor: [Nitrous Oxide] this term only
#16	MeSH descriptor: [Bupivacaine] this term only
#17	MeSH descriptor: [Meperidine] this term only
#18	MeSH descriptor: [Morphine] this term only
#19	MeSH descriptor: [Heroin] this term only
#20	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#21	MeSH descriptor: [Baths] this term only
#22	MeSH descriptor: [Water] this term only
#23	MeSH descriptor: [Immersion] this term only
#24	(analges* or anaesthe* or anesthe* or pain control* or pain relief or pain relieving or epidural* or spinal or "gas and air" or nitrous oxide or entonox or bupivacain* or meperidin* or morphine or diamorphine or pethidin* or remifentanil)
#25	(TENS or electroanalgesi* or ((transcutaneous or cutaneous or percutaneous or transdermal or electric nerve) near/2 stimulation))
#26	(hypnobirth* or hypno-birth* or (hypnoti* near birth*) or hypnotherap*)
#27	(birthing pool* or (birth* near pool*) or (water near birth*))
#28	{or #10-#27}
#29	#4 and #9 and #28

Health economics searches

For the Cochrane Library, see above

Date of initial search: 07/02/2018

Database(s): Embase Classic+Embase 1947 to 2018 February 06, 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	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or monochorionic or dichorionic or trichorionic).tw.
5	or/1-4
6	Labor Pain/
7	exp Delivery, Obstetric/ or exp Labor, Obstetric/ or exp Parturition/
8	or/6-7 use ppez
9	labor pain/
10	exp obstetric delivery/ or exp labor/ or birth/
11	or/9-10 use emczd
12	(deliver* or childbirth or birth* or labo?r* or c?esar* or c-section* or VBAC or forceps or vacuum or ventouse).tw.
13	8 or 11 or 12
14	Pain/pc
15	exp Analgesia/
16	Anesthesia, Obstetrical/
17	exp Anesthesia, Epidural/
18	Analgesics, Opioid/
19	Nitrous Oxide/
20	Bupivacaine/
21	Meperidine/
22	Morphine/
23	Heroin/
24	Transcutaneous Electric Nerve Stimulation/
25	Baths/
26	Water/
27	Immersion/
28	exp Hypnosis/
29	or/14-28 use ppez
30	exp analgesia/
31	anesthesia/
32	anesthetic agent/
33	obstetric anesthesia/
34	epidural anesthesia/
35	narcotic analgesic agent/
36	nitrous oxide/

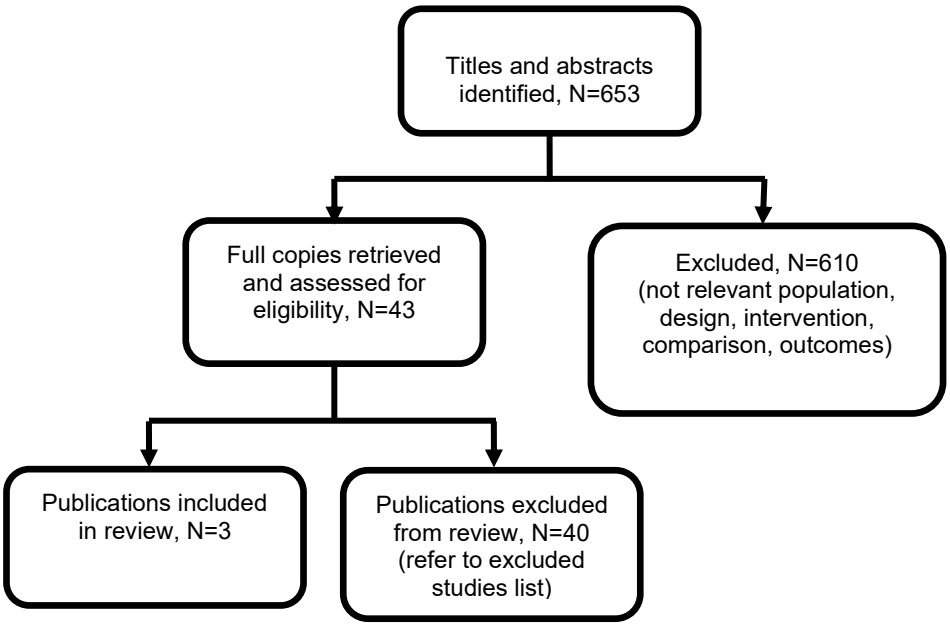
#	Searches
37	bupivacaine/
38	pethidine/
39	morphine/
40	diamorphine/
41	transcutaneous electrical nerve stimulation/
42	water immersion labor pool/
43	water birth/
44	hypnosis/
45	or/30-44 use emczd
46	(analges* or anaesthe* or anesthe* or pain control* or pain relief or pain relieving or epidural* or spinal or "gas and air" or nitrous oxide or entonox or bupivacain* or meperidin* or morphine or diamorphine or pethidin* or remifentanil).tw.
47	(TENS or electroanalgesi* or ((transcutaneous or cutaneous or percutaneous or transdermal or electric nerve) adj2 stimulation)).tw.
48	(hypnobirth* or hypno-birth* or (hypnoti* adj birth*) or hypnotherap*).tw.
49	(birthing pool* or (birth* adj pool*) or (water adj birth*)).tw.
50	or/46-49
51	29 or 45 or 50
52	5 and 13 and 51
53	limit 52 to english language
54	Letter/ use ppez
55	letter.pt. or letter/ use emczd
56	note.pt.
57	editorial.pt.
58	Editorial/ use ppez
59	News/ use ppez
60	exp Historical Article/ use ppez
61	Anecdotes as Topic/ use ppez
62	Comment/ use ppez
63	Case Report/ use ppez
64	case report/ or case study/ use emczd
65	(letter or comment*).ti.
66	or/54-65
67	randomized controlled trial/ use ppez
68	randomized controlled trial/ use emczd
69	random*.ti,ab.
70	or/67-69
71	66 not 70
72	animals/ not humans/ use ppez
73	animal/ not human/ use emczd
74	nonhuman/ use emczd
75	exp Animals, Laboratory/ use ppez
76	exp Animal Experimentation/ use ppez
77	exp Animal Experiment/ use emczd
78	exp Experimental Animal/ use emczd
79	exp Models, Animal/ use ppez
80	animal model/ use emczd
81	exp Rodentia/ use ppez
82	exp Rodent/ use emczd
83	(rat or rats or mouse or mice).ti.
84	or/71-83
85	53 not 84
86	remove duplicates from 85

#	Searches
87	Economics/
88	Value of life/
89	exp "Costs and Cost Analysis"/
90	exp Economics, Hospital/
91	exp Economics, Medical/
92	Economics, Nursing/
93	Economics, Pharmaceutical/
94	exp "Fees and Charges"/
95	exp Budgets/
96	or/87-95 use ppez
97	health economics/
98	exp economic evaluation/
99	exp health care cost/
100	exp fee/
101	budget/
102	funding/
103	or/97-102 use emczd
104	budget*.ti,ab.
105	cost*.ti.
106	(economic* or pharmaco?economic*).ti.
107	(price* or pricing*).ti,ab.
108	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
109	(financ* or fee or fees).ti,ab.
110	(value adj2 (money or monetary)).ti,ab.
111	or/104-109
112	96 or 103 or 111
113	86 and 112

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

Figure 1: Flow diagram of clinical article selection for the optimal method of analgesia and anaesthesia during labour and birth in twin and triplet pregnancy review



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
 	
Ogbonna, B., Daw, E., Epidural analgesia and the length of labour for vaginal twin delivery, Journal of Obstetrics and Gynaecology, 6, 166-168, 1986
 	
Ref Id
 	
772627
 	
Country/ies where the study was carried out
 	
UK
 	
Study type
Retrospective cohort
 	
Aim of the study
To compare epidural analgesia with other
	Sample size
	
	N=64 women with twin pregnancy who had vaginal birth.
	n=34/64 (53%) received epidural analgesia,
	n=30/64 (47%) received other analgesia.
	
	Characteristics
	Maternal age (number):
	≤19 years: epidural group = 6, no epidural group = 4
	20-24 years: epidural group = 14, no epidural group = 10
	25-29 years: epidural group = 9, no
		Interventions
		Epidural analgesia
			Details
			Epidural analgesia was defined as bupivacaine hydrochloride, without adrenaline, 0.25%, 0.5% or 0.375% was used.
			n=25 mothers received between 4 and 8 ml of 0.5%, n=2 mothers received between 8 and 14 ml of 0.375%, and n=7 mothers received between 8 and 15 ml of 0.25% bupivacaine.
			The dose received and the strength of bupivacaine used did not relate in any way to the length of labour.
			Other analgesia was defined as either pethidine in doses of 100 or 150 mg not more often than 4-hourly, or nitrous oxide and oxygen by face mask, as Entonox®.
				Results
				Maternal outcome
				Mode of birth:
				epidural analgesia group (n=34):
				twin 1: normal VB = 18, forceps = 13, breech = 3;
				twin 2: normal VB =10, forceps = 11, breech = 10, ventouse = 2, CS = 1 (for transverse lie of second twin)
				other analgesia group (n=30):
				twin 1: normal VB =27, forceps = 1, breech = 2;
				twin 2: normal VB =17, forceps = 1, breech = 12
					Limitations
					Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale:
					Selection: unclear risk of bias (not reported how the exposed and the non-exposed cohorts were selected. Not clear whether these cohort were different as description of the population is minimal. There is certainty that the outcomes of interest were not present at start of the study given that the outcomes could not occur before labour).
					Comparability: high risk of bias (the study does not control for any factor)
					Outcome: unclear risk of bias (not reported how the outcomes were assessed; the follow-up was long enough for outcomes to occur; all subjects were accounted for).
					
					Other information: None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
analgesia to determine the effect on the length of labour. **Study dates** Not reported. **Source of funding** Not reported.	epidural group = 12 ≥30 years: epidural group = 5, no epidural group = 4 Parity (number): 1: epidural group = 18, no epidural group = 9 2: epidural group = 8, no epidural group = 8 3: epidural group = 5, no epidural group = 9 ≥4: epidural group = 3, no epidural group = 4 **Inclusion criteria** Women with twin pregnancy undergoing VB. **Exclusion criteria** Elective CS.				
Full citation Weekes,A.R, Cheridjian,V.E, Mwanje,D.K.,	**Sample size** N=142 women with twin	**Interventions** Continuous lumbar epidural analgesia.	**Details** Epidural analgesia defined as bupivacaine 0.5% with adrenaline 1/400,000. An initial test dose of 2 ml was	**Results** **Maternal** <u>Mode of birth:</u> epidural analgesia group (n=50):	**Limitations** Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lumbar epidural analgesia in labour in twin pregnancy, British Medical Journal, 2, 730-732, 1977 **Ref Id** 772722 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort **Aim of the study** To compare the course of labour and the fetal outcome in twin pregnancies managed with and without continuous lumbar epidural analgesia. **Study dates**	pregnancy eligible for VB n=50/142 (35%) received epidural analgesia, n=92/142 (65%) received parenteral analgesia **Characteristics** Maternal age (years, mean (SD)): epidural group: 26.98 (5.32) no epidural group: 27.35 (4.98) Number of primiparae: epidural group: 23 no epidural group: 31 Number of multiparae: epidural group: 27 no epidural group: 61 Number of those with induced labour:		given, and incremental doses of 4 ml were then given as required; 6 ml was administered in the sitting position when the cervix was fully dilated and the presenting part visible. Parenteral analgesia was provided during labour by pethidine 150 mg and promethazine hydrochloride 25 mg as required, supplemented by nitrous oxide and oxygen (Entonox®). n=10 women in this group required a general anaesthetic to expedite the birth of the second twin.	twin 1: spontaneous vertex = 20, forceps = 20, assisted breech = 9, breech extraction = 1, internal version and breech extraction = 0; twin 2: spontaneous vertex = 14, forceps = 9, assisted breech = 14, breech extraction = 12, internal version and breech extraction = 1 parenteral analgesia group (n=92): twin 1: spontaneous vertex = 45, forceps = 33, assisted breech = 13, breech extraction = 1, internal version and breech extraction = 0; twin 2: spontaneous vertex = 18, forceps = 32, assisted breech = 24, breech extraction = 8, internal version and breech extraction = 10. **Neonatal** Perinatal mortality (not defined): epidural group (n=50): 2 (due to respiratory distress syndrome) no epidural group (n=92): 10 (n=6 due to respiratory distress syndrome, n=1 due to a tentorial tear, n=1 due to severe rhesus incompatibility).	**Selection**: unclear risk of bias (not reported how the exposed and the non-exposed cohorts were selected. Not clear whether these cohort were different as description of the population is minimal. There is certainty that the outcomes of interest were not present at start of the study given that the outcomes could not occur before labour). **Comparability**: high risk of bias (the study does not control for any factor) **Outcome:** unclear risk of bias (not reported how the outcomes were assessed; the follow-up was long enough for outcomes to occur; all subjects were accounted for). **Other information:** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported. **Source of funding** Not reported.	epidural group: 12 no epidural group: 20 Gestational age <36 weeks: epidural group: 5 no epidural group: 20 Gestational age 36 weeks: epidural group: 45 no epidural group: 72 Presentation of 1st twin: epidural group: head=40, breech=10 no epidural group: head=78, breech=14 **Inclusion criteria** Women who gave birth to twins in a hospital in Liverpool. **Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Women who had twin abortions, elective and emergency CS, and those with a macerated stillbirth of one or both twins.				

Full citation
 	
Williams,K.P, Galerneau,F., Intrapartum influences on cesarean delivery in multiple gestation, Acta Obstetricia et Gynecologica Scandinavica, 82, 241-245, 2003
 	
Ref Id
 	
772729
 	
Country/ies where the study was carried out
 	
USA
 	
Study type
Retrospective cohort
	Sample size
	N=927 women with twin pregnancy eligible for VB n=689/927 (74%) had epidural, n=238/927 (26%) had no epidural.
	
	Characteristics
	The total incidence of CS was 266/927 (29%); of these, 21/927 (2.2%) were performed for the birth of the 2nd twin after VB of the 1st twin.
	Parity: nulliparous = 468, multiparous = 459;
		Interventions
		Epidural use (not defined).
			Details
			Antepartum and intrapartum data were entered into a computerised database on all women with twin gestations giving birth at a hospital.
			Specific data were obtained from the antenatal charts, including the physician present at birth, cervical dilation at the time of epidural placement, Apgar scores, gravidity, parity, and birth outcomes.
			The mean cervical dilation at epidural placement was 4 cm or greater; 10% of labouring women received an epidural at less than 4 cm cervical dilation (according to the authors, exclusions of this group from the analysis did not change the outcome).
				Results
				Maternal
				<u>Mode of birth:</u>
				CS 1st twin/CS 2nd twin:
				epidural group = 140 (20.3%);
				no epidural group =105 (44.1%)
				
				VB 1st twin/CS 2nd twin:
				epidural group = 11 (1.5%);
				no epidural group = 10 (4.2%)
					Limitations
					Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale:
					Selection: unclear risk of bias (the exposed cohort is somewhat representative of the average cohort of women pregnant with twins as the cohort (consecutively) was selected from a hospital using data from hospital charts; the non-exposed cohort was drawn from the same hospital as the exposed cohort. There is certainty that the outcomes of interest were not present at start of the study given that the outcomes could not occur before labour).
					Comparability: high risk of bias (the study does not control for any factor; epidural used is not defined).
					Outcome: high risk of bias (the outcomes were assessed through record linkage because the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate which risk factors occurring in the intrapartum period are associated with increased risk of abdominal birth in a group of twin pregnancies eligible for VB. **Study dates** Between January 1990 and January 1999. **Source of funding** Not reported.	presentation of 2nd twin: vertex = 548, other = 379; presentation of 2nd twin: vertex or breech = 866, other = 61 (it looks like an error in reporting as presentation on 2nd twin is reported twice); induction: yes = 666, no = 261. **Inclusion criteria** Consecutive inclusions of twin pregnancies: gestational age of 32 weeks, determined by an early ultrasound performed in the second trimester or certain last menstrual period; both twins viable; eligibility for VB as defined by twin A being cephalic; and no previous CS.				authors reviewed hospital charts; the follow-up was long enough for outcomes to occur; however, not all subjects were accounted for in the analysis). **Other information:** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Women with twin gestations who underwent an elective or repeat CS.				

CS: caesarean section; SD: standard deviation; VB: vaginal birth

Appendix E – Forest plots

Forest plots for review question: What is the optimal method of analgesia and anaesthesia during labour 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 the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

Table 6: Comparison: analgesia versus no analgesia for mode of birth for twin pregnancy, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Analgesia	No analgesia	Relative (95% CI)	Absolute	Quality	Importance
Caesarean section for both twins												
1	Observational studies	Very serious [2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	140/689 (20.3%)	105/238 (44.1%)	RR 0.46 (0.37 to 0.57)	238 fewer per 1000 (from 190 fewer to 278 fewer)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Vaginal birth for first twin and caesarean section for second twin												
1	Observational studies	Very serious [2]	No serious inconsistency	No serious indirectness	Serious[3]	None	11/689 (1.6%)	10/238 (4.2%)	RR 0.38 (0.16 to 0.88)	26 fewer per 1000 (from 5 fewer to 35 fewer)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; MID: RR: risk ratio; VB: vaginal birth

2 Unclear risk of selection bias; high risk of comparability bias as the study does not control for any factor; high risk of attrition bias as not all subjects were accounted for in the analysis; analgesia not defined
3 The quality of the evidence was downgraded by 1 level because the 95% CI crosses one default MID threshold

Table 7: Comparison: continuous lumbar epidural analgesia versus parenteral analgesia for perinatal mortality for twin pregnancy, outcomes for the baby

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epidural analgesia	Parenteral analgesia	Relative (95% CI)	Absolute	Quality	Importance
1	Observational studies	Very serious1	No serious inconsistency	No serious indirectness	Very serious[2]	None	2/50 (4%)	10/92 (10.9%)	RR 0.37 (0.08 to 1.61)	68 fewer per 1000 (from 100 fewer to 66 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

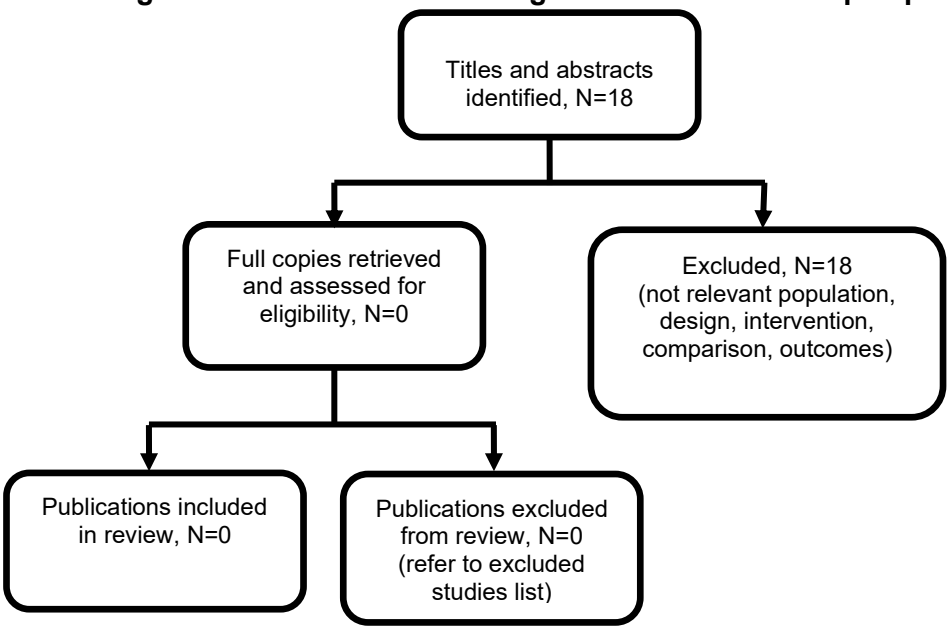
CI: confidence interval; RR: risk ratio
1 Unclear risk of selection bias; unclear risk of outcome bias; high risk of comparability bias as the study does not control for any factor; perinatal mortality not defined
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

No economic evidence was identified for this review.

Figure 2: Flow diagram of economic article selection for the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic profiles for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

No economic analysis was conducted for this review.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

Clinical studies

Study	Reason for exclusion
Aaron, J. B., Halperin, J., Fetal survival in 376 twin deliveries, American journal of obstetrics and gynecology (Print), 69, 794-804, 1955	More than half of the babies were premature
Aaron, J. B., Silverman, S. H., Halperin, J., Fetal survival in twin delivery, American journal of obstetrics and gynecology (Print), 81, 331-334, 1961	Comparison not relevant
Adams, D. M, Chervenak, F. A., Intrapartum management of twin gestation, Clinical Obstetrics & Gynecology, 33, 52-60, 1990	Narrative review on the intrapartum management of twin pregnancy
Anim-Somuah, Millicent, Smyth, Rebecca Md, Cyna, Allan M, Cuthbert, Anna, Epidural versus non-epidural or no analgesia for pain management in labour, Cochrane Database of Systematic Reviews, 2018	Potentially relevant studies were assessed for the inclusion
Ayres,A., Johnson,T.R.B., Management of multiple pregnancy: Labor and delivery, Obstetrical and Gynecological Survey, 60, 550-554, 2005	Narrative review on the intrapartum management of twin pregnancy
Behforouz, N, Dounas, M, Benhamou, D., Epidural anaesthesia for caesarean delivery in triple and quadruple pregnancies, Acta Anaesthesiologica ScandinavicaActa Anaesthesiol Scand, 42, 1088-91, 1998	Non relevant population as women were scheduled for an elective CS and not vaginal birth
Brown, D. C., Hammond, D. C., Evidence-based clinical hypnosis for obstetrics, labor and delivery, and preterm labor, International Journal of Clinical and Experimental Hypnosis, 55, 355-371, 2007	Not multiple pregnancy
Carroll, M. A, Yeomans, E. R., Vaginal delivery of twins, Clinical Obstetrics & Gynecology, 49, 154-66, 2006	Narrative review on the management of labour in twin pregnancy
Chamberlain, G., Steer, P., ABC of labour care. Unusual presentations and positions and multiple pregnancy, British Medical Journal, 318, 1192-1194, 1999	Clinical review on malpresentations and malpositions of the fetus
Cochran, J. L., Hill, S. A., Birth of twins under impromptu psychosomatic anesthesia, Brit, J. Med. Hypnot. 7, 3-5, 1956	A full-text copy of the article could not be obtained
Crawford, J. S, Weaver, J. B., Anaesthetic management of twin and breech deliveries, Clinics in Obstetrics & Gynaecology, 9, 291-6, 1982	Narrative paper about the obstetric management of breech presentation in twin pregnancy
Crawford,J.S., An appraisal of lumbar epidural blockade in labour in patients with multiple pregnancy, British Journal of Obstetrics and Gynaecology, 82, 929-935, 1975	Not all fetuses were alive at the time of labour; no relevant outcomes were reported
Daniels, J. C., Hehre, F. W., Anesthetic considerations for complicated obstetrics: I. A	Mixed population as some women had vaginal birth, others had a caesarean section

Study	Reason for exclusion
retrospective study of 527 twin deliveries, Anesthesia and Analgesia, 46, 527-539, 1967	
de Veciana, M, Major, C, Morgan, M. A., Labor and delivery management of the multiple gestation, Obstetrics & Gynecology Clinics of North America, 22, 235-46, 1995	Narrative article about the intrapartum management of twin pregnancy
Dewan, D. M., Anesthesia for preterm delivery, breech presentation, and multiple gestation, Clinical Obstetrics & Gynecology, 30, 566-78, 1987	Narrative review on the use of anaesthesia in high-risk pregnancies during labour
Dowswell, Therese, Bedwell, Carol, Lavender, Tina, Neilson, James P, Transcutaneous electrical nerve stimulation (TENS) for pain management in labour, Cochrane Database of Systematic Reviews, 2009	Potentially relevant studies were assessed for the inclusion
Dusitkasem, S., Herndon, B. H., Somjit, M., Stahl, D. L., Bitticker, E., Coffman, J. C., Comparison of Phenylephrine and Ephedrine in Treatment of Spinal-Induced Hypotension in High-Risk Pregnancies: A Narrative Review, Frontiers in MedicineFront Med (Lausanne), 4, 2, 2017	Non relevant population as women had a caesarean section and not vaginal birth
Freeman, L. M., Bloemenkamp, K. W., Franssen, M. T., Papatsonis, D. N., Hajenius, P. J., Hollmann, M. W., Woiski, M. D., Porath, M., van den Berg, H. J., van Beek, E., Borchert, O. W., Schuitemaker, N., Sikkema, J. M., Kuipers, A. H., Logtenberg, S. L., van der Salm, P. C., Oude Rengerink, K., Lopriore, E., van den Akker-van Marle, M. E., le Cessie, S., van Lith, J. M., Struys, M. M., Mol, B. W., Dahan, A., Middeldorp, J. M., Patient controlled analgesia with remifentanil versus epidural analgesia in labour: randomised multicentre equivalence trial, BMJ, 350, h846, 2015	Insufficient data reported (only in a figure)
Gullestad,S., Sagen,N., Epidural block in twin labour and delivery, Acta Anaesthesiologica Scandinavica, 21, 504-508, 1977	Study design not relevant to protocol (case-control study)
Hyndman, N., Molloy, M., Anaesthetic management of twin deliveries at a tertiary care centre: A service provision project, International Journal of Obstetric Anesthesia, 1), S29, 2016	The abstract presents the data of the analysis of the current local practice in the management of twin births on a labour ward
James, F. M, 3rd, Crawford, J. S, Davies, P, Naiem, H., Lumbar epidural analgesia for labor and delivery of twins, American Journal of Obstetrics & Gynecology, 127, 176-80, 1977	Comparison not relevant
Jarvis, G. J., Whitfield, M. F., Epidural analgesia and the delivery of twins, Journal of Obstetrics and Gynaecology, 2, 90-92, 1981	Comparison not relevant
Jaschevatzky,O.E, Shalit,A, Levy,Y, Grunstein,S., Epidural analgesia during labour in twin pregnancy, British Journal of Obstetrics and Gynaecology, 84, 327-331, 1977	Study design not relevant to protocol (case-control study); also one of the inclusion criteria in the study was gestational age ≥23 weeks
Klomp, Trudy, van, Poppel Mireille, Jones, Leanne, Lazet, Janine, Di, Nisio Marcello, Lagro-Janssen, Antoine Lm, Inhaled analgesia for pain management in labour, Cochrane Database of Systematic Reviews, 2012	Singleton pregnancies

Study	Reason for exclusion
Kryc, J. J., Anesthesia for the high risk obstetric patient, Clinics in Perinatology, 9, 113-34, 1982	Narrative article about the anaesthetic management of high risk pregnancy
Laube, D. W., Multiple pregnancy, operative delivery, anesthesia, and analgesia, Current Opinion in Obstetrics & GynecologyCurr Opin Obstet Gynecol, 2, 40-4, 1990	Narrative review on the intrapartum management of multiple gestation
Little, W. A., Friedman, E. A., The twin delivery - Factors influencing second twin mortality, Obstetrics and Gynecology, 13, 611-623, 1958	Narrative review on the intrapartum management of twin pregnancy. Authors also describe the results of their own study about the factors affecting the mortality rate of the second twin including anaesthesia. However, not all fetuses were alive before labour
Lucovnik, M., Blajic, I., Verdenik, I., Mirkovic, T., Stopar Pintaric, T., Impact of epidural analgesia on cesarean and operative vaginal delivery rates classified by the Ten Groups Classification System, International journal of obstetric anesthesia, 2018	No separate results for twin and triplet pregnancies
Madden, K., Middleton, P., Cyna, A. M., Matthewson, M., Jones, L., Hypnosis for pain management during labour and childbirth, Cochrane Database of Systematic Reviews, 2016 (5) (no pagination), 2016	Potentially relevant studies were assessed for the inclusion
Malinow, A. M, Ostheimer, G. W., Anesthesia for the high-risk parturient, Obstetrics & Gynecology, 69, 951-64, 1987	Narrative review on the use of anaesthesia during high-risk pregnancies
Marino,T, Goudas,L.C, Steinbok,V, Craigo,S.D, Yarnell,R.W., The anesthetic management of triplet cesarean delivery: a retrospective case series of maternal outcomes, Anesthesia and Analgesia, 93, 991-995, 2001	Non relevant population as women had a caesarean section and not vaginal birth
Meehan,F.P, Magani,I.M, Mortimer,G., Perinatal mortality in multiple pregnancy patients, Acta Geneticae Medicae et Gemellologiae, 37, 331-337, 1988	Not relevant population as not all women had a planned vaginal birth, some had an elective caesarean section
Pollack,K.L., Chestnut,D.H., Anesthesia for complicated vaginal deliveries, Anesthesiology Clinics of North America, 8, 115-129, 1990	Narrative article about the anaesthetic management of complicated vaginal births
Pratt,S.D., Anesthesia for breech presentation and multiple gestation, Clinical Obstetrics & Gynecology, 46, 711-731, 2003	Narrative review on the use of anaesthesia in high-risk pregnancies
Redick, L. F., Anesthesia for twin delivery, Clinics in Perinatology, 15, 107-22, 1988	Narrative article about the physiologic and pathophysiologic aspects of labour, and the intrapartum management of analgesia and anaesthesia for twin pregnancy
Saxena, N., Lewis, E., Anaesthetic interventions for vaginal twin deliveries; role of epidural analgesia, International Journal of Obstetric Anesthesia, 1), S42, 2010	Conference abstract
Scott Wheeler, A., James, F. M., Anesthesia for complicated obstetrics, Journal of the American Association of Nurse Anesthetists, 47, 300-308, 1979	Narrative review on the basic anaesthetic considerations in complicated pregnancies
Smith, Lesley A, Burns, Ethel, Cuthbert, Anna, Parenteral opioids for maternal pain management	Potentially relevant studies were assessed for the inclusion

Study	Reason for exclusion
in labour, Cochrane Database of Systematic Reviews, 2018	
Sng, Ban Leong, Zeng, Yanzhi, de, Souza Nurun Nisa A, Leong, Wan Ling, Oh, Ting Ting, Siddiqui, Fahad Javaid, Assam, Pryseley N, Han, Nian-Lin R, Chan, Edwin Sy, Sia, Alex T, Automated mandatory bolus versus basal infusion for maintenance of epidural analgesia in labour, Cochrane Database of Systematic Reviews, 2018	Potentially relevant studies were assessed for the inclusion
Writer, W. D. R., Breech presentation and multiple pregnancy: Obstetrical aspects and anaesthetic management, Clinics in Anaesthesiology, 4, 305-320, 1986	Narrative article about the intrapartum management of anaesthesia for multiple pregnancy

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal method of analgesia and anaesthesia during labour in twin and triplet pregnancy?

No research recommendations were made for this review.