National Institute for Health and Care Excellence

Draft for Consultation

Twin and triplet pregnancy

[C1] Evidence review for mode of birth

NICE guideline tbc

Evidence review

March 2019

Draft for consultation

This evidence review was developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Mode of birth

Review question

What is the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Introduction

In otherwise uncomplicated twin pregnancies at term where the presentation of the first twin is cephalic, the risk of perinatal morbidity and mortality is increased for the second twin.

NICE guideline CG129 did not include recommendations on intrapartum care because this area was not included in the original scope. Existing NICE guidelines Intrapartum care for healthy women and babies (CG190), Inducing labour (CG70) and Preterm labour and birth (NG25) do not make specific recommendations for twin and triplet pregnancy. The NICE guideline on Caesarean Section makes (CG132) two clinical recommendations relating to twin and triplet pregnancy from reviews conducted in 2004.

The aim of this review is to compare the effectiveness of planned caesarean section compared with planned vaginal birth to optimise maternal and neonatal outcomes in twin and triplet births. This information can be used to address the uncertainty around the mode of birth 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 (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 with all fetuses confirmed alive Setting: hospital
Intervention	Planned caesarean section
Comparison	Planned vaginal birth
Outcomes	**Critical** For the woman: • mortality For the baby: • perinatal or neonatal mortality (excluding mortality due to lethal fetal anomalies) • disability in childhood (neurodevelopmental: cerebral palsy, brain injury, nerve palsy; learning disability or cognitive impairment) **Important:** For the woman: • maternal morbidity (for example, septicaemia/sepsis, organ failure (liver, renal, respiratory), uterine rupture, hysterectomy, postpartum haemorrhage (>1000ml), long-term consequences (urinary and fecal incontinence, pelvic organ prolapse) • actual mode of birth • composite outcome For the baby:

	• neonatal morbidity (for example, seizures, birth trauma (fractures), respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, neonatal encephalopathy or birth asphyxia or severe hypoxic- ischaemic encephalopathy – grade 2&3) • composite outcome

For full details see 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

One Cochrane review by Hofmeyr 2015 which includes 2 randomised controlled trials (RCTs) (Barrett 2013; Rabinovici 1987), 2 follow-up reports of the Barrett 2013 RCT (Asztalos 2016; Hutton 2015) regarding twin pregnancy. Apart from the follow-up reports of the Barett 2013 RCT, no further RCTs were identified that were published after the search cut-off date of Hofmeyr 2015 for twin pregnancy. Where information relevant to the evidence review protocol was not reported in the Cochrane review, data from the original studies by Barret 2013 and Rabinovici 1987 were extracted.

Three retrospective cohort studies (Lappen 2016; Mol 2018; Peress 2018) concerning triplet pregnancy were included in this review.

The included studies are summarised in Table 2.

Evidence was identified for the majority of maternal and neonatal outcomes in twin pregnancy except for the maternal morbidities of organ failure (liver, renal, respiratory), uterine rupture, pelvic organ prolapse and the neonatal morbidities of brain injury, bronchopulmonary dysplasia and birth asphyxia.

Evidence was identified for the maternal outcomes of actual mode of birth, peripartum hysterectomy and postpartum haemorrhage, and for the neonatal outcomes of perinatal mortality, neonatal morbidity, respiratory distress syndrome, intraventricular haemorrhage (grade 3/4), necrotising enterocolitis, and neonatal asphyxia in triplet pregnancy. No evidence was identified for the maternal mortality, maternal morbidity outcomes of septicaemia/sepsis, organ failure (liver, renal, respiratory), uterine rupture, long-term consequences (urinary and fecal incontinence, pelvic organ prolapse) and for neonatal outcome such as disability in childhood.

Composite maternal and neonatal outcomes for twins and triplets were added post hoc because they were mainly related to 'serious neonatal morbidity' which was prioritised as a critical outcome for decision making.

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

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

Excluded studies

5 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

7 Table 2 provides a brief summary of the included study.

8 **Table 2: Summary of included studies for twin and triplet pregnancy**

Study	Population	Intervention/ Comparison	Outcomes	Comments
Asztalos 2016 RCT 25 countries (including Australia, Canada, USA, Europe)	See Barrett 2013 N=4,603 children N=2,323 women	See Barrett 2013	For the baby at 2-year follow-up: • neonatal mortality • serious morbidity: ○ necrotising enterocolitis ○ cystic periventricular leukomalacia ○ neurodevelopmental delay ○ cerebral palsy ○ cognitive delay ○ birth trauma	2-year follow-up of the Barrett 2013 RCT related to neurodevelopmental outcomes
Hofmeyr 2015 (Barrett 2013, RCT, 25 countries (including Australia, Canada, USA, Europe); Rabinovici 1987, RCT, Israel)	Barrett 2013 N=2,804 women with twin pregnancy Women with a twin pregnancy between 32 weeks 0 days and 38 weeks 6 days of gestation. First twin was in the cephalic presentation and both fetuses were alive with an estimated weight between	Barrett 2013 and Rabinovici 1987 Planned CS versus planned VB Barrett 2013 Elective births by means of CS (for women in the planned CS) or labour induction (for women in the planned vaginal birth group) was planned between 37 weeks 5 days and 38 weeks 6 days of gestation	Barrett 2013 For the woman up to 28 days postpartum: • mortality • serious maternal morbidity: ○ haemorrhage ○ sepsis (confirmed by blood culture) ○ hysterectomy ○ actual mode of birth • composite mortality or serious morbidity For the baby up to 28 days after birth: • mortality • birth trauma: ○ long-bone/ other fracture • intracerebral haemorrhage • ≥2 seizures within 72 hrs after birth • necrotising enterocolitis • cystic periventricular leukomalacia	Barrett 2013 Presentation at birth (n/total n) Both twins in cephalic presentation: • planned VB (n=1393): 845/1393 (60.7%) • CS (n=1393): 798/1391 (57.4%) First twin in cephalic presentation and second twin in non-cephalic presentation: • planned VB: 507/1393 (36.4%) • CS: 542/1391 (39%) First twin in non-cephalic presentation and second twin in

Study	Population	Intervention/ Comparison	Outcomes	Comments
	1,500 g and 4,000 g, confirmed by means of ultrasonography within 7 days before randomisation <u>Rabinovici 1987</u> N=60 women with twin pregnancy		• respiratory distress syndrome • neonatal sepsis within 72 hrs of age • intraventricular haemorrhage (Grade 1 or 2) • composite of fetal/neonatal mortality or serious morbidity <u>Rabinovici 1987</u> For the woman: • mortality • actual mode of birth For the baby: • mortality • birth trauma (not defined) • neonatal encephalopathy (not defined) • nerve palsy (including brachial plexus injury) • intracerebral haemorrhage • intraventricular haemorrhage (Grade 3 or 4)	cephalic or non-cephalic presentation: • planned VB: 41/1393 (2.9%) • CS: 51/1391 (3.7%) <u>Rabinovici 1987</u> Women were either induced or had a spontaneous labour Presentation at birth (n/total n) The first fetus in vertex presentation and the second twin in breech presentation/ transverse lie Vertex –breech presentation: • planned VB: 21/33 (39%) • CS: 18/27 (66.7%) Vertex transverse presentation: • planned VB: 12/33 (39%) • CS: 9/27 (33%)
Hutton 2015 (3-month follow-up to Barrett 2013) RCT 25 countries (including Australia, Canada, USA, Europe)	See Barrett 2013 N=2,570 women with twin pregnancy	See Barrett 2013	For the woman at 3-month follow-up: • long-term consequences: ○ problematic urinary /faecal incontinence For the baby at 3-months follow-up: • mortality	Study includes one singleton pregnancy
Lappen 2016	N=80 women	Planned CS versus	For the woman: • actual mode of birth	Study data originated from a

Study	Population	Intervention/ Comparison	Outcomes	Comments
Retrospective cohort study USA	with triplet pregnancy, N=240 neonates	attempted VB	• peripartum hysterectomy For the baby postpartum: • neonatal asphyxia	large multicentre cohort of women with triplet pregnancies
Mol 2018 Retrospective cohort The Netherlands	N=386 women with triplet pregnancy, N=1,158 neonates	Planned CS versus planned VB	For the woman: • actual mode of birth For the baby: • intrapartum/neonatal mortality up to 28 days after birth • intrapartum/neonatal mortality up to 28 days after birth: ○ first baby ○ second baby ○ third baby • composite of adverse neonatal morbidity outcomes • composite of adverse neonatal morbidity outcomes: ○ first baby ○ second baby ○ third baby • intrapartum/neonatal mortality up to 28 days after birth or composite of adverse neonatal morbidity outcomes	Study data originated from a retrospective national cohort registered in the Netherlands Perinatal Registry which covers approximately 96% of all births in the Netherlands
Peress 2018 Retrospective cohort USA	N=83 women with triplet pregnancy, N=249 neonates	Planned CS versus planned VB	For the woman: • actual mode of birth • peripartum hysterectomy • postpartum haemorrhage (not defined) For the baby: • respiratory distress syndrome • intraventricular haemorrhage (grade 3/4) • necrotising enterocolitis • composite of adverse neonatal morbidity outcomes	

CS: caesarean section; RCT: randomised controlled trial; VB: vaginal 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. The committee considered that maternal choice was likely to be important in framing guideline recommendations and that if the clinical evidence demonstrated a clear benefit of a particular mode of birth then the cost effectiveness was likely to be self-evident without the need for a formal analysis.

In order to assist committee discussion, resource use and unit cost data relating to twin and triplet pregnancies were considered (see Appendix J).

Evidence statements

Comparison: planned caesarean section versus planned vaginal birth for women with twin or triplet pregnancy

Outcomes for the woman

Twin pregnancy

Mortality (follow-up 28 days in 1 study)

Very low quality evidence from 2 RCTs in women with twin pregnancy (N=2,844) showed no clinically important difference in the number of deaths at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Haemorrhage (blood loss ≥1500 ml, follow-up 28 days)

Low quality evidence from 1 RCT in women with twin pregnancy (N=2,782) showed no clinically important difference in the occurrence of haemorrhage at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Sepsis (follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=2,782) showed no clinically important difference in the occurrence of sepsis at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Hysterectomy (follow-up 28 days)

Low quality evidence from 1 RCT in women with twin pregnancy (N=2,782) showed no clinically important difference in the number of hysterectomies at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Problematic urinary incontinence (follow-up 3 months)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=2,570) showed no clinically important difference in the occurrence of problematic urinary incontinence at the 3-mont follow-up between women who had planned caesarean section or planned vaginal birth.

Problematic faecal incontinence (follow-up 3 months)

Low quality evidence from 1 RCT in women with twin pregnancy (N=2,570) showed no clinically important difference in the occurrence of problematic faecal incontinence at the 3-mont follow-up between women who had planned caesarean section or planned vaginal birth.

Actual mode of birth - caesarean section for both twins

Low quality evidence from 2 RCTs in women with twin pregnancy (N=2,845) showed a clinically important difference in the number of the actual mode of birth, that is caesarean section for both twins, between women who had planned caesarean section or planned vaginal birth. One thousand two hundred seventy nine out of 1,419 (90%) women who were planned for caesarean section gave birth via caesarean section.

Actual mode of birth - vaginal and caesarean section

High quality evidence from 1 RCT in women with twin pregnancy (N=2,785) showed a clinically important difference in the number of the actual mode of birth, that is vaginal and caesarean section, between women who had planned caesarean section or planned vaginal birth. Fifty nine out of 1,393 (4.2%) women who were planned for vaginal birth had a combined vaginal-caesarean section birth (that is 1 twin born vaginally and the other twin via caesarean section). Eleven out of 1,393 (0.8%) women who were planned for caesarean section had a combined vaginal-caesarean section birth.

Actual mode of birth - vaginal for both twins

Low quality evidence from 2 RCTs in women with twin pregnancy (N=2,845) showed a clinically important difference in the number of the actual mode of birth, that is vaginal birth for both twins, between women who had planned caesarean section or planned vaginal birth. Eight hundred and fourteen out of 1,426 women (57%) who were planned for vaginal birth gave birth vaginally.

Composite of mortality or serious morbidity (follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=2,784) showed no clinically important difference in the incidence of composite outcome of mortality or serious morbidity between women who had planned caesarean section or planned vaginal birth.

Triplet pregnancy

Peripartum hysterectomy

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=80) showed no clinically important difference in the incidence of peripartum hysterectomy events between women who had planned caesarean section or planned vaginal birth. Very low quality evidence from another observational study in women with triplet pregnancy (N=83) showed no clinically important difference in the incidence of peripartum hysterectomy events between women who had planned caesarean section or planned vaginal birth.

Postpartum haemorrhage (not defined)

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=83) showed no clinically important difference in the incidence of postpartum haemorrhage events between women who had planned caesarean section or planned vaginal birth.

Actual mode of birth

Low quality evidence from 1 observational study in women with triplet pregnancy (whole cohort N=80) showed a clinically important difference in the number of the actual mode of birth between women who had planned caesarean section or planned vaginal birth. Four out of 24 women (17%) who were planned for vaginal birth gave birth vaginally.

Low quality evidence from the same observational study in women with triplet pregnancy (N=47) showed a clinically important difference in the number of the actual mode of birth between women who had planned caesarean section or planned vaginal birth and whose babies were born at ≥34 weeks and who were induced or augmented. Four out of 18 women (22%) who were planned for vaginal birth gave birth vaginally.

Very low quality evidence from another observational study in women with triplet pregnancy (N=386) showed a clinically important difference in the number of the actual mode of birth between women who had planned caesarean section or planned vaginal birth. Seventy three out of 167 women (44%) who were planned for vaginal birth gave birth vaginally.

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=83) showed a clinically important difference in the number of the actual mode of birth between women who had planned caesarean section or planned vaginal birth. Twelve out of 21 women (57%) who were planned for vaginal birth gave birth vaginally.

Outcomes for the baby

Twin pregnancy

Fetal mortality (before onset of labour/during birth)

Low quality evidence from 1 RCT in women with twin pregnancy (N=5,565) showed no clinically important difference in the number of fetal deaths before onset of labour or during birth between women who had planned caesarean section or planned vaginal birth.

Neonatal mortality (follow-up 28 days in 1 study)

Very low quality evidence from 2 RCTs in women with twin pregnancy (N=5,685) showed no clinically important difference in the number of neonatal deaths at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Neonatal mortality (2-year follow-up)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=4,603) showed no clinically important difference in the number of neonatal deaths at the 2-year follow-up between women who had planned caesarean section or planned vaginal birth.

Neurodevelopmental delay (2-year follow-up)

Low quality evidence from 1 RCT in women with twin pregnancy (N=4,545) showed no clinically important difference in the number of infants with neurodevelopmental delay at the 2-year follow-up between women who had planned caesarean section or planned vaginal birth.

Cerebral palsy (2-year follow-up)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=4,545) showed no clinically important difference in the number of infants with cerebral palsy at the 2-year follow-up between women who had planned caesarean section caesarean section caesarean section or planned vaginal birth.

Motor delay (2-year follow-up)

Low quality evidence from 1 RCT in women with twin pregnancy (N=4,545) showed no clinically important difference in the number of infants with motor delay at the 2-year follow-up between women who had planned CS or planned vaginal birth.

Cognitive delay (2-year follow-up)

Low quality evidence from 1 RCT in women with twin pregnancy (N=4,543) showed no clinically important difference in the number of infants with cognitive delay at the 2-year follow-up between women who had planned caesarean section or planned vaginal birth.

Nerve palsy (including brachial plexus injury, follow-up 28 days)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=120) showed no clinically important difference in the number of infants with nerve palsy between women who had planned caesarean section or planned vaginal birth.

Birth trauma: long-bone fracture present at 72 hours of age or at discharge from hospital (follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with long-bone fracture present at 72 hours of age or at discharge from hospital between women who had planned caesarean section or planned vaginal birth.

Birth trauma: other bone fracture present at 72 hours of age or at discharge from hospital (follow-up 28 days)

Low quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with other bone fracture present at 72 hours of age or at discharge from hospital between women who had planned caesarean section or planned vaginal birth.

Birth trauma (not defined)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=120) showed no clinically important difference in the number of infants with birth trauma between women who had planned caesarean section or planned vaginal birth.

Birth trauma (not defined, 2-year follow-up)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=4,562) showed no clinically important difference in the number of infants with birth trauma at the 2-year follow-up between women who had planned caesarean section or planned vaginal birth.

≥2 seizures within 72 hr after birth

Low quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with ≥2 seizures within 72 hr after birth between women who had planned caesarean section or planned vaginal birth.

Intraventricular haemorrhage (Grade 1 or 2, follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed a clinically important beneficial effect in women who had planned caesarean section compared with planned vaginal birth in the number of infants with intraventricular haemorrhage (Grade 1 or 2) at the 28-day follow-up.

Intraventricular haemorrhage (Grade 3 or 4)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=120) showed no clinically important difference in the number of infants with intraventricular haemorrhage (grade 3 or 4) between women who had planned caesarean section or planned vaginal birth.

Cystic periventricular leukomalacia (follow-up 28 days)

Low quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with cystic periventricular leukomalacia at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Cystic periventricular leukomalacia (2-year follow-up)

Low quality evidence from 1 RCT in women with twin pregnancy (N=4,562) showed no clinically important difference in the number of infants with cystic periventricular leukomalacia at 2-year follow-up between women who had planned caesarean section caesarean section or planned vaginal birth.

Neonatal encephalopathy (not defined)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=120) showed no clinically important difference in the number of infants with neonatal encephalopathy between women who had planned caesarean section or planned vaginal birth.

Necrotising enterocolitis (follow-up 28 days)

Low quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with necrotising enterocolitis at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Necrotising enterocolitis (2-year follow-up)

Very low quality evidence from 1 RCT in women with twin pregnancy (N=4,562) showed no clinically important difference in the number of infants with necrotising enterocolitis at 2-year follow-up between women who had planned caesarean section or planned vaginal birth.

Respiratory distress syndrome (follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=5,524) showed no clinically important difference in the number of infants with respiratory distress syndrome at the 28-day follow-up between women who had planned caesarean section or planned vaginal birth.

Composite of fetal/neonatal mortality or serious morbidity (follow-up 28 days)

Moderate quality evidence from 1 RCT in women with twin pregnancy (N=5,565) showed no clinically important difference in the number of infants who experienced a composite outcome

of fetal/neonatal death or serious morbidity between women who had planned caesarean section or planned vaginal birth.

Triplet pregnancy

Intrapartum/neonatal mortality up to 28 days after birth - overall

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants who experienced intrapartum or neonatal mortality up to 28 days after birth between women who had planned caesarean section or planned vaginal birth.

Intrapartum/neonatal mortality up to 28 days after birth – first baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants born first who experienced intrapartum or neonatal mortality up to 28 days after birth between women who had planned caesarean section or planned vaginal birth.

Intrapartum/neonatal mortality up to 28 days after birth – second baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants born second who experienced intrapartum or neonatal mortality up to 28 days after birth between women who had planned caesarean section or planned vaginal birth.

Intrapartum/neonatal mortality up to 28 days after birth – third baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants born third who experienced intrapartum or neonatal mortality up to 28 days after birth between women who had planned caesarean section or planned vaginal birth.

Respiratory distress syndrome

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants with respiratory distress syndrome between women who had planned caesarean section or planned vaginal birth.

Intraventricular haemorrhage (grade 3/4)

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants with intraventricular haemorrhage (grade 3/4) between women who had planned caesarean section or planned vaginal birth.

Necrotising enterocolitis

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants with necrotising enterocolitis between women who had planned caesarean section or planned vaginal birth.

Neonatal asphyxia (postpartum)

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=240) showed a clinically important beneficial effect in women who had planned caesarean section compared with planned vaginal birth in the number of infants with neonatal asphyxia.

Composite of adverse neonatal morbidity outcomes – overall

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed a clinically important beneficial effect in women who had planned caesarean section compared with planned vaginal birth in the number of infants who experienced composite of adverse neonatal morbidity outcomes.

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=249) showed no clinically important difference in the number of infants who experienced composite of adverse neonatal morbidity outcomes between women who had planned caesarean section or planned vaginal birth.

Composite of adverse neonatal morbidity outcomes – first baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants born first who experienced composite of adverse neonatal morbidity outcomes between women who had planned caesarean section or planned vaginal birth.

Composite of adverse neonatal morbidity outcomes – second baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed that there may be a clinically important beneficial effect in women who had planned caesarean section compared with planned vaginal birth in the number of infants born second who experienced composite of adverse neonatal morbidity outcomes between women who had planned caesarean section or planned vaginal birth; however there is uncertainty around the estimate.

Composite of adverse neonatal morbidity outcomes – third baby

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed no clinically important difference in the number of infants born third who experienced composite of adverse neonatal morbidity outcomes between women who had planned caesarean section or planned vaginal birth.

Intrapartum/neonatal mortality up to 28 days after birth or composite of adverse neonatal morbidity outcomes

Very low quality evidence from 1 observational study in women with triplet pregnancy (N=386) showed that there may be a clinically important difference in the number of infants who experienced intrapartum or neonatal mortality up to 28 days after birth or composite of adverse neonatal morbidity outcomes between women who had planned caesarean section or planned vaginal birth; however there is uncertainty around the estimate.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal mortality and perinatal or neonatal mortality were prioritised as critical outcomes by the committee. Perinatal or neonatal mortality 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 due to the impact of these conditions on

the children themselves and also the emotional and physical impact of caring for these children by their families.

The committee agreed that as well as the actual mode of birth, serious maternal morbidity such as septicaemia/sepsis, organ failure (liver, renal, respiratory), uterine rupture, hysterectomy, major postpartum haemorrhage (>1000ml), long-term consequences (urinary and fecal incontinence, pelvic organ prolapse) should be important outcomes. This was because they can have long term impact on the woman's psychological and physical health. Many of these women would have been considered low risk prior to birth and the likelihood of encountering such issues should remain low.

Serious neonatal morbidity such as seizures, birth trauma (fractures), respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, neonatal encephalopathy or birth asphyxia (or severe hypoxic-ischemic encephalopathy – grade 2&3) were also identified as important outcomes by the committee because although some may be transient, they may also have a long-term impact on the child's health.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as very low to high. Overall, study design, risk of bias and imprecision in the studies was one of the main factors that lowered the confidence in the evidence.

The committee noted that in the Barrett 2013 trial women had to meet specific criteria in order to be eligible be enrolled in the trial. The committee particularly discussed the inclusion criteria of this trial, for women with pregnancies 32 to 38^{+6} weeks gestation, where twin 1 was cephalic, the twins had an estimated fetal weight of 1.5 to 4 kg and there was no obvious size discordance between twin 1 and twin 2.

They also highlighted that the trial had expert attendants and that it was therefore not fully generalisable to all women who are planning the birth of twins. However the committee noted that it is currently recommended that the core team of specialist obstetricians, specialist midwives and ultrasonographers, should all have experience and knowledge of managing twin and triplet pregnancies (see recommendations in 'specialist care' section of the guideline).

Benefits and harms

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 in a woman's life 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. Due to the high risk of preterm birth for women with twin or triplet pregnancy such discussions (including mode of birth) should be initiated by week 24 and conducted at the latest by week 28 of her 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 decided to divide their recommendations based on the risks associated with different types of twin or triplet pregnancy into (from lowest to highest risk): dichorionic diamniotic or monochorionic diamniotic twin pregnancy, monochorionic monoamniotic twin pregnancy, and triplet pregnancy.

Twin pregnancy: dichorionic diamniotic or monochorionic diamniotic

In relation to dichorionic diamniotic or monochorionic diamniotic twin pregnancy and based on the evidence indicating that there were no differences between maternal and neonatal

mortality and morbidity between the groups of women who had planned caesarean and women who had vaginal birth, the committee decided that either of these would appear to be safe options in uncomplicated pregnancies. They therefore agreed that this should be explained to the women when planning mode of birth. However, given the limitations of the inclusion criteria in the larger trial, and based on their experience and expertise the committee agreed that this should only be recommended for a woman whose pregnancy has progressed beyond 32 weeks pregnancy where the pregnancy remains uncomplicated, there are no obstetric contraindications to labour, the first twin is in a cephalic presentation and there is no significant size discordance between the twins. Based on their knowledge of the evidence from retrospective cohort studies (which were not included for twins since RCT data was available), indicating a potentially high risk to the second twin associated with vaginal birth, the committee were cautious not to make a stronger recommendation in favour of vaginal birth.

Based on the evidence (which was consistent with the committee's experience of current UK clinical practice), it was acknowledged that even if these conditions are met and a woman opts for a vaginal birth, she may still need an emergency caesarean section. The committee agreed that the small proportion of women who undergo an emergency caesarean section for the birth of the second twin are potentially at the highest risk of neonatal morbidity and mortality, and maternal morbidity. Therefore they recommended that this risk should be explained to women when planning mode of birth antenatally.

The committee agreed, based on their experience and expertise, that women where the first twin was in a non-cephalic presentation should be offered caesarean section. The concerns regarding vaginal birth where twin one is breech, would be cord prolapse, particularly in preterm or footling presentations, and interlocking of twins, although this is a rare occurrence. Whilst the evidence in this area remains limited, the committee agreed that the safest option would be to offer caesarean section in these cases.

The committee agreed that it is reasonable to offer women caesarean section when presenting in established preterm labour at 26 to 32 weeks if twin one is in a non-cephalic presentation. They agreed that there remains a small risk of fetal head entrapment associated with preterm breech birth and therefore birth by caesarean section should be discussed with the woman. There may also be a higher risk of cord prolapse in cases where the breech is not engaged. Transverse presentation remains a contraindication to vaginal birth as it would be in a singleton pregnancy. The committee recognised that there was a lack of evidence in this area but based on the risks versus benefits, they agreed that caesarean section would be a safe option.

The evidence for mode of birth in twin and triplet pregnancies under 26 weeks is lacking. The committee agreed that a discussion should take place with the woman of the overall risks versus benefits of vaginal birth versus caesarean section at this gestation. The committee agreed that it would be useful to involve the neonatal team in the discussion about the viability of the babies. However, even though consulting a neonatologist would be the preferred option, the committee recognised that this may cause a delay and these are emergency situations where decisions have to be made under considerable time pressure. They therefore came to the conclusion that it would be preferable not to be prescriptive about the involvement of the neonatal team in the recommendation. Despite the lack of evidence the committee agreed that a research recommendation for mode of birth at a gestation below 26 weeks would not be possible to carry out since this is a high risk group and decisions would always have to be made on a case by case basis.

Based on the evidence the committee acknowledged that although the incidence of grade 1 and 2 intraventricular haemorrhage was higher in babies who had a vaginal birth, compared to those born by caesarean section, they believed this to be a relatively benign and common finding in preterm babies, and noted that there were no more severe grade 3 and 4 intraventricular haemorrhage events that would be reflective of long-term brain injury.

Twin pregnancy: monochorionic monoamniotic

In relation to mode of birth in the higher risk monochorionic monoamniotic twin pregnancies (which is a very small proportion of all women with twin pregnancy) the committee agreed that women should be offered caesarean section. A caesarean section is indicated in the following situations: at the time of the planned birth (see evidence review D related to timing of birth), after any complication is diagnosed in her pregnancy requiring earlier delivery or if she was in established preterm labour and there was a reasonable chance of survival of the babies. The risk of cord entanglement prior to birth remains high in these pregnancies regardless of the mode of birth and, while the evidence is limited in this area, caesarean section remains the preferred mode of birth.

Triplet pregnancy

Whilst the committee agreed that there was no absolute contraindication to vaginal birth, there was limited and very low to low quality evidence in this area with only retrospective cohort studies identified. For most of the outcomes there was no difference between caesarean section and vaginal birth. However, one study suggested higher morbidity as well as overall mortality associated with vaginal birth. Even though the evidence was of low to very low quality the committee agreed that this was consistent with their experience. Therefore due to the risk of serious harm the committee, based on the evidence and their experience and expertise, agreed that caesarean section (if viability was confirmed) would be the safest option. A caesarean section is then indicated in the following situations: at the time of the planned birth (see evidence review D related to timing of birth), after any complication is diagnosed in her pregnancy requiring earlier delivery or if she is in established preterm labour and there is a reasonable chance of survival of the babies. Despite the limited evidence the committee did not recommend further research because they agreed that a mode of birth trial would not be ethical since the safest option for triplet pregnancy would be a caesarean section.

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 the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy. In order to facilitate this assessment, resource use and unit cost data relating to twin and triplet pregnancies were considered (see Appendix J).

Whilst the committee noted that vaginal birth is cheaper than a planned caesarean section they were also aware that 30%-40% of planned twin vaginal births result in an expensive emergency caesarean section. Given that the evidence reviewed also did not demonstrate a clear clinical benefit of a particular mode of birth for dichorionic diamniotic or monochorionic diamniotic twin pregnancies the committee did not consider that the cost effectiveness of a particular mode of birth was clear in these groups. Therefore, they considered that informed maternal choice for preferred mode of birth was not contraindicated on cost effectiveness grounds.

Other factors the committee took into account

The committee considered whether there were vulnerable groups for whom additional recommendations were necessary, but concluded that none were necessary.

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Appendices

Appendix A – Review protocol

3.1: Review protocol – What is for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Table 3: Review protocol for mode of birth

ID (to be deleted in final version)	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?
II	Type of review question	Intervention
III	Objective of the review	The optimal mode of birth in twin and triplet pregnancy has been a subject of debate. This review aims to address the uncertainty around the mode of birth in these pregnancies
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 alive Setting: hospital
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Planned caesarean section
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	Planned vaginal birth
VII	Outcomes and prioritisation	**Critical** For the woman: • mortality For the baby: • perinatal or neonatal mortality (excluding mortality due to lethal fetal anomalies) • disability in childhood (neurodevelopmental: cerebral palsy, brain injury, nerve palsy; learning disability or cognitive impairment) **Important** For the woman: • maternal morbidity (for example, septicaemia/sepsis, organ failure (liver, renal, respiratory), uterine rupture, hysterectomy, postpartum haemorrhage (>1000ml), long-term consequences (urinary and fecal incontinence, pelvic organ prolapse) • actual mode of birth • composite outcome For the baby: • neonatal morbidity (for example, seizures, birth trauma (fractures), respiratory distress

ID (to be deleted in final version)	Field (based on PRISMA-P)	Content
		syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, neonatal encephalopathy or birth asphyxia or severe hypoxic-ischemic encephalopathy – grade 2/3) • composite outcome
VIII	Eligibility criteria – study design	Systematic reviews Randomised controlled trials (RCTs) Cohort studies for term and preterm triplet pregnancy (prospective cohort studies will be prioritised over retrospective) Conference abstracts will not be considered
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 fibroid, >1 previous CS and specific indications for CS such as breech presentation, placenta praevia and morbidly adherent placenta) • studies that do not report results specifically for twin and/or triplet pregnancies
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: **For twin pregnancy**: • dichorionic diamniotic • monochorionic diamniotic • monochorionic monoamniotic • cephalic, non-cephalic **For triplet pregnancy:** • trichorionic triamniotic • dichorionic triamniotic • monochorionic triamniotic • dichorionic diamniotic (a monochorionic twins set) • monochorionic monamniotic • cephalic, non-cephalic The following groups will used to explore any significant heterogeneity identified: 1. Gestational age for twin and triplet pregnancy: • <28 weeks • 28 – <32 weeks • 32 – <34 weeks • 34 – 36/37 weeks

ID (to be deleted in final version)	Field (based on PRISMA-P)	Content
		2. Previous CS versus no previous CS for twin and triplet pregnancy 3. Discordance (between largest and smallest fetus) for twin and triplet pregnancy: • <20% • 20-25% • >25%
XI	Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question, 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 Meta-analyses will be performed using Cochrane Review Manager (RevMan5) and WinBUGS if available data permit '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
XIV	Identify if an update	This topic was not included in the previous 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 G (clinical evidence tables) or H (economic evidence tables)

ID (to be deleted in final version)	Field (based on PRISMA-P)	Content
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)
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 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
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

1 *AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register for*
2 *Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CS: caesarean section; DARE: Database of*
3 *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 for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Clinical searches

Date of initial search: 29/11/2017

Database(s): Embase Classic+Embase 1947 to 2017 November 28, Maternity & Infant Care Database (MIDIRS) 1971 to October 2017, 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 10, Maternity & Infant Care Database (MIDIRS) 1971 to August 2018 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	(pregnancy - mulitple or twin* or triplet*).hw. use mwic
4	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
5	(chorionicity or monochorionic or dichorionic or trichorionic).tw.
6	or/1-5
7	exp obstetric delivery/
8	exp obstetric operation/
9	exp childbirth/
10	birth/
11	or/7-10 use emczd
12	exp Delivery, Obstetric/
13	exp Parturition/
14	exp Labor, Obstetric/
15	or/12-14 use ppez
16	childbirth.hw.
17	c?esarean section.hw.
18	forceps.hw.
19	labo?r.hw.
20	mode of delivery.hw.
21	obstetric delivery.hw.
22	vacuum extraction.hw.
23	vaginal birth.hw.
24	or/16-23 use mwic
25	(mode of delivery or method of delivery or childbirth* or obstetric deliver* or c?esar* or c-section* or elective birth* or planned birth* or planned deliver* or vagina* birth* or vagina* deliver* or normal birth* or normal deliver* or natural birth* natural deliver* or VBAC or assisted birth* or assisted deliver* or forceps or vacuum or ventouse).tw.

#	Searches
26	or/11,15,24-25
27	6 and 26
28	limit 27 to english language [Limit not valid in MWIC; records were retained]
29	Letter/ use ppez
30	letter.pt. or letter/ use emczd
31	note.pt.
32	editorial.pt.
33	Editorial/ use ppez
34	News/ use ppez
35	exp Historical Article/ use ppez
36	Anecdotes as Topic/ use ppez
37	Comment/ use ppez
38	Case Report/ use ppez
39	case report/ or case study/ use emczd
40	(letter or comment*).ti.
41	or/29-40
42	randomized controlled trial/ use ppez
43	randomized controlled trial/ use emczd
44	randomised controlled trials.hw. use mwic
45	random*.ti,ab.
46	or/42-45
47	41 not 46
48	animals/ not humans/ use ppez
49	animal/ not human/ use emczd
50	(animals not (human or humans)).hw. use mwic
51	nonhuman/ use emczd
52	exp Animals, Laboratory/ use ppez
53	exp Animal Experimentation/ use ppez
54	exp Animal Experiment/ use emczd
55	exp Experimental Animal/ use emczd
56	exp Models, Animal/ use ppez
57	animal model/ use emczd
58	exp Rodentia/ use ppez
59	exp Rodent/ use emczd
60	(rat or rats or mouse or mice).ti.
61	or/47-60
62	28 not 61
63	Meta-Analysis/
64	Meta-Analysis as Topic/
65	systematic review/
66	meta-analysis/
67	(meta analy* or metanaly* or metaanaly*).ti,ab.
68	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
69	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
70	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

#	Searches
71	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72	(search* adj4 literature).ab.
73	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74	cochrane.jw.
75	((pool* or combined) adj2 (data or trials or studies or results)).ab.
76	(meta-analysis or systematic reivews).hw.
77	or/67-76 use mwic
78	or/63-64,67,69-74 use ppez
79	or/65-68,70-75 use emczd
80	or/77-79
81	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
82	81 use ppez
83	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
84	83 use ppez
85	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
86	85 use emczd
87	(clinical trials or controlled clinical trials or crossover studies or randomised controlled trials).hw. use mwic
88	82 or 84
89	or/86-88
90	Epidemiologic Studies/
91	Case Control Studies/
92	Retrospective Studies/
93	Cohort Studies/
94	Longitudinal Studies/
95	Follow-Up Studies/
96	Prospective Studies/
97	Cross-Sectional Studies/
98	or/90-97 use ppez
99	clinical study/
100	case control study/
101	family study/
102	longitudinal study/
103	retrospective study/
104	prospective study/
105	cohort analysis/
106	or/99-105 use emczd
107	(epidemiologic methods or cohort studies or observational studies or longitudinal studies or prospective study or prospective studies or cross-sectional studies or case control studies or comparative study or retrospective studies).hw. use mwic
108	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.

#	Searches
109	or/98,106-108
110	80 or 89 or 109
111	62 and 110
112	remove duplicates from 111

Date of initial search: 27/11/2017

Database(s): The Cochrane Library, issue 11 of 12, November 2017

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) N3 (birth* or pregnan* or gestation* or foetus* or fetus or foetal or fetal))
#3	(chorionicity or monochorionic or dichorionic or trichorionic)
#4	{or #1-#3}
#5	MeSH descriptor: [Delivery, Obstetric] explode all trees
#6	MeSH descriptor: [Parturition] explode all trees
#7	MeSH descriptor: [Labor, Obstetric] explode all trees
#8	(mode of delivery or method of delivery or childbirth* or obstetric deliver* or caesar* or cesar* or c-section* or elective birth* or planned birth* or planned deliver* or vagina* birth* or vagina* deliver* or normal birth* or normal deliver* or natural birth* natural deliver* or VBAC or assisted birth* or assisted deliver* or forceps or vacuum or ventouse)
#9	{or #5-#8}
#10	#4 and #9

Health Economics Searches

For the Cochrane Library, see above

Date of initial search: 27/11/2017

Database(s): Embase Classic+Embase 1947 to 2017 November 26, Maternity & Infant Care Database (MIDIRS) 1971 to October 2017, 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 10, Maternity & Infant Care Database (MIDIRS) 1971 to August 2018 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	(pregnancy - mulitple or twin* or triplet*).hw. use mwic

#	Searches
4	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
5	(chorionicity or monochorionic or dichorionic or trichorionic).tw.
6	or/1-5
7	exp obstetric delivery/
8	exp obstetric operation/
9	exp childbirth/
10	birth/
11	or/7-10 use emczd
12	exp Delivery, Obstetric/
13	exp Parturition/
14	exp Labor, Obstetric/
15	or/12-14 use ppez
16	childbirth.hw.
17	c?esarean section.hw.
18	forceps.hw.
19	labo?r.hw.
20	mode of delivery.hw.
21	obstetric delivery.hw.
22	vacuum extraction.hw.
23	vaginal birth.hw.
24	or/16-23 use mwic
25	(mode of delivery or method of delivery or childbirth* or obstetric deliver* or c?esar* or c-section* or elective birth* or planned birth* or planned deliver* or vagina* birth* or vagina* deliver* or normal birth* or normal deliver* or natural birth* natural deliver* or VBAC or assisted birth* or assisted deliver* or forceps or vacuum or ventouse).tw.
26	or/11,15,24-25
27	6 and 26
28	limit 27 to english language [Limit not valid in MWIC; records were retained]
29	Letter/ use ppez
30	letter.pt. or letter/ use emczd
31	note.pt.
32	editorial.pt.
33	Editorial/ use ppez
34	News/ use ppez
35	exp Historical Article/ use ppez
36	Anecdotes as Topic/ use ppez
37	Comment/ use ppez
38	Case Report/ use ppez
39	case report/ or case study/ use emczd
40	(letter or comment*).ti.
41	or/29-40
42	randomized controlled trial/ use ppez
43	randomized controlled trial/ use emczd
44	randomised controlled trials.hw. use mwic
45	random*.ti,ab.
46	or/42-45
47	41 not 46
48	animals/ not humans/ use ppez
49	animal/ not human/ use emczd
50	(animals not (human or humans)).hw. use mwic
51	nonhuman/ use emczd
52	exp Animals, Laboratory/ use ppez
53	exp Animal Experimentation/ use ppez
54	exp Animal Experiment/ use emczd
55	exp Experimental Animal/ use emczd
56	exp Models, Animal/ use ppez

#	Searches
57	animal model/ use emczd
58	exp Rodentia/ use ppez
59	exp Rodent/ use emczd
60	(rat or rats or mouse or mice).ti.
61	or/47-60
62	28 not 61
63	Economics/
64	Value of life/
65	exp "Costs and Cost Analysis"/
66	exp Economics, Hospital/
67	exp Economics, Medical/
68	Economics, Nursing/
69	Economics, Pharmaceutical/
70	exp "Fees and Charges"/
71	exp Budgets/
72	or/63-71 use ppez
73	health economics/
74	exp economic evaluation/
75	exp health care cost/
76	exp fee/
77	budget/
78	funding/
79	or/73-78 use emczd
80	economics.hw.
81	Cost-benefit analysis.hw.
82	Cost*.hw.
83	Health care costs.hw.
84	financ*.hw.
85	funding.hw.
86	or/80-85 use mwic
87	budget*.ti,ab.
88	cost*.ti.
89	(economic* or pharmaco?economic*).ti.
90	(price* or pricing*).ti,ab.
91	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
92	(financ* or fee or fees).ti,ab.
93	(value adj2 (money or monetary)).ti,ab.
94	or/87-92
95	72 or 79 or 86 or 94
96	62 and 95
97	remove duplicates from 96

1

2

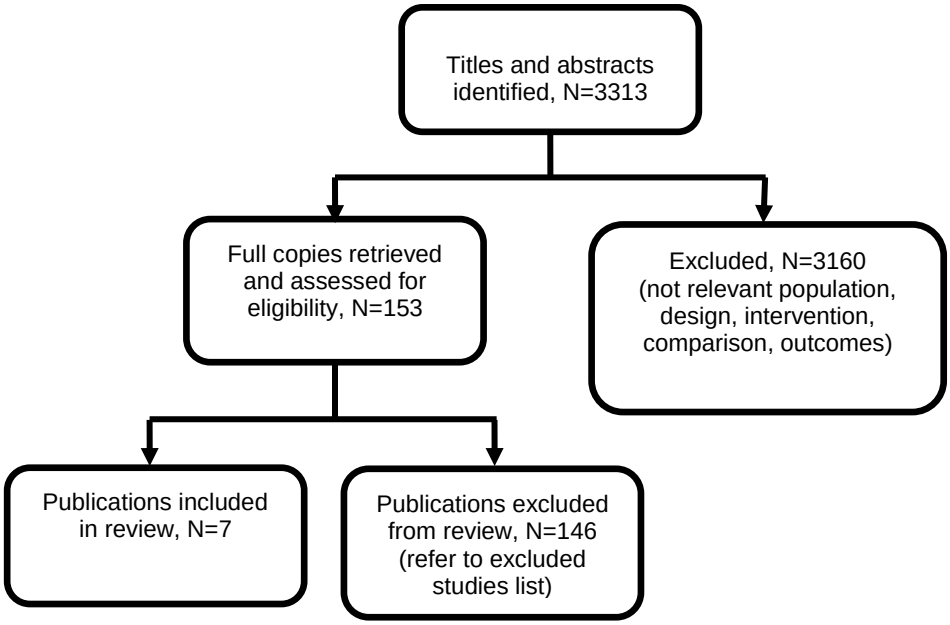
3

4

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Figure 1: Flow diagram of clinical article selection for the optimal mode of birth in twin and triplet pregnancy



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Asztalos, E. V., Hannah, M. E., Hutton, E. K., Willan, A. R., Allen, A. C., Armson, B. A., Gafni, A., Joseph, K. S., Ohlsson, A., Ross, S., Sanchez, J. J., Mangoff, K., Barrett, J. F., Twin Birth Study: 2-year neurodevelopmental follow-up of the randomized trial of planned cesarean or planned vaginal delivery for twin pregnancy, American Journal of Obstetrics & Gynecology, 214, 371.e1-371.e19, 2016	**Sample size** At 2-year follow-up N=2,323 twin pregnancies, N=4,603 children Planned vaginal birth: N=2,283 children (1,151 women) CS: N=2,320 children (1,172 women) **Characteristics** See Barrett 2013. **Inclusion criteria** See Barrett 2013. **Exclusion criteria** See Barrett 2013. In addition, children with Down	**Interventions** Planned CS	**Details** See Barrett 2013. **Power calculation** 2,200 pregnancies (4,400 children, 2,200 per intervention group) were required to detect a reduction in the risk of death or abnormal neurodevelopmental outcome from 2% with a planned vaginal birth to 0.05% with a planned caesarean birth, with 80% power, assuming a 20% loss to follow-up rate. **Intention-to-treat analysis** All results were analysed on an intention-to-treat basis.	**Results** **Neonatal outcomes at 2-year follow-up** Neonatal mortality (n, %) Planned vaginal birth = 8 (0.4) CS = 11 (0.5) Serious neonatal morbidity (n, %) Birth trauma (n, %) Planned vaginal birth = 5 (0.2) CS = 4 (0.2) Necrotising enterocolitis (n, %) Planned vaginal birth = 2 (0.1) CS = 1 (0.04) Cystic periventricular leukomalacia (n, %) Planned vaginal birth = 0 CS = 2 (0.19) Neurodevelopmental delay - (n/total n, %) Planned vaginal birth = 110/2260 (4.87) CS = 104/2285 (4.6) OR (95% CI): 0.95 (0.67-1.34); p=0.76*	**Limitations** See Barrett 2013. **Incomplete outcome data:** High risk of bias (>15% lost to follow-up). **Other information** Neurodevelopmental delay defined as a motor or cognitive delay of >3 months (age at time of assessment compared with developmental age as determined by the clinician completing the clinical neurodevelopmental assessment or the presence of cerebral palsy on clinical assessment).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 659256 **Country/ies where the study was carried out** 25 countries (including Australia, Canada, USA, Europe) **Study type** Multicentre, international randomised controlled trial (2-year follow-up to The Twin Birth Study, Barrett 2013) **Aim of the study** To present 2-year neurodevelopmental outcomes of the children in the randomised trial comparing planned caesarean versus vaginal birth for twin pregnancy.	syndrome, fragile X syndrome, or other chromosomal disorders known to contribute to neurodevelopmental delay were excluded.			<u>Cerebral palsy</u> Planned vaginal birth = 1/2260 (0.04) CS = 2/2285 (0.1) <u>Cognitive delay</u> Planned vaginal birth = 105/2258 (4.7) CS = 95/2285 (4.2) OR (95% CI): 0.91 (0.64-1.30); p=0.59* *Fetus/infant or child as unit of analysis and generalised estimating equations to account for the correlation between 2 fetuses/infants/children from the same pregnancy. Model included stratification variables of parity and gestational age at randomisation.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates December 2003 to April 2011 **Source of funding** Supported by a grant from the Canadian Institutes of Health Research					
Full citation Hofmeyr GJ, Barrett JF, Crowther CA. Planned caesarean section for women with a twin pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD006553. Includes 2 studies:	Barrett 2013 **Sample size** N=2,804 twin pregnancies (N=1,398 planned CS; N=1,406 planned vaginal birth) **Characteristics** Maternal characteristics: **Age ≥30 years (n, %)**: vaginal birth = 632/1393 (45.4), CS = 632/1393 (45.4)	Barrett 2013 **Interventions** Planned CS	Barrett 2013 **Details** Participating centres assessed fetal growth and well-being with the use of ultrasonography at least every 4 weeks and with the use of non-stress or biophysical profile tests twice weekly if needed; were prepared to perform a caesarean section within 30 minutes if necessary; and had anaesthetic, obstetrical, and nursing staff available in the hospital	Barrett 2013 **Results** **Maternal outcomes - 28 days postpartum** Mortality (n, %) Planned vaginal birth = 1 (0.1) CS = 1 (0.1) Serious maternal morbidity, - haemorrhage (n, %) Planned vaginal birth = 108 (7.8); blood loss ≥1500 ml = 32 (2.3) CS = 84 (6.0); blood loss ≥1500 ml = 26 (1.9) Sepsis (confirmed by blood culture) (n, %) Planned vaginal birth = 1 (<0.1) CS = 0	Barrett 2013 **Limitations** Limitations were assessed using the Cochrane risk of bias tool to assess risk of bias for RCTs. **Random sequence generation:** Low risk of bias (computerised randomisation stratified according to parity and gestational age with the use of random block sizes). **Allocation concealment:** Low risk of bias (central randomisation using a computerised randomisation process). **Blinding:** Low risk of bias (blinding to intervention not possible. Where

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Barrett, J. F., Hannah, M. E., Hutton, E. K., Willan, A. R., Allen, A. C., Armson, B. A., Gafni, A., Joseph, K. S., Mason, D., Ohlsson, A., Ross, S., Sanchez, J. J., Asztalos, E. V., Twin Birth Study Collaborative, Group, A randomized trial of planned cesarean or vaginal delivery for twin pregnancy.[Erratum appears in N Engl J Med. 2013 Dec 12;369(24):2364], New England Journal of Medicine, 369, 1295-305, 2013 Rabinovici, J., Barkai, G., Reichman, B., Serr, D. M., Mashiach, S., Randomized	**Gestational age (weeks, mean (SD))**: vaginal birth = 34.9 (1.8), CS = 34.9 (1.8) **<32 week 0 days (n, %):** vaginal birth = 1 (0.1), CS = 0 **32 weeks 0 days to 33 weeks 6 days (n, %):** vaginal birth = 477 (34.2), CS = 475 (34.1) **34 weeks 0 days to 36 weeks 6 days (n, %):** vaginal birth = 665 (47.7), CS 679 (48.7) **37 weeks 0 days to 38 weeks 6 days (n, %):** vaginal birth = 250 (17.9), CS = 239 (17.2) **Estimated fetal weight (g, mean (SD))**: **First twin:** vaginal birth = 2238 (419), CS = 2238 (424) **Second twin**: vaginal birth = 2232 (422), CS = 2223 (413) **Chorionicity (n, %): dichorionic and**		at the time of planned vaginal birth. Continuous electronic monitoring of the fetal heart rate was recommended during active labour. After the birth of the first twin, the use of ultrasonography was encouraged in order to check the presentation of the second twin. Elective births by means of caesarean section (for women in the planned caesarean group) or labour induction (for women in the planned vaginal birth group) was planned between 37 weeks 5 days and 38 weeks 6 days of gestation. Where the first twin was born vaginally in women in the planned caesarean group, a caesarean section was attempted for the second twin, if possible.	<u>Hysterectomy (n, %)</u> Planned vaginal birth = 3 (0.2) CS = 3 (0.2) <u>Actual mode of birth (n/total n, %)*</u> Planned vaginal birth: CS for both twins = 551/1393 (39.6); vaginal and caesarean = 59/1393 (4.2); vaginal for both twins = 783/1393 (56.2) CS: CS for both twins = 1252/1392 (89.9); vaginal and caesarean = 11/1392 (0.8); vaginal for both twins = 129/1392 (9.3) *data extracted from the original paper <u>Presentation at birth (n/total n, %)</u> <u>Both twins in cephalic presentation</u> Planned vaginal birth (n=1393): 845/1393 (60.7 CS (n=1393): 798/1391 (57.4 <u>First twin in cephalic presentation and second twin in non-cephalic presentation</u> Planned vaginal birth: 507/1393 (36.4 CS: 542/1391 (39.0) <u>First twin in non-cephalic presentation and second twin in cephalic or non-cephalic presentation</u> Planned vaginal birth: 41/1393 (2.9)	possible, outcomes for infants were masked for mode of birth). **Incomplete outcome data:** Low risk of bias (Less than 15% of women lost to follow-up. Of the 1,398 initially included women in the planned CS group, 6 women (12 fetuses) were lost to follow-up and there were 24 neonatal deaths or stillbirths. Of the 1,406 initially included women in the planned vaginal birth group, 14 women (30 fetuses) were lost to follow-up and there were 17 neonatal deaths or stillbirths. **Selective reporting:** Low risk of bias (All outcomes reported). **Other bias:** Unclear risk of bias (potential bias from outcomes reported that were not planned a priori; subgroup analyses were underpowered). **Other information** Data were mainly extracted from Hofmeyr 2015 systematic review; if insufficient data reported in the systematic review then additional data were extracted from the original studies (for example study characteristics).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
management of the second nonvertex twin: vaginal delivery or cesarean section, American Journal of Obstetrics & Gynecology, 156, 52-6, 1987 **Ref Id** 659261 **Country/ies where the study was carried out** 25 countries (including Australia, Canada, USA, Europe) **Study type** Multicentre, international randomised controlled trial (The Twin Birth Study) **Aim of the study**	**diamnionic:** vaginal birth = 970 (69.6), CS = 961 (69.0) **Monochorionic and diamnionic:** vaginal birth = 326 (23.4), CS = 334 (24.0) **Unknown**: vaginal birth = 97 (7.0), CS = 98 (7.0) **Presentation of twin B (n, %):** **Cephalic:** vaginal birth = 783 (56.2), CS = 792 (56.9) **Non-cephalic:** vaginal birth = 610 (43.8), CS = 601 (43.1); **breech:** vaginal birth = 380, CS = 364, **transverse oblique lie:** vaginal birth = 230, CS = 237 **Membranes ruptured at randomisation (n/total n, %):** vaginal birth = 76 (5.5), CS = 83 (6.0)		The pregnancy was reassessed at the time of labour, and if there was a contraindication to labour or vaginal birth, a caesarean section was undertaken. Use of oxytocin to speed up labour and the use of epidural analgesia were left to the discretion of the obstetrician. If the second twin was in the cephalic presentation, amniotomy was delayed until the fetal head was engaged and spontaneous vaginal birth was anticipated. If the second twin was in the non-cephalic presentation, the best mode of birth was decided by the obstetrician (spontaneous or assisted vaginal breech birth, total breech extraction with or without internal podalic version, external	CS: 51/1391 (3.7) <u>Composite of maternal mortality or serious maternal morbidity*:</u> planned vaginal birth = 118/1392 (8.5%) CS = 102/1392 (7.3%) *defined as maternal death or serious maternal morbidity before 28 days post-partum, defined as one or more of the following: death; haemorrhage (blood loss ≥1500 ml, need for blood transfusion, or need for dilation and curettage after birth); laparotomy; genital tract injury (need for hysterectomy; vulvar or perineal hematoma requiring evacuation; broad-ligament hematoma confirmed by means of ultrasonography, CT, or MRI; intraoperative damage to the bladder, ureter, or bowel requiring repair; fistula involving the genital tract; or third-degree or fourth-degree perineal laceration involving the anal sphincter or mucosa); thromboembolism (deep-vein thrombosis, thrombophlebitis, or pulmonary embolism) requiring anticoagulant therapy; systemic infection (temperature ≥38.5°C on two or more occasions at least 24 hours apart, not including the first 24 hours after birth, or pneumonia confirmed by means of radiography or, if there was sepsis, confirmed	

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To compare the risk of fetal or neonatal death or serious neonatal morbidity for planned caesarean versus planned vaginal birth. **Study dates** December 2003 to April 2011. **Source of funding** Supported by a grant from the Canadian Institutes of Health Research.	**Inclusion criteria** Women with a twin pregnancy between 32 weeks 0 days and 38 weeks 6 days of gestation. First twin was in the cephalic presentation and both fetuses were alive with an estimated weight between 1,500 g and 4,000 g, confirmed by means of ultrasonography within 7 days before randomisation. **Exclusion criteria** Monoamniotic twins, fetal reduction at ≥13 weeks of gestation, lethal fetal anomaly, contraindication to labour or vaginal birth (e.g. fetal compromise, second twin substantially larger than the first twin, fetal anomaly or other condition that might cause problems at birth,		cephalic version and vaginal cephalic birth, or intrapartum caesarean section). **Statistical analysis** For the composite primary outcome with planned CS versus planned vaginal birth, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with the use of a logistic model with the fetus/infant as the unit of analysis and generalised estimating equations to account for the correlation between the 2 fetuses/infants from the same pregnancy. Post-hoc analysis included 2-ssample t-tests to compare treatment group means with respect to gestational age at birth, time from randomisation to birth of the first twin, and the interval between the twin births. Planned subgroup analyses were conducted by testing the	by means of blood culture); major medical life-threatening illness (the acute respiratory distress syndrome, amniotic-fluid embolism, disseminated intravascular coagulation, bowel obstruction, or paralytic ileus requiring the use of nasogastric suctioning); wound infection requiring prolongation of the hospital stay, readmission to the hospital, or repeated treatment as an outpatient; wound dehiscence or breakdown; or other serious maternal complication. **Neonatal outcomes - follow-up 28 days after birth** Mortality (n, %) Planned vaginal birth = 17 (0.6); fetal death = 9 (0.3) (before onset of labour = 8 (0.3), during birth = 1 (<0.1), unknown = 0); neonatal death = 8 (0.3) CS = 24 (0.9); fetal death = 13 (0.5) (before onset of labour = 11 (0.4), during birth = 0, unknown = 2 (0.1)); neonatal mortality = 11 (0.4) Birth trauma (n, %) Long-bone fracture Planned vaginal birth (2,765 infants) =4 (0.1) CS = 0 Other bone fracture Planned vaginal birth = 1 (<0.,1) CS = 1 (<0.1)	

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	and previous vertical uterine incision or more than one previous low-segment caesarean birth), and previous participation in the Twin Birth Study.		interaction between the treatment group and the following baseline variables: parity (0 versus ≥1); gestational age at randomisation (32 weeks 0 days to 33 weeks 6 days, 34 weeks 0 days to 36 weeks 6 days, or 37 weeks 0 days to 38 weeks 6 days); maternal age (<30 years versus ≥30 years); presentation of the second twin (cephalic versus non-cephalic); chorionicity (dichorionic versus monochorionic); and the national perinatal mortality in the mother's country of residence (<15 deaths per 1000 births, 15 to 20 deaths per 1000 births, or ≥20 deaths per 1000 births). **Power calculation** A sample of 2,800 pregnancies (5,600 twins) were required to detect a reduction in the risk of the composite primary outcome of fetal or neonatal death or serious neonatal	Intracerebral haemorrhage Planned vaginal birth = 1 (<0.1) CS = 3 (0.1) ≥2 seizures within 72 hrs after birth (n, %) Planned vaginal birth = 3 (0.1) CS = 3 (0.1) Necrotising enterocolitis (n, %) Planned vaginal birth = 3 (0.1) CS = 1 (<0.1) Cystic periventricular leukomalacia (n, %) Planned vaginal birth = 0 CS = 2 (0.1) Respiratory distress syndrome (n/total n, %) Planned vaginal birth = 341/2765 (12.3) CS = 382/2759 (13.8) Neonatal sepsis within 72 hours of age (n, %) Planned vaginal birth = 2 (0.1) CS = 1 (0.04) Intraventricular haemorrhage (Grade 1 or 2) (n, %) Planned vaginal birth = 18 (0.7) CS = 6 (0.2)	

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			morbidity from 4% to 2% with a policy of planned caesarean birth, with 80% power, allowing for a 10% rate of crossover between groups.	<u>Composite of fetal or neonatal mortality or serious neonatal morbidity*:</u> planned vaginal birth = 52/2782 (1.9%) CS = 60/2783 (2.2%) *defined as fetal or neonatal mortality or serious neonatal morbidity. Neonatal mortality was assessed for the period from 0 to 27 days after birth. Serious neonatal morbidity was defined as one or more of the following: birth trauma (spinal cord injury, basal or depressed skull fracture, fracture of a long bone [humerus, radius, ulna, femur, tibia, or fibula]; injury to a peripheral nerve [brachial plexus or phrenic or facial nerve] present at 72 hours of age or at discharge from the hospital; subdural or intracerebral haemorrhage confirmed by mean of ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]); Apgar score of less than 4 at 5 minutes; coma, stupor, or decreased response to pain; seizures on at least two occasions before 72 hours of age; need for assisted ventilation with the use of an endotracheal tube, inserted within	

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				72 hours after birth and remaining in place for at least 24 hours; septicaemia confirmed by means of blood culture or meningitis confirmed by means of cerebrospinal fluid culture within 72 hours after birth; necrotising enterocolitis, defined as intestinal perforation, pneumatosis intestinalis, or air in the portal vein diagnosed by means of surgery or radiography; bronchopulmonary dysplasia, defined as the need for supplemental oxygen at a postnatal gestational age of 36 weeks and confirmed by means of radiography; grade III or IV intraventricular haemorrhage confirmed by means of ultrasonography; or cystic periventricular leukomalacia confirmed by means of ultrasonography.	
	Rabinovici 1987 **Sample size** N=60 women with cephalic/non-cephalic twin pregnancies who were allocated to vaginal birth (n=33) or CS (n=27).	Rabinovici 1987 **Interventions** Planned CS	Rabinovici 1987 **Details** Fetal confinements were assessed by a plain abdominal x-ray film and by an ultrasound examination that included estimation of fetal weight, amniotic fluid volume, localisation	Rabinovici 1987 **Results** **Neonatal outcomes:** Mortality: vaginal birth = 0/66, CS = 0/54 Birth trauma (not defined by the authors): vaginal birth = 0/66, CS = 0/54 Neonatal encephalopathy (not defined by the authors): vaginal birth = 0/66, CS = 0/54	Rabinovici 1987 **Limitations** Limitations were assessed using the Cochrane risk of bias tool to assess risk of bias for RCTs. **Random sequence generation:** unclear risk of bias (allocation was changed randomly by a non-involved person without prior notice on a time basis).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Characteristics Two women allocated to the vaginal birth group had a CS and in four the second twin changed to cephalic presentation. These six women were excluded from the data analysis. Maternal age (mean (SD)): Vaginal birth = 30.3 (4.3), CS = 29.8 (5.2) Week's gestation at birth (mean (SD)): Vaginal birth = 37.7 (1.6), CS = 37.5 (1.5) Nuliparity (no.): Vaginal birth = 6 (22.2%), CS = 7 (26.9%) Birth weight (mean (SD)): first twin: vaginal birth = 2477 (370), CS = 2533 (423) second twin: vaginal birth = 2459 (510), CS = 2484 (632)		of the placenta and umbilical cord, and exclusions of gross fetal anomalies. In the CS group, a lower segment CS was undertaken, preferably with epidural analgesia, but dependent on preference of anaesthetist. In the VB group, VB following evaluation of labour progress using 'Friedman curve'; continuous electronic fetal monitoring was performed of both babies. After the birth of the first twin and before rupture of the second amniotic sac, the lie of the second twin was assessed clinically and confirmed by real-time ultrasonography. If breech, then an assisted breech birth was performed. In case of fetal distress or poor progress despite oxytocin, total breech	Nerve palsy (including brachial plexus injury): vaginal birth = 0/66, CS = 0/54 Intracerebral haemorrhage: vaginal birth = 0/66, CS = 0/54 Intraventricular haemorrhage: grade 3 or 4: vaginal birth = 0/66, CS = 0/54 **Maternal outcomes:** Mortality: vaginal birth = 0/33, CS = 0/27 Actual mode of birth: vaginal birth = 31/33 (2 women in the planned vaginal birth group gave birth via CS), CS = 27/27	**Allocation concealment:** high risk of bias (allocation was changed randomly by a non-involved person without prior notice on a time basis. 20% difference in group sizes not accounted for (27 versus 33)). **Blinding:** unclear risk of bias (blinding not feasible; it is not mentioned whether neonatal assessments was blinded). **Incomplete outcome data:** high risk of bias (6 women allocated to planned vaginal birth were excluded from primary analysis for birth not according to protocol (2 CS and 4 vertex vaginal births). Analysis was not conducted on an ITT basis. **Selective reporting:** low risk of bias (all outcomes reported). **Other bias:** high risk of bias (baseline imbalance: CS n = 27 versus vaginal birth n = 33). **Other information** Data were mainly extracted from Hofmeyr 2015 systematic review; if insufficient data reported in the systematic review then additional data were extracted from the original studies (for example study characteristics).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Twin pregnancy with induced or spontaneous labour, both twins alive, the first fetus in vertex presentation and the second twin in breech presentation or in transverse lie, estimated gestational age between 35 and 42 weeks, presumably normal fetal anatomy, no signs suggestive of acute placental insufficiency or abruptio placentae, normal amniotic fluid volume, normal fetal heart rate testing, no maternal or obstetric indications foe specific route of labour (such as cephalopelvic disproportion, previous uterine surgery or uterine anomalies that contraindicated vaginal birth), and		extraction was performed. Artificial rupture of the second sac was undertaken as late as possible. If the second twin was in oblique or transverse lie, internal version and complete breech extraction under general analgesia or epidural analgesia. In all cases of vaginal birth a lateral episiotomy was performed. Vertex –breech presentation Planned vaginal birth: 21/33 (39%) CS: 18/27 (66.7%) Vertex transverse presentation Planned vaginal birth: 12/33 (39%) CS: 9/27 (33%)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cervix <7 cm dilated. **Exclusion criteria** Not reported				
Full citation Hutton, E. K., Hannah, M. E., Ross, S., Joseph, K. S., Ohlsson, A., Asztalos, E. V., Willan, A. R., Allen, A. C., Armson, B. A., Gafni, A., Mangoff, K., Sanchez, J. J., Barrett, J. F., Twin Birth Study Collaborative, Group, Maternal outcomes at 3 months after planned caesarean section versus planned vaginal birth for twin pregnancies in the Twin Birth Study: a randomised controlled trial, BJOG: An	**Sample size** N=2,570 twin pregnancies Planned vaginal birth: N=1285 women CS: N=1285 women (includes 1 singleton pregnancy) **Characteristics** See Barrett 2013. **Maternal characteristics:** **Age ≥30 years (n, %)**: Planned vaginal birth = 595 (46.3), CS = 587 (45.68) **Age <30 years (n, %):** Planned vaginal birth = 690 (53.7), CS = 698 (54.32) **Inclusion criteria**	**Interventions** Planned CS	**Details** See Barrett 2013. **Intention-to-treat analysis** All results were analysed on an intention-to-treat basis.	**Results** **Maternal outcomes:** <u>Long-term consequences - problematic urinary incontinence* (n %)</u> Planned vaginal birth (n=1285) = 82 (6.38) CS (n=1285) = 70 (5.45); p=0.31 <u>Problematic fecal incontinence* (n, %)</u> Planned vaginal birth = 17 (1.33) CS = 18 (1.41); p=0.85 **Neonatal outcomes:** <u>Neonatal outcomes at 3-month follow-up</u> <u>Mortality (n, %)</u> Planned vaginal birth = 13 (0.51) CS = 21 (0.82)	**Limitations** See Barrett 2013. **Other information** *Problematic urinary incontinence defined a priori as a little or big problem with incontinence [losing or leaking urine when coughing, laughing or sneezing etc. (urinary); losing or leaking faeces/stool, fluid or mucus unexpectedly from the bowels (fecal); or passing gas/wind unexpectedly (flatal) within the past 7 days].

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International Journal of Obstetrics & Gynaecology, 122, 1653-62, 2015 **Ref Id** 430549 **Country/ies where the study was carried out** 25 countries (including Australia, Canada, USA, Europe) **Study type** Multicentre, international randomised controlled trial (The Twin Birth Study) **Aim of the study** To compare outcomes at 3 months post-partum for women undergoing planned vaginal	See Barrett 2013. **Exclusion criteria** See Barrett 2013.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
birth versus planned caesarean section in the Twin Birth Study. **Study dates** See Barrett 2013. **Source of funding** See Barrett 2013					
Full citation Lappen, J. R., Hackney, D. N., Bailit, J. L., Maternal and neonatal outcomes of attempted vaginal compared with planned cesarean delivery in triplet gestations, American Journal of Obstetrics and Gynecology, 215, 493.e1-493.e6, 2016 **Ref Id**	**Sample size** N=80 triplet pregnancies, N=240 children Attempted vaginal birth: N=24 triplet pregnancies, N=72 neonates Planned CS: N=56 pregnancies, N=168 neonates **Characteristics** Maternal age (average (SD)): attempted vaginal	**Interventions** Planned CS	**Details** The planned CS group included only women undergoing CS and excluded anyone coded as having an induction or augmentation of labour, episiotomy, perineal laceration, recorded time of labour onset or complete dilation or CS for intrapartum indication (failed operative vaginal birth or labour dystocia). Women giving birth by CS with the code indications of "elective" and "fetal	**Results** **Maternal outcomes:** <u>Actual mode of birth:</u> Attempted vaginal birth: successful vaginal birth: 4/24 triplet sets (16.7%) <u>Peripartum hysterectomy:</u> Attempted vaginal birth = 0/24 CS = 0/56 <u>Stratified analysis by gestational age</u> N=47 triplets who were born at a gestational age >=34 weeks via induced or augmented labour (attempted vaginal birth = 18 (38.3%), CS = 29 (61.7%)) Actual mode of birth:	**Limitations** Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale: **Selection**: moderate (for maternal outcomes) to high risk of bias (for neonatal outcomes) (the exposed cohort is somewhat representative of the average cohort of women pregnant with triplets as the cohort was selected from a multicentre cohort study using detailed medical record data. Although the non-exposed cohort was drawn from the same community as the exposed cohort, they differ in some baseline characteristics such as antenatal corticosteroids and prematurity which were higher in women who

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
620146 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** To determine the likelihood of success in an attempted vaginal birth and assess maternal and neonatal outcomes of attempted vaginal versus planned CS of triplets. **Study dates** 2002 through 2008 **Source of funding**	birth = 31.5 (4.8), CS = 33.9 (5) Caucasian race: attempted vaginal birth = 18 (75%), CS = 27 (48%) Pre-pregnancy BMI (average (SD)): attempted vaginal birth = 23.5 (4.5), CS = 26.7 (7) Birth gestational age (weeks, average (SD)): attempted vaginal birth = 31.5 (4.8), CS = 33.9 (5) Birth gestational age range (N): 28 0/7 to 31 6/7: attempted vaginal birth = 6 (25%), CS = 9 (16.1%) 32 0/7 to 34 6/7: attempted vaginal birth = 12 (50%), CS = 30 (53.6%) >35 0/7: attempted vaginal birth = 6 (25%), CS = 17 (30.4%) Preterm labour: attempted vaginal birth = 11 (45.8%), CS = 7 (12.5%)		malpresentation" were also included in the planned CS group. The attempted vaginal birth group was defined to include all women with evidence of spontaneous, induced or augmented labour and excluded anyone giving birth by planned or prelabour CS (as defined above). The analysis for binary neonatal outcomes was performed using Poisson regression with clustering to account for correlation within between neonates within a triplet pregnancy.	Attempted vaginal birth: successful vaginal birth = 4/18 triplet sets (22.2%) **Neonatal outcomes:** <u>Neonatal asphyxia:</u> Attempted vaginal birth: 6/72 (8.3) CS: 2/168 (1.2)	had an attempted vaginal birth. 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**: moderate risk of bias (the study control for some factors) **Outcome:** low risk of bias (the outcomes were assessed through record linkage because the authors reviewed medical records; the follow-up was long enough for outcomes to occur; all subjects were accounted for). Other: statistical analysis accounted for the correlation (nonindependence) between neonates within a multifetal pregnancy. **Other information** Strengths of the study: Data used for the analysis originate from a large multicentre cohort of pregnant women. Statistical analysis accounted for the correlation (nonindependence) between neonates within a multifetal pregnancy

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The data included in this article were obtained from the Consortium on Safe Labour, which was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, through contract no. HHSN267200603425C	Antenatal corticosteroids (N): attempted vaginal birth = 11 (45.8%), CS = 12 (2.4%) No women had a combined mode of birth. **Inclusion criteria** Women who gave birth at a gestational age >=28 weeks. **Exclusion criteria** Women with a history of CS, pregnancies complicated by congenital or chromosomal anomalies, antenatal death of >=1 fetuses, twin-twin transfusion syndrome				
Full citation Mol, B. W., Bergenhenegouwen, L., Velzel, J., Ensing, S., van de Mheen, L.,	**Sample size** N=386 triplet pregnancies, N=1,158 neonates Planned vaginal birth: 167/386 (43%),	**Interventions** Planned CS	**Details** This study was performed using data from a retrospective national cohort registered in the	**Results** **Maternal outcomes:** <u>Actual mode of birth:</u> Attempted vaginal birth: successful vaginal birth = 73/167 (44% women)	**Limitations** Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale: **Selection**: high risk of bias (the exposed cohort is likely to be

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ravelli, A. C., Kok, M., Perinatal outcomes according to the mode of delivery in women with a triplet pregnancy in The Netherlands, Journal of Maternal-Fetal and Neonatal Medicine, 1-7, 2018 **Ref Id** 888850 **Country/ies where the study was carried out** The Netherlands **Study type** Retrospective cohort **Aim of the study** To evaluate the association of (intended) mode of birth and perinatal mortality	planned CS: 219/386 (57%) **Characteristics** Maternal age (mean (SD)): planned CS group = 32.5 (4.1), planned vaginal birth group = 31.7 (4.2); Chorionicity: TCTA: planned CS group = 87 (40%), planned vaginal birth group = 70 (42%), DCTA: planned CS group = 65 (30%), planned vaginal birth group = 47 (28%), MCTA: planned CS group = 11 (5%), planned vaginal birth group = 6 (4%); Gestational age at birth (mean (SD)): planned CS group = 33.5 (2.1), planned vaginal birth group = 32.4 (2.9) 26+0 - 31+6 weeks: planned CS group = 27 (12%), planned vaginal birth group = 55 (33%),		Netherlands Perinatal Registry. The Registry consists of population-based data containing information on pregnancies, births, and (re)admissions until 28 d after birth. The Registry database is obtained by a validated linkage of three different registries: the midwife registry, the obstetricians registry, and the neonatology registry of hospital admissions of newborn infants. The coverage of the Registry is approximately 96% of all births in the Netherlands and currently includes over 1.9 million records derived from births in the last decade. Neonatal outcomes were intrapartum death and neonatal death up to 28 d after birth. Neonatal morbidity was defined as Neonatal Intensive Care Units (NICU) admission, neonatal sepsis,	**Neonatal outcomes according to the intended mode of birth: Overall 26-40 weeks** <u>Intrapartum/neonatal mortality up to 28 days after birth - overall:</u> Attempted vaginal birth = 4/167 CS = 5/219 <u>Intrapartum/neonatal mortality up to 28 days after birth – first baby:</u> Attempted vaginal birth = 4/167 CS = 3/219 <u>Intrapartum/neonatal mortality up to 28 days after birth – second baby:</u> Attempted vaginal birth = 1/167 CS = 2/219 <u>Intrapartum/neonatal mortality up to 28 days after birth – third baby:</u> Attempted vaginal birth = 2/167 CS = 1/219 <u>Composite of adverse neonatal morbidity outcomes* – overall:</u> Attempted vaginal birth = 60/167 CS = 56/219 <u>Composite of adverse neonatal morbidity outcomes* – first baby:</u> Attempted vaginal birth = 35/167 CS = 31/219	representative of the average cohort of women pregnant with triplets as this study was performed using data from a retrospective national cohort registered in the Netherlands Perinatal Registry which covers approximately 96% of all births in the Netherlands. However, some baseline characteristics differ between the two groups, with a statistically significantly higher mean gestational age at birth and higher mean birth weight of all children in women who had a planned caesarean section as compared with planned vaginal birth. 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**: moderate risk of bias (the study control for some factors) **Outcome**: low risk of bias (the outcomes were assessed using data from a retrospective national cohort registered in the Netherlands Perinatal Registry; the follow-up was long enough for outcomes to occur; all subjects were accounted for). **Other:** statistical analysis accounted for the dependency between the children of the same triplet pregnancy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and morbidity in a large national cohort of women who gave birth to triplets in The Netherlands **Study dates** Between 1999 and 2008 **Source of funding** First author is supported by a NHMRC Practitioner Fellowship [GNT1082548] and reports consultancy for ObsEva, Merck Merck KGaA and Guerbet	32+0 - 36+6 weeks: planned CS group = 183 (84%), planned vaginal birth group = 107 (64%), 37+0 - 40+0 weeks: planned CS group = 9 (4%), planned vaginal birth group = 5 (3%); Birth weight (grams, mean (SD): Foetus 1: planned CS group = 1962 (432), planned vaginal birth group = 1769 (492) Foetus 2: planned CS group = 1910 (482), planned vaginal birth group = 1768 (499) Foetus 3: planned CS group = 1900 (476), planned vaginal birth group = 1746 (501) **Inclusion criteria** All women with a triplet pregnancy who gave birth beyond 26 weeks between 1 January		intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), and infant respiratory distress syndrome (IRDS).	<u>Composite of adverse neonatal morbidity outcomes* – second baby:</u> Attempted vaginal birth = 40/167 CS = 35/219 <u>Composite of adverse neonatal morbidity outcomes* – third baby:</u> Attempted vaginal birth = 39/167 CS = 39/219 <u>Intrapartum/neonatal mortality up to 28 days after birth or composite of adverse neonatal morbidity outcomes:</u> Attempted vaginal birth = 56/167 CS = 55/219 *defined as NICU admission, neonatal sepsis, intraventricular haemorrhage, bronchopulmonary dysplasia, and infant respiratory distress syndrome.	**Other information** Strengths of the study: Perinatal outcomes were analysed taking into account the dependency between the children of the same triplet pregnancy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	1999 and 31 December 2008. Women were included independently of chorionicity and mode of conception **Exclusion criteria** Women with were severe congenital abnormalities and intrauterine fetal death. Also women who gave birth before 26+0 weeks of gestation because in the time period of the study active management between 24+0 and 26+0 weeks was not general practice in the Netherlands				
Full citation Peress, D., Dude, A., Peaceman, A., Yee, L. M., Maternal and neonatal outcomes in triplet gestations by trial	**Sample size** N=83 triplet pregnancies, N=249 children Attempted vaginal birth: N=21 pregnancies, N=63 neonates	**Interventions** Planned CS	**Details** A retrospective cohort study of all women who gave birth to a triplet gestation at 24.0 weeks' gestation or beyond at Northwestern Memorial Hospital from 1 January	**Results** **Maternal outcomes:** <u>Actual mode of birth:</u> Attempted vaginal birth: successful vaginal birth: 12/21 triplet sets (57.1%)	**Limitations** Limitations assessed with the Newcastle-Ottawa Quality Assessment Scale: **Selection**: high risk of bias (the exposed cohort is likely to be representative of the average cohort

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of labor versus planned cesarean delivery, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 1-6, 2018 **Ref Id** 898002 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** To use detailed clinical records to describe the rate of vaginal birth among those undergoing triplet vaginal trial of labour, identify factors associated with vaginal trial of labour, and	Planned CS: N=62 pregnancies, N=186 neonates **Characteristics** Maternal age (years, mean (SD)): attempted vaginal birth = 32 (4.7), CS = 33.9 (4.8) Multiparous: attempted vaginal birth = 11 (52.3%), CS = 16 (25.8%) Chorionicity: dichorionic/triamniotic: attempted vaginal birth = 6 (28.6%), CS = 43 (69.4%) trichorionic/triamniotic: attempted vaginal birth = 15 (71.4%), CS = 19 (30.7%) Preterm labour: attempted vaginal birth = 18 (85.7%), CS = 33 (53.2%) **Inclusion criteria**		2005 to 1 March 2016. Eligible records were identified from a database of all ultrasounds performed in the author's department. Following birth, the neonatal hospital records were used to obtain all neonatal data.	<u>Peripartum hysterectomy:</u> Attempted vaginal birth = 0/21 CS =3/62 <u>Postpartum haemorrhage:</u> Attempted vaginal birth = 8/21 CS =33/62 **Neonatal outcomes:** <u>Respiratory distress syndrome:</u> Attempted vaginal birth = 17/63 CS = 45/186 <u>Intraventricular haemorrhage (grade 3&4):</u> Attempted vaginal birth = 1/63 CS = 0/186 <u>Necrotising enterocolitis:</u> Attempted vaginal birth = 4/63 CS = 10/186 <u>Composite of adverse neonatal morbidity outcomes*:</u> Attempted vaginal birth = 18/63 CS = 60/186	of women pregnant with triplets as this study was performed using data from the authors institution. However, some baseline characteristics differ between the two groups, where more women in the planned VB group were multiparous (52.3% versus 25.8%), had more trichorionic/triamniotic triplets (71.4% versus 30.7%) but less dichorionic/triamniotic triplets (28.6% versus 69.4%), and more of them had preterm labour (85.7% versus 53.2%). 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:** moderate risk of bias (the study control for some factors) **Outcome:** low risk of bias (the outcomes were identified via ultrasound records and hospital neonatal records; the follow-up was long enough for outcomes to occur; all subjects were accounted for) **Other**: none **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
determine maternal and neonatal outcomes by birth approach in a well-characterised, updated triplet cohort. **Study dates** Between January 2005 and March 2016 **Source of funding** LMY is supported by the NICHD, K12 HD050121-11. Research reported in this publication was supported, in part, by the National Institutes of Health's National Center for Advancing Translational Sciences, grant Number UL1TR001422	Women with triplet pregnancy. Also, women were not excluded if they had a prior caesarean birth as long as they were otherwise eligible for a trial of labour after caesarean. **Exclusion criteria** Women were excluded if they did not give birth at Northwestern Memorial Hospital, experienced antenatal death of one or more fetuses, or had twin-to-twin transfusion syndrome. Additionally, women whose triplet gestations were electively or spontaneously reduced to a singleton or twin gestation were excluded, and those who had a contradiction to a			*defined as respiratory distress syndrome, necrotising enterocolitis, grade 3/4 intraventricular haemorrhage, retinopathy of prematurity, and sepsis	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	trial of labour, such as a placenta praevia or a prior classical caesarean birth.				

1

2

1
2

Appendix E – Forest plots

Forest plots for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies 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 mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Table 4: Comparison: planned caesarean section versus planned vaginal birth for women with twin or triplet pregnancy, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
Twin pregnancy												
Maternal mortality (1 study follow-up 28 days)												
2	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	none	1/1419 (0.07%)	1/1425 (0.07%)	RR 1 (0.06 to 15.97)	0 fewer per 1000 (from 1 fewer to 11 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Haemorrhage (blood loss ≥ 1500 ml) (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	26/1391 (1.9%)	32/1391 (2.3%)	RR 0.81 (0.49 to 1.36)	4 fewer per 1000 (from 12 fewer to 8 more)	⨁⨁⊖⊖ LOW	IMPORTANT
Sepsis (confirmed by blood culture) (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	0/1391 (0%)	1/1391 (0.07%)	POR 0.14 (0.00 to 6.82)	RD 0 (-0.00 to 0.00)	⨁⨁⨁⊖ MODERATE	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
Hysterectomy (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	3/1391 (0.22%)	3/1391 (0.22%)	RR 1 (0.2 to 4.95)	0 fewer per 1000 (from 2 fewer to 9 more)	⨁⨁⊖⊖ LOW	IMPORTANT
Problematic urinary incontinence (follow-up 3 months)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	70/1285 (5.4%)	82/1285 (6.4%)	RR 0.85 (0.63 to 1.16)	10 fewer per 1000 (from 24 fewer to 10 more)	⨁⨁⨁⊖ MODERATE	IMPORTANT
Problematic faecal incontinence (follow-up 3 months)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	18/1285 (1.4%)	17/1285 (1.3%)	RR 1.06 (0.55 to 2.05)	1 more per 1000 (from 6 fewer to 14 more)	⨁⨁⊖⊖ LOW	IMPORTANT
Actual mode of birth - CS for both twins												
2	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1279/1419 (90.1%) 1279/1419 (90%) with planned	553/1426 (38.8%)	RR 2.32 (2.17 to 2.48)	512 more per 1000 (from 454 more to 574 more)	⨁⨁⊖⊖ LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
							CS had planned CS					
Actual mode of birth - vaginal birth and CS												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	11/1392 (0.79%) 11/1392 (0.8%) with planned CS had VB and CS	59/1393 (4.2%) 59/1393 (4%) with planned VB had VB and CS	RR 0.19 (0.1 to 0.35)	34 fewer per 1000 (from 28 fewer to 38 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Actual mode of birth – vaginal birth for both twins												
2	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	129/1419 (9.1%)	814/1426 (57.1%) 814/1426 (57%) with planned VB had VB	RR 0.16 (0.13 to 0.19)	479 fewer per 1000 (from 462 fewer to 497 fewer)	⨁⨁⨀⨀ LOW	IMPORTANT
Composite of mortality or serious morbidity[5] (follow-up 28 days)												

Quality assessment							Number of women		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	102/1392 (7.3%)	118/1392 (8.5%)	RR 0.86 (0.67 to 1.11)	12 fewer per 1000 (from 28 fewer to 9 more)	⨁⨁⨁⨁ MODERATE	IMPORTANT
Triplet pregnancy												
Peripartum hysterectomy												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	0/56 (0%)	0/24 (0%)	Not calculable	RD 0 (-0.06 to 0.06)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[3]	None	3/62	0/21	POR 3.94 (0.28 to 55.01)	RD 0.05 (-0.04 to 0.13)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Postpartum haemorrhage (not defined)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	33/62	8/21	RR 1.4 (0.77 to 2.53)	152 more per 1000 (from 88 fewer to 583 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Actual mode of birth												
1 (whole cohort, n=80)	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	56/56 (100%)	4/24 (16.7%)	RR 5.51 (2.38	752 more per 1000 (from 230 more to	⨁⨁⊖⊖ LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
								4/24 (17%) with planned VB had VB for all 3 triplets	to 12.72)	1000 more)		
1 (those born at ≥34 weeks via induced/ augmented labour, n=47)	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	29/29 (100%)	4/18 (22.2%) 4/18 (22%) with planned VB had VB	RR 4.15 (1.85 to 9.32)	700 more per 1000 (from 189 more to 1000 more)	⨁⨁⨀⨀ LOW	IMPORTANT
1	Observational studies	Serious risk of bias[7]	No serious inconsistency	No serious indirectness	No serious imprecision	None	219/219 (100%)	73/167 (43.7%) 73/167 (43.7%) with planned VB had VB	RR 2.28 (1.92 to 2.71)	560 more per 1000 (from 402 more to 747 more)	⨁⨀⨀⨀ VERY LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	62/62 (100%)	12/21 (57.1%) 12/21 (57.1%) with planned VB had VB	RR 1.75 (1.21 to 2.52)	429 more per 1000 (from 120 more to 869 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; CS: Caesarean section; MID: minimally important difference; POR: Peto odds ratio; RD: risk difference; RR: risk ratio; VB: vaginal birth

1 Rabinovici 1987: Unclear risk of bias for random sequence generation and high risk of bias for allocation concealment as it was changed randomly by a non-involved person without prior notice on a time basis. 20% difference in group sizes not accounted for (27 versus 33). Unclear risk of bias for blinding as it is not mentioned whether neonatal assessments was blinded. High risk of bias for incomplete outcome data as 6 women allocated to planned vaginal birth were excluded from primary analysis for birth not according to protocol (2 CSs and 4 vertex vaginal births). Analysis was not conducted on an ITT basis. High risk of bias due to the baseline imbalance: CS n = 27 versus vaginal birth n = 33

2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

3 There is no agreed default MID for Peto odds ratio or risk difference. Due to low event rates and their impact on the width of confidence intervals imprecision was rated as 'serious' to avoid quality rating inflation for outcomes using this measure

4 The quality of evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

5 Defined as maternal death or serious maternal morbidity before 28 days post-partum, defined as one or more of the following: death; haemorrhage (blood loss ≥1500 ml, need for blood transfusion, or need for dilation and curettage after birth); laparotomy; genital tract injury (need for hysterectomy; vulvar or perineal hematoma requiring evacuation; broad-ligament hematoma confirmed by means of ultrasonography, CT, or MRI; intraoperative damage to the bladder, ureter, or bowel requiring repair; fistula involving the genital tract; or third-degree or fourth-degree perineal laceration involving the anal sphincter or mucosa); thromboembolism (deep-vein thrombosis, thrombophlebitis, or pulmonary embolism) requiring anticoagulant therapy; systemic infection (temperature ≥38.5°C on two or more occasions at least 24 hours apart, not including the first 24 hours after birth, or pneumonia confirmed by means of radiography or, if there was sepsis, confirmed by means of blood culture); major medical life-threatening illness (the acute respiratory distress syndrome, amniotic-fluid embolism, disseminated intravascular coagulation, bowel obstruction, or paralytic ileus requiring the use of nasogastric suctioning); wound infection requiring prolongation of the hospital stay, readmission to the hospital, or repeated treatment as an outpatient; wound dehiscence or breakdown; or other serious maternal complication

6 High risk of selection bias as, although the non-exposed cohort was drawn from the same community as the exposed cohort, they differ in some baseline characteristics such as nulliparity, chorionicity and preterm labour

7 Some baseline characteristics differ between the planned CS and planned VB groups, for example a statistically significantly higher mean gestational age at birth and higher mean birth weight of all children was observed in women who had a planned CS as compared with those who had a planned VB

Table 5: Comparison: planned caesarean section versus planned vaginal birth for women with twin or triplet pregnancy, outcomes for the baby

Quality assessment							Number of neonates		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
Twin pregnancy												
Fetal mortality (before onset of labour/during birth)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	13/2783 (0.47%)	9/2782 (0.32%)	RR 1.44 (0.62 to 3.37)	14 more per 10,000 (from 12 fewer to 77 more)	⨁⨁⊖⊖ LOW	CRITICAL
Neonatal mortality (1 study follow-up 28 days)												
2	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[1]	None	11/2837 (0.39%)	8/2848 (0.28%)	RR 1.37 (0.55 to 3.41)	10 more per 10,000 (from 13 fewer to 68 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Neonatal mortality (follow-up 2 years)												
1	Randomised trial	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[1]	None	11/2320 (0.47%)	8/2283 (0.35%)	RR 1.35 (0.55 to 3.36)	1 more per 1000 (from 2 fewer to 8 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Neurodevelopmental delay (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	104/2285 (4.6%)	110/2260 (4.9%)	RR 0.94 (0.72	3 fewer per 1000 (from 14	⨁⨁⊖⊖ LOW	CRITICAL

Quality assessment							Number of neonates		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**		
									to 1.21)	fewer to 10 more)		
Cerebral palsy (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/2285 (0.09%)	1/2260 (0.04%)	RR 1.98 (0.18 to 21.8)	4 more per 10,000 (from 4 fewer to 92 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Motor delay (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	62/2285 (2.7%)	78/2260 (3.5%)	RR 0.79 (0.57 to 1.09)	7 fewer per 1000 (from 15 fewer to 3 more)	⨁⨁⊖⊖ LOW	CRITICAL
Cognitive delay (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	95/2285 (4.2%)	105/2258 (4.7%)	RR 0.89 (0.68 to 1.17)	5 fewer per 1000 (from 15 fewer to 8 more)	⨁⨁⊖⊖ LOW	CRITICAL
Nerve palsy (including brachial plexus injury)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/54 (0%)	0/66 (0%)	Not calculable	RD 0 (-0.03 to 0.03)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Birth trauma - long-bone fracture present at 72 hours of age or at discharge from hospital (follow-up 28 days)												

Quality assessment							Number of neonates		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	0/2759 (0%)	4/2765 (0.14%)	POR 0.14 (0.02 to 0.96)	RD 0 (-0.00 to 0.00)	⨁⨁⨁⨀ MODERATE	IMPORTANT
Birth trauma - Other bone fracture present at 72 hours of age or at discharge from hospital (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/2759 (0.04%)	1/2765 (0.04%)	RR 1 (0.06 to 16.01)	0 fewer per 10,000 (from 3 fewer to 54 more)	⨁⨁⨀⨀ LOW	IMPORTANT
Birth trauma (not defined)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/54 (0%)	0/66 (0%)	Not calculable	RD 0 (-0.03 to 0.03)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
Birth trauma (not defined, follow-up 2 years)												
1	Randomised trial	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/2296 (0.17%)	5/2266 (0.22%)	0.79 (0.21 to 2.94)	0 fewer per 1000 (from 2 fewer to 4 more)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
≥2 seizures within 72 hr after birth (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	3/2759 (0.11%)	3/2765 (0.11%)	RR 1 (0.2 to 4.96)	0 fewer per 1000 (from 1 fewer to 4 more)	⨁⨁⨀⨀ LOW	IMPORTANT

Quality assessment							Number of neonates		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
Intraventricular haemorrhage (Grade 1 or 2) (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	6/2759 (0.22%)	18/2765 (0.65%)	RR 0.33 (0.13 to 0.84)	4 fewer per 1000 (from 1 fewer to 6 fewer)	⨁⨁⨁⊖ MODERATE	IMPORTANT
Intraventricular haemorrhage (Grade 3 or 4)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/54 (0%)	0/66 (0%)	Not calculable	RD 0 (-0.03 to 0.03)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Cystic periventricular leukomalacia (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	2/2759 (0.07%)	0/2765 (0%)	POR 7.41 (0.46 to 118.46)	RD 0 (0.00 to 0.00)	⨁⨁⨁⊖ MODERATE	IMPORTANT
Cystic periventricular leukomalacia (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[5]	None	2/2296 (0.09%)	0/2266 (0%)	POR 7.3 (0.46 to 116.69)	RD 0 (-0.00 to 0.00)	⨁⨁⊖⊖ LOW	IMPORTANT
Neonatal encephalopathy (not defined)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/54 (0%)	0/66 (0%)	Not calculable	RD 0 (-0.03 to 0.03)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of neonates		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**		
Necrotising enterocolitis (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/2759 (0.04%)	2/2765 (0.07%)	RR 0.5 (0.05 to 5.52)	0 fewer per 1000 (from 1 fewer to 3 more)	⨁⨁⨀⨀ LOW	IMPORTANT
Necrotising enterocolitis (follow-up 2 years)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/2296 (0.04%)	2/2266 (0.09%)	RR 0.49 (0.04 to 5.44)	0 fewer per 1000 (from 1 fewer to 4 more)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
Respiratory distress syndrome (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	146/2759 (5.3%)	125/2765 (4.5%)	RR 1.17 (0.93 to 1.48)	8 more per 1000 (from 3 fewer to 22 more)	⨁⨁⨁⨀ MODERATE	IMPORTANT
Composite of fetal/neonatal mortality or serious morbidity[6] (follow-up 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	60/2783 (2.2%)	52/2782 (1.9%)	RR 1.15 (0.80 to 1.67)	3 more per 1000 (from 4 fewer to 13 more)	⨁⨁⨁⨀ MODERATE	IMPORTANT
Triplet pregnancy												
Intrapartum/neonatal mortality up to 28 days after birth - overall												

Quality assessment							Number of neonates		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/219 (2.3%)	4/167 (2.4%)	RR 0.95 (0.26 to 3.5)	1 fewer per 1000 (from 18 fewer to 60 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Intrapartum/neonatal mortality up to 28 days after birth – first baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Very serious[1]	None	3/219 (1.4%)	4/167 (2.4%)	RR 0.57 (0.13 to 2.52)	10 fewer per 1000 (from 21 fewer to 36 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Intrapartum/neonatal mortality up to 28 days after birth – second baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/219 (0.91%)	1/167 (0.6%)	RR 1.53 (0.14 to 16.68)	3 more per 1000 (from 5 fewer to 94 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Intrapartum/neonatal mortality up to 28 days after birth – third baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/219 (0.46%)	2/167 (1.2%)	RR 0.38 (0.03 to 4.17)	7 fewer per 1000 (from 12 fewer to 38 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Respiratory distress syndrome												
1	Observational studies	Very serious[8]	No serious inconsistency	No serious indirectness	Very serious[1]	None	45/186 (24.2%)	17/63 (27%)	RR 0.9 (0.56 to 1.45)	27 fewer per 1000 (from 119 fewer to	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of neonates		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**		
										121 more)		
Intraventricular haemorrhage (grade 3/4)												
1	Observational studies	Very serious[8]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/186 (0%)	1/63 (1.6%)	POR 0.02 (0.00 to 1.74)	RD -0.02 (-0.05 to 0.02)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Necrotising enterocolitis												
1	Observational studies	Very serious[8]	No serious inconsistency	No serious indirectness	Very serious[1]	None	10/186 (5.4%)	4/63 (6.3%)	RR 0.85 (0.28 to 2.61)	10 fewer per 1000 (from 46 fewer to 102 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Neonatal asphyxia (postpartum)												
1	Observational studies	Very serious[9]	No serious inconsistency	No serious indirectness	No imprecision	None	2/168 (1.2%)	6/72 (8.3%)	RR 0.14 (0.03 to 0.69)	72 fewer per 1000 (from 26 fewer to 81 fewer)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Composite of adverse neonatal morbidity outcomes – overall												
1 [10]	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[4]	None	56/219 (25.6%)	60/167 (35.9%)	RR 0.71 (0.53 to 0.96)	104 fewer per 1000 (from 14 fewer to 169 fewer)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of neonates		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Planned CS**	**Planned vaginal birth**	**Relative (95% CI)**	**Absolute**		
1 [11]	Observational studies	Very serious[8]	No serious inconsistency	No serious indirectness	Very serious[1]	None	60/186 (32.3%)	18/63 (28.6%)	RR 1.13 (0.73 to 1.76)	37 more per 1000 (from 77 fewer to 217 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Composite of adverse neonatal morbidity outcomes[10] – first baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[4]	None	31/219 (14.2%)	35/167 (21%)	RR 0.68 (0.44 to 1.05)	67 fewer per 1000 (from 117 fewer to 10 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Composite of adverse neonatal morbidity outcomes[10] – second baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[4]	None	35/219 (16%)	40/167 (24%)	RR 0.67 (0.44 to 1.00)	79 fewer per 1000 (from 134 fewer to 0 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Composite of adverse neonatal morbidity outcomes[10] – third baby												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[4]	None	39/219 (17.8%)	39/167 (23.4%)	RR 0.76 (0.51 to 1.13)	56 fewer per 1000 (from 114 fewer to 30 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Intrapartum/neonatal mortality up to 28 days after birth or composite of adverse neonatal morbidity outcomes[10]												
1	Observational studies	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[4]	None	55/219 (25.1%)	56/167 (33.5%)	RR 0.75 (0.55	84 fewer per 1000 (from 151	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of neonates		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Planned CS	Planned vaginal birth	Relative (95% CI)	Absolute	Quality	Importance
									to 1.02)	fewer to 7 more)		

CI: confidence interval; CS: Caesarean section; MID: minimally important difference; POR: Peto odds ratio; RD: risk difference; RR: risk ratio

1 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

2 Rabinovici 1987: Unclear risk of bias for random sequence generation and high risk of bias for allocation concealment as it was changed randomly by a non-involved person without prior notice on a time basis. 20% difference in group sizes not accounted for (27 versus 33). Unclear risk of bias for blinding as it is not mentioned whether neonatal assessments was blinded. High risk of bias for incomplete outcome data as 6 women allocated to planned vaginal birth were excluded from primary analysis for birth not according to protocol (2 CSs and 4 vertex vaginal births). Analysis was not conducted on an ITT basis. High risk of bias due to the baseline imbalance: CS n = 27 versus vaginal birth n = 33

3 High risk of bias for incomplete outcome data (>15% lost to follow-up)

4 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

5 There is no agreed default MID for Peto odds ratio or risk difference. Due to low event rates and their impact on the width of confidence intervals imprecision was rated as 'serious' to avoid quality rating inflation for outcomes using this measure

6 Defined as fetal or neonatal mortality or serious neonatal morbidity. Neonatal mortality was assessed for the period from 0 to 27 days after birth. Serious neonatal morbidity was defined as one or more of the following: birth trauma (spinal cord injury, basal or depressed skull fracture, fracture of a long bone [humerus, radius, ulna, femur, tibia, or fibula]; injury to a peripheral nerve [brachial plexus or phrenic or facial nerve] present at 72 hours of age or at discharge from the hospital; subdural or intracerebral haemorrhage confirmed by mean of ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]); Apgar score of less than 4 at 5 minutes; coma, stupor, or decreased response to pain; seizures on at least two occasions before 72 hours of age; need for assisted ventilation with the use of an endotracheal tube, inserted within 72 hours after birth and remaining in place for at least 24 hours; septicaemia confirmed by means of blood culture or meningitis confirmed by means of cerebrospinal fluid culture within 72 hours after birth; necrotising enterocolitis, defined as intestinal perforation, pneumatosis intestinalis, or air in the portal vein diagnosed by means of surgery or radiography; bronchopulmonary dysplasia, defined as the need for supplemental oxygen at a postnatal gestational age of 36 weeks and confirmed by means of radiography; grade III or IV intraventricular haemorrhage confirmed by means of ultrasonography; or cystic periventricular leukomalacia confirmed by means of ultrasonography

7 High risk of selection bias as, although the non-exposed cohort was drawn from the same community as the exposed cohort, they differ in some baseline characteristics such as mean gestational age at birth and mean birth weight

8 High risk of selection bias as, although the non-exposed cohort was drawn from the same community as the exposed cohort, they differ in some baseline characteristics such as multiparity, trichorionic/triamniotic triplets and preterm labour which were higher in women who had an attempted VB

9 High risk of selection bias as, although the non-exposed cohort was drawn from the same community as the exposed cohort, they differ in some baseline characteristics such as antenatal corticosteroids and prematurity which were higher in women who had an attempted VB

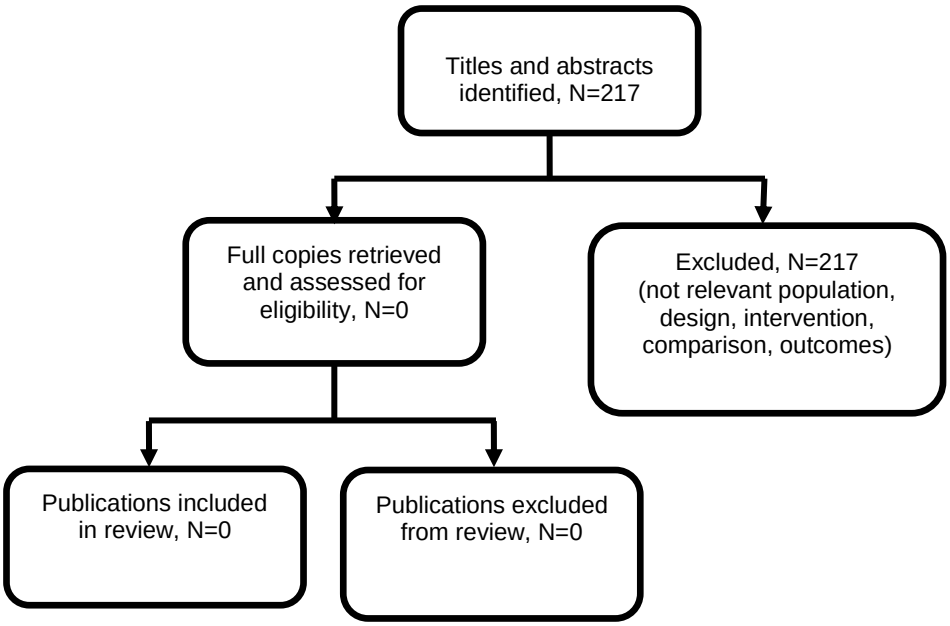
10 Defined as Neonatal Intensive Care Units admission, neonatal sepsis, intraventricular haemorrhage, bronchopulmonary dysplasia, and infant respiratory distress syndrome

11 Defined as respiratory distress syndrome, necrotising enterocolitis, grade 3/4 intraventricular haemorrhage, retinopathy of prematurity, and sepsis

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Figure 2: **Flow diagram of economic article selection for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy**



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies 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 mode of birth to improve outcomes for mothers and babies 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 mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

No economic evidence was identified for this review but resource use and unit cost data was presented to inform the committee discussion.

Table 6 gives the number of twin and triplet pregnancies in England and Wales in 2016.

Table 6: Number of twin and triplet live and stillbirths in England and Wales in 2016 (ONS)

Multiplicity	Live births	Still births
Twin	21,392	180
Triplet (and above)	495	5

ONS: Office for National Statistics

Table 7 gives unit costs for alternative modes of birth derived from 2016-17 NHS Reference costs. We have then followed the approach of Ledger 2006 by applying a multiplier of 1.34 to allow for the fact that a twin birth would utilise more health care resources than a singleton birth.

Table 7: Birth costs

Mode of birth	Weighted average cost	Twin Birth [a]
Unassisted vaginal birth	£2,297	£3,079
Assisted vaginal birth	£3,367	£4,512
Planned caesarean section	£3,557	£4,767
Emergency caesarean section	£4,781	£6,406

(a) Applying a multiplier of 1.34

Table 8 gives the mode of birth for twin pregnancies reported in the National Sentinel Caesarean Section audit 2001, although the committee considered that the proportion of planned caesarean sections was likely to have risen since then.

Table 8: Estimated proportion of different modes of birth for twin pregnancies

Mode of birth	Proportion of births
Unassisted vaginal birth	36.3%
Assisted vaginal birth	4.7%
Planned caesarean section	22.0%
Emergency caesarean section	37.0%

Appendix K – Excluded studies

Excluded studies for review question: What is for the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

Clinical studies

Study	Reason for exclusion
Adinma, J. I., Agbai, A. O., Multiple births in Nigerian Igbo women: incidence and outcomes, Journal of Obstetrics & GynaecologyJ Obstet Gynaecol, 17, 42-4, 1997	Non relevant comparison
Ahmed, F., Naeem, N., Yasir, S., Management of nonvertex second twin, Journal of Obstetrics & Gynaecology of India, 63, 177-81, 2013	Study design not relevant to protocol for twin pregnancy - it is retrospective cohort study
Alamia,V.,Jr., Royek,A.B., Jaekle,R.K., Meyer,B.A., Preliminary experience with a prospective protocol for planned vaginal delivery of triplet gestations, American Journal of Obstetrics and Gynecology, 179, 1133-1135, 1998	Non relevant comparison
Albasri, S. F., Shouib, G. M., Bajouh, O. S., Nasrat, H. A., Ahmad, E., Algreisi, F. M., Maternal and neonatal outcomes in twin and triplet gestations in Western Saudi Arabia, Saudi Medical Journal, 38, 657-661, 2017	Non relevant comparison
Alexander, J. M., Gilstrap, L. C., 3rd, Cox, S. M., Ramin, S. M., The relationship of infection to method of delivery in twin pregnancy, American Journal of Obstetrics & Gynecology, 177, 1063-6, 1997	Study design not relevant to protocol for twin pregnancy - it is a retrospective study of medical records
Alexander, J. M., Leveno, K. J., Rouse, D., Landon, M. B., Gilbert, S. A., Spong, C. Y., Varner, M. W., Caritis, S. N., Harper, M., Wapner, R. J., Sorokin, Y., Miodovnik, M., O'Sullivan, M. J., Sibai, B. M., Langer, O., Gabbe, S. G., Eunice Kennedy Shriver National Institute of Child, Health, Human Development Maternal-Fetal Medicine Units, Network, Cesarean delivery for the second twin, Obstetrics & Gynecology, 112, 748-52, 2008	Study design not relevant to protocol for twin pregnancy - it is a prospective cohort study
Almeida,P., Domingues,A.P., Belo,A., Fonseca,E., Moura,P., Triplet pregnancies: perinatal outcome evolution, Revista Brasileira de Ginecologia e Obstetricia, 36, 393-397, 2014	Non-comparative study - evaluation of obstetric, maternal and perinatal outcomes
Alran,S., Sibony,O., Luton,D., Touitou,S., Fourchotte,V., Feraud,O., Oury,J.F., Blot,P., Maternal and neonatal outcome of 93 consecutive triplet pregnancies with 71% vaginal delivery, Acta Obstetricia et Gynecologica Scandinavica, 83, 554-559, 2004	Study design not relevant to protocol - retrospective case series comparing triplet pregnancies by trial or labour versus elective caesarean section
Al-Suleiman, S. A., Al-Jama, F. E., Rahman, J., Rahman, M. S., Obstetric complications and perinatal outcome in triplet pregnancies, Journal of Obstetrics & GynaecologyJ Obstet Gynaecol, 26, 200-4, 2006	Non-comparative case series; retrospective review of triplet pregnancy to determine frequencies of maternal and neonatal outcomes
Al-Sunaidi,M., Al-Shahrani,M.S., Fetomaternal and neonatal outcome of triplet pregnancy. Promising results, Saudi Medical Journal, 32, 685-688, 2011	Non-comparative retrospective review of triplet pregnancyDescription of maternal and fetal-neonatal outcomes

Study	Reason for exclusion
Anastasio, H. B., Aviram, A., Easter, S. R., Saccone, G., Berghella, V., Barrett, J., Prediction of successful twin vaginal birth: A secondary analysis of the twin birth study, American Journal of Obstetrics and Gynecology, 218, S144-S145, 2018	Conference abstract
Anselem, O., Mephon, A., Le Ray, C., Marcellin, L., Cabrol, D., Goffinet, F., Continued pregnancy and vaginal delivery after 32 weeks of gestation for monoamniotic twins, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 194, 194-8, 2015	Study design not relevant to protocol for twin pregnancy - it is a retrospective study in monoamniotic twin pregnancies
Armson,B.A., O'Connell,C., Persad,V., Joseph,K.S., Young,D.C., Baskett,T.F., Determinants of perinatal mortality and serious neonatal morbidity in the second twin, Obstetrics and Gynecology, 108, 556-564, 2006	Study design not relevant to protocol for twin pregnancy - it is a retrospective cohort study
Aviram, A., Weiser, I., Ashwal, E., Bar, J., Wiznitzer, A., Yogev, Y., Combined vaginal-cesarean delivery of twins: risk factors and neonatal outcome--a single center experience, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 28, 509-14, 2015	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study assessing mode of birth for women with twin gestations in which one twin is in cephalic presentation
Bakr,A.F., Karkour,T., What is the optimal gestational age for twin delivery, BMC Pregnancy and Childbirth, 6 ,;#2006. Article Number, -, 2006	Study design not relevant to protocol for twin pregnancy. Prospective cohort study assessing timing of birth and perinatal outcome
Barrett, J. F. R., Randomised controlled trial for twin delivery [5], British Medical Journal, 326, 448, 2003	Editorial comment/letter
Barrett, J. F. R., Hannah, M. E., Hutton, E. K., Willan, A. R., Allen, A. C., Armson, B. A., Gafni, A., Joseph, K. S., Mason, D., Ohlsson, A., Ross, S., Sanchez, J. J., Asztalos, E. V., Randomized trial of planned cesarean or vaginal delivery for twin pregnancy, Obstetrical & Gynecological Survey, 69, 61-2, 2014	Abstract and Editorial Comment
Barrett, J. F., Ritchie, W. K., Twin delivery, Best Practice & Research in Clinical Obstetrics & Gynaecology, 16, 43-56, 2002	Discussion on mode of birth in twin pregnancy. Includes indications for caesarean section, vertex and non-vertex, and cephalic versus breech extraction
Barrett,J.F.R., Delivery of the term twin, Best Practice and Research in Clinical Obstetrics and Gynaecology, 18, 625-630, 2004	Discussion paper and outline on the Twin Birth Randomised Controlled Trial (RCT)
Barrett,J.M., Staggs,S.M., Van Hooydonk,J.E., Growdon,J.H., Killam,A.P., Boehm,F.H., The effect of type of delivery upon neonatal outcome in premature twins, American Journal of Obstetrics and Gynecology, 143, 360-367, 1982	Study design not relevant to protocol for twin pregnancy - retrospective study of all twin births
Barzilay, E., Mazaki-Tovi, S., Amikam, U., de Castro, H., Haas, J., Mazkereth, R., Sivan, E., Schiff, E., Yinon, Y., Mode of delivery of twin gestation with very low birthweight: is vaginal delivery safe?, American Journal of Obstetrics & Gynecology, 213, 219.e1-8, 2015	Study design not relevant to protocol for twin pregnancy - it is retrospective cohort study of twin pregnancy

Study	Reason for exclusion
Bibbo, C., Robinson, J. N., Management of twins: vaginal or cesarean delivery?, Clinical Obstetrics & Gynecology, 58, 294-308, 2015	Study design not relevant to protocol; discussion on twin births
Bjelic-Radisic,V., Pristauz,G., Haas,J., Giuliani,A., Tamussino,K., Bader,A., Lang,U., Schlembach,D., Neonatal outcome of second twins depending on presentation and mode of delivery, Twin Research and Human Genetics, 10, 521-527, 2007	Study design not relevant to protocol for twin pregnancy. Retrospective analysis of database examining neonatal outcome of second twins depending on presentation and mode of birth
Blickstein, I., Weissman, A., Ben-Hur, H., Borenstein, R., Insler, V., Vaginal delivery of breech-vertex twins, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 38, 879-882, 1993	Study design not relevant to protocol for twin pregnancy - retrospective analysis comparing vaginal versus caesarean births
Blickstein,I., Goldman,R.D., Kupferminc,M., Delivery of breech first twins: a multicenter retrospective study, Obstetrics and Gynecology, 95, 37-42, 2000	Study design not relevant to protocol for twin pregnancy. Retrospective case-control assessing risk of vaginal birth of breech first twins
Blickstein,I., Schwartz-Shoham,Z., Lancet,M., Borenstein,R., Vaginal delivery of the second twin in breech presentation, Obstetrics and Gynecology, 69, 774-776, 1987	Study design not relevant to protocol for twin pregnancy. Retrospective case control comparing vertex-breech tin-pairs with vertex-vertex pairs
Boulot,P., Hedon,B., Pelliccia,G., Sarda,P., Montoya,F., Mares,P., Humeau,C., Arnal,F., Laffargue,F., Viala,J.L., Favourable outcome in 33 triplet pregnancies managed between 1985-1990, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 43, 123-129, 1992	Non-comparative study. Examines management at home and all births by caesarean section
Breathnach, F. M., McAuliffe, F. M., Geary, M., Daly, S., Higgins, J. R., Dornan, J., Morrison, J. J., Burke, G., Higgins, S., Dicker, P., Manning, F., Carroll, S., Malone, F. D., Perinatal Ireland Research, Consortium, Optimum timing for planned delivery of uncomplicated monochorionic and dichorionic twin pregnancies, Obstetrics & Gynecology, 119, 50-9, 2012	Study design not relevant to protocol for twin pregnancy. Prospective cohort study comparing uncomplicated twins undergoing planned preterm birth versus monochorionic twins that continued in utero beyond 34 weeks gestation, and dichorionic twins who continued beyond 36 weeks
Breathnach, F. M., McAuliffe, F. M., Geary, M., Daly, S., Higgins, J. R., Dornan, J., Morrison, J. J., Burke, G., Higgins, S., Dicker, P., Manning, F., Carroll, S., Malone, F. D., Perinatal Ireland Research, Consortium, Prediction of safe and successful vaginal twin birth, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 205, 237.e1-7, 2011	Study design not relevant to protocol for twin pregnancy - it is a secondary analysis of a cohort study
Breslin, E., Khare, M., Perinatal outcomes in planned vaginal deliveries of monochorionic-diamniotic twins, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A159, 2014	Conference abstract
Bricelj, K., Tul, N., Lasic, M., Bregar, A. T., Verdenik, I., Lucovnik, M., Blickstein, I., Respiratory morbidity in twins by birth order, gestational age and mode of delivery, Journal of Perinatal Medicine, 44, 899-902, 2016	Study design not relevant to protocol for twin pregnancy - it is an observational study

Study	Reason for exclusion
Brown,L., Karrison,T., Cibils,L.A., Mode of delivery and perinatal results in breech presentation, American Journal of Obstetrics and Gynecology, 171, 28-34, 1994	Study design not relevant to protocol for twin pregnancy; observational consecutive case series - singleton and twin pregnancies
Caukwell,S., Murphy,D.J., The effect of mode of delivery and gestational age on neonatal outcome of the non-cephalic- presenting second twin, American Journal of Obstetrics and Gynecology, 187, 1356-1361, 2002	Study design not relevant to protocol for twin pregnancy; retrospective cohort of non-cephalic second twin compared with cephalic second twin
Chauhan,S.P., Roberts,W.E., McLaren,R.A., Roach,H., Morrison,J.C., Martin,J.N.,Jr., Delivery of the nonvertex second twin: breech extraction versus external cephalic version, American Journal of Obstetrics and Gynecology, 173, 1015-1020, 1995	Study design not relevant to protocol for twin pregnancy. Retrospective case series assessing outcomes after vaginal birth of first fetus, whether either total breech extraction or external cephalic version of second fetus was performed
Chervenak, F. A., Johnson, R. E., Berkowitz, R. L., Grannum, P., Hobbins, J. C., Is routine cesarean section necessary for vertex-breech and vertex-transverse twin gestations?, American Journal of Obstetrics & Gynecology, 148, 1-5, 1984	Study design not relevant to protocol for twin pregnancy; retrospective case series
Clarke,J.P., Roman,J.D., A review of 19 sets of triplets: the positive results of vaginal delivery, Australian and New Zealand Journal of Obstetrics and Gynaecology, 34, 50-53, 1994	Study design not relevant to protocol - retrospective case series in triplet pregnancy
Crawford, J. S., A prospective study of 200 consecutive twin deliveries, Anaesthesia, 42, 33-43, 1987	Study design not relevant to protocol for twin pregnancy; prospective consecutive series summarising gestational age at birth, mode of birth and technique of analgesia/anaesthesia
Crosby,W.M., Twin pregnancy: an appraisal of management options, Journal - Oklahoma State Medical Association, 82, 516-527, 1989	A full-text copy of the article could not be obtained
Crowther, C. A., Caesarean delivery for the second twin, Cochrane Database of Systematic Reviews, CD000047, 2000	Cochrane review withdrawn from publication because it has been replaced and updated by a new review entitled ‘Planned caesarean section for women with a twin pregnancy’
Crowther, C. A., Caesarean delivery for the second twin (Cochrane Review). (Date of most recent amendment 21 November 2000; date of most recent substantive update: 16 July 1995), The Cochrane Database of Systematic Reviews, 1996	Cochrane review - one included study relevant to this review protocol has been identified (Rabinovici 1987)
Crowther, C. A., Hamilton, R. A., Triplet pregnancy: a 10-year review of 105 cases at Harare Maternity Hospital, Zimbabwe, Acta Geneticae Medicae et Gemellologiae, 38, 271-8, 1989	Population not relevant to protocol. Includes a proportion of women (32.4%) who were diagnosed with triplets at birth
Cruceyra Betriu, M., De Haro Garcia, M., De La Calle Fernandez-Miranda, M., Gonzalez Gonzalez, A., Maternal and fetal complications in twin pregnancies: Health impact,	Conference abstract of retrospective case study in twin pregnancies

Study	Reason for exclusion
Journal of Maternal-Fetal and Neonatal Medicine, 23, 405, 2010	
Dagenais, C., Lewis-Mikhael, A. M., Grabovac, M., Mukerji, A., McDonald, S. D., What is the safest mode of delivery for extremely preterm cephalic/non-cephalic twin pairs? A systematic review and meta-analyses, BMC Pregnancy & ChildbirthBMC Pregnancy Childbirth, 17, 397, 2017	Studies from this review were assessed for a potential inclusion
Daly,S., Higgins,J., Burke,G., Mahony,R., Higgins,S., Geary,M., Breathnach,F., Dicker,P., Manning,F., Malone,F., Dornan,J., McAuliffe,F., Morrison,J.J., How safe is vaginal twin birth? Evidence from the prospective ESPRiT study, American Journal of Obstetrics and Gynecology, #2011 31st Annual Meeting of the Society for Maternal-Fetal Medicine, S59-Fetal, 2011	Conference abstract
Davison,L., Easterling,T.R., Jackson,J.C., Benedetti,T.J., Breech extraction of low-birth-weight second twins: can cesarean section be justified?, American Journal of Obstetrics and Gynecology, 166, 497-502, 1992	Study design not relevant to protocol for twin pregnancy; retrospective non-RCT comparing breech extraction of low-birth-weight second twins compared with their siblings born by caesarean section
de Castro, H., Haas, J., Schiff, E., Sivan, E., Yinon, Y., Barzilay, E., Trial of labour in twin pregnancies: a retrospective cohort study, BJOG: An International Journal of Obstetrics & Gynaecology, 123, 940-5, 2016	Study design not relevant to protocol for twin pregnancy; retrospective cohort study assessing success rate of vaginal birth
Del Castillo Ortiz, N., Romero Guadix, B., Aibar Villan, L., Lopez Criado, M. S., Carmona Salgado, M. A., Puertas Prieto, A., Finalizacion del parto en gestaciones gemelares con primer feto en presentacion cefalica, Journal of Maternal-Fetal and Neonatal Medicine, 23, 462-463, 2010	Abstract for retrospective case-control study of twin births analysing mode of birth of second twin compared with first twin in cephalic presentation
Delaney, T., Young, D. C., Trial of labour compared to elective Caesarean in twin gestations with a previous Caesarean delivery, Journal of Obstetrics & Gynaecology Canada: JOGCJ Obstet Gynaecol Can, 25, 289-92, 2003	Study design not relevant to protocol for twin pregnancy. Retrospective analysis of database comparing outcomes in twin gestations with a vertex-presenting first twin undergoing elective caesarean section or trial of labour
Dias, T., Thilaganathan, B., Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: The Twins Timing of Birth Randomised Trial, BJOG: An International Journal of Obstetrics and Gynaecology, 119, 1676, 2012	Correspondence and Authors' reply
Dincsoy,M.Y., Kim,Y.M., Ponce,E., Williams,H., Naroji,S.K., Intracranial hemorrhage in low-birth-weight twins during neonatal period, American Journal of Perinatology, 4, 220-224, 1987	Study design not relevant to protocol for twin pregnancy - it is a retrospective chart review
Dodd, J. M., Crowther, C. A., Haslam, R. R., Robinson, J. S., Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: The Twins Timing of Birth Randomised Trial, Obstetrical and Gynecological Survey, 67, 675-676, 2012	Editorial/comment on Twins Timing of Birth Randomised trial
Dodd, J. M., Crowther, C. A., Haslam, R. R., Robinson, J. S., Twins Timing of Birth Trial, Group, Elective birth at 37 weeks of gestation versus standard care for women with an	Comparison not relevant to protocol; elective birth from 37 weeks of

Study	Reason for exclusion
uncomplicated twin pregnancy at term: the Twins Timing of Birth Randomised Trial, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 119, 964-73, 2012	gestation versus birth planned from 38 weeks of gestation
Dodd, J. M., Deussen, A. R., Grivell, R. M., Crowther, C. A., Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy, Cochrane Database of Systematic Reviews, CD003582, 2014	Cochrane review of ineligible comparators; elective birth at 37 weeks gestation versus ongoing expectant management with a plan for birth at a later time
Dommergues,M., Mahieu-Caputo,D., Mandelbrot,L., Huon,C., Moriette,G., Dumez,Y., Delivery of uncomplicated triplet pregnancies: is the vaginal route safer? A case-control study, American Journal of Obstetrics and Gynecology, 172, 513-517, 1995	Study design not relevant to protocol; retrospective case-control study assessing the safety of vaginal birth of triplets compared with caesarean section
Dong, Y., Luo, Z. C., Yang, Z. J., Chen, L., Guo, Y. N., Branch, W., Zhang, J., Huang, H., Is Cesarean Delivery Preferable in Twin Pregnancies at >=36 Weeks Gestation?, PLoS ONE [Electronic Resource], 11, e0155692, 2016	Study design not relevant to protocol for twin pregnancy - it is a retrospective cohort study
Drassinower,D., Timofeev,J., Huang,C.C., Landy,H.J., Racial disparities in outcomes of twin pregnancies: elective cesarean or trial of labor?, American Journal of Obstetrics and Gynecology, 211, 160-167, 2014	Study design not relevant to protocol for twin pregnancy. Secondary analysis of Consortium on Safe Labour data assessing twin gestations in vertex-vertex presentation grouped according to race
Easter, S. R., Lieberman, E., Carusi, D., Fetal presentation and successful twin vaginal delivery, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 214, 116.e1-116.e10, 2016	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study assessing mode of birth of second twin in vertex/vertex and vertex/nonvertex presenting twins
Easter, S. R., Robinson, J. N., Lieberman, E., Carusi, D., Association of Intended Route of Delivery and Maternal Morbidity in Twin Pregnancy, Obstetrics & GynecologyObstet Gynecol, 129, 305-310, 2017	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study assessing caesarean birth versus trial of labour
Ei-Jallad, M. F., Abu-Heija, A. T., Ziadeh, S., Obeidat, A., Is the second-born twin at high risk?, Journal of Obstetrics and Gynaecology, 18, 133-135, 1998	Study design not relevant to protocol for twin pregnancy. Retrospective analysis comparing outcome of second twin versus first twin
Elliott,J.P., Istwan,N.B., Collins,A., Rhea,D., Stanziano,G., Indicated and non-indicated preterm delivery in twin gestations: impact on neonatal outcome and cost, Journal of Perinatology, 25, 4-7, 2005	Study design not relevant to protocol for twin pregnancy. Retrospective analysis of large database
Engelbrechtsen, L., Nielsen, E. H., Perin, T., Oldenburg, A., Tabor, A., Skibsted, L., Danish Fetal Medicine Study, Group, Cesarean section for the second twin: a population-based study of occurrence and outcome, Birth, 40, 10-6, 2013	Study design not relevant to protocol for twin pregnancy. Population-based, retrospective cohort study assessing short-term neonatal outcome of second twin birth by caesarean section after vaginal birth of first-born twin
Essel, J. K., Opai-Tetteh, E. T., Is routine caesarean section necessary for breech-breech and breech-transverse twin gestations?, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 86, 1196-1200, 1996	Study design not relevant to protocol for twin pregnancy. Prospective observational study assessing vaginal birth versus caesarean section

Study	Reason for exclusion
Feingold, M., Cetrulo, C., Peters, M., Chaudhury, A., Shmoys, S., Geifman, O., Mode of delivery in multiple birth of higher order, Acta Geneticae Medicae et Gemellologiae, 37, 105-9, 1988	Retrospective review of triplets comparing births between 1977-1986 (11 caesarean and 4 vaginal) and 1954-1976 (14 vaginal and 1 caesarean)
Fernandez Renart, A., Carrasco Trigueros, M. A., Martin Moreno, E., Garrido Luque, B., Twin childbirth assistance. Experience in our environment, Journal of Maternal-Fetal and Neonatal Medicine, 23, 463, 2010	Abstract of retrospective descriptive analysis in twin pregnancy
Fill Malfertheiner, S., Weigl, M., Dudakova, A., Seelbach-Gobel, B., Birth management and fetal outcome in multiple gestation: analysis of 1.444 births, Archives of Gynecology and Obstetrics, 1-9, 2017	Study design not relevant to protocol for twin pregnancy. Large-scale retrospective analysis
Fleming, A. D., Rayburn, W. F., Mandsager, N. T., Hill, W. C., Levine, M. G., Lawler, R., Perinatal outcomes of twin pregnancies at term, Journal of Reproductive Medicine, 35, 881-5, 1990	Study design not relevant to protocol for twin pregnancy; retrospective review of hospital charts and perinatal data
Ford,A.A., Bateman,B.T., Simpson,L.L., Vaginal birth after cesarean delivery in twin gestations: a large, nationwide sample of deliveries, American Journal of Obstetrics and Gynecology, 195, 1138-1142, 2006	Study design not relevant to protocol for twin pregnancy. Nationwide Inpatient Sample administrative database
Fox, N. S., Cohen, N., Odom, E., Gupta, S., Lam-Rachlin, J., Saltzman, D. H., Rebarber, A., Long-term outcomes of twins based on the intended mode of delivery, Journal of Maternal-Fetal & Neonatal Medicine, 1-6, 2017	Study design not relevant to protocol for twin pregnancy. Survey of women with twin pregnancy >34 weeks births from 2005 to 2014
Ganchimeg, T., Morisaki, N., Vogel, J. P., Cecatti, J. G., Barrett, J., Jayaratne, K., Mittal, S., Ortiz-Panozo, E., Souza, J. P., Crowther, C., Ota, E., Mori, R., W. H. O. Multicountry Survey on Maternal, Newborn Health Research, Network, Mode and timing of twin delivery and perinatal outcomes in low- and middle-income countries: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health, BJOG: An International Journal of Obstetrics & Gynaecology, 121 Suppl 1, 89-100, 2014	Study design not relevant to protocol for twin pregnancy. Secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health
Garabedian, C., Poulain, C., Duhamel, A., Subtil, D., Houfflin-Debarge, V., Deruelle, P., Intrapartum management of twin pregnancies: are uncomplicated monochorionic pregnancies more at risk of complications than dichorionic pregnancies?, Acta Obstetricia et Gynecologica Scandinavica, 94, 301-7, 2015	Study design not relevant to twin pregnancy; retrospective analysis analysing mode of birth and neonatal morbidity according to chorionicity
Gezer,A., Rashidova,M., Guralp,O., Ocer,F., Perinatal mortality and morbidity in twin pregnancies: the relation between chorionicity and gestational age at birth, Archives of Gynecology and Obstetrics, 285, 353-360, 2012	Study design not relevant to protocol for twin pregnancy. Analysis of twin gestation cases to determine perinatal mortality and morbidity rates according to chorionicity and gestational age at birth
Ginsberg,N.A., Levine,E.M., Delivery of the second twin, International Journal of Gynaecology and Obstetrics, 91, 217-220, 2005	Study design not relevant to protocol for twin pregnancy. Retrospective analysis of twin births to determine the likelihood of caesarean section for the first twin after vaginal birth of the first twin

Study	Reason for exclusion
Gocke,S.E., Nageotte,M.P., Garite,T., Towers,C.V., Dorcester,W., Management of the nonvertex second twin: primary cesarean section, external version, or primary breech extraction, American Journal of Obstetrics and Gynecology, 161, 111-114, 1989	Study design not relevant to protocol for twin pregnancy; retrospective case series
Gonen, R., Heyman, E., Asztalos, E. V., Ohlsson, A., Pitson, L. C., Shennan, A. T., Milligan, J. E., The outcome of triplet, quadruplet, and quintuplet pregnancies managed in a perinatal unit: obstetric, neonatal, and follow-up data, American Journal of Obstetrics & Gynecology, 162, 454-9, 1990	Study design not relevant to protocol - retrospective medical records review
Gonzalez-Mesa, E., Cazorla-Granados, O., Gonzalez-Valenzuela, M. J., The influence of obstetric variables on school achievement, intelligence and neuropsychological development in a sample of Spanish twins at the age of six: a retrospective study, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 29, 1595-602, 2016	Study design not relevant to protocol for twin pregnancy. Retrospective cross-sectional study of 6-year old twins
Goossens, S. M., Hukkelhoven, C. W., de Vries, L., Mol, B. W., Nijhuis, J. G., Roumen, F. J., Clinical indicators associated with the mode of twin delivery: an analysis of 22,712 twin pairs, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 195, 133-40, 2015	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study in women with planned caesarean section and women with planned vaginal birth
Grisaru, D., Fuchs, S., Kupferminc, M. J., Har-Toov, J., Niv, J., Lessing, J. B., Outcome of 306 twin deliveries according to first twin presentation and method of delivery, American Journal of Perinatology, 17, 303-307, 2000	Study design not relevant to protocol for twin pregnancy. Retrospective review of medical records in women undergoing vaginal trial of labour or caesarean section
Grobman,W.A., Peaceman,A.M., Haney,E.I., Silver,R.K., MacGregor,S.N., Neonatal outcomes in triplet gestations after a trial of labor, American Journal of Obstetrics and Gynecology, 179, 942-945, 1998	Study design not relevant to protocol; retrospective case-control in triplet pregnancy
Haest,K.M., Roumen,F.J., Nijhuis,J.G., Neonatal and maternal outcomes in twin gestations > or =32 weeks according to the planned mode of delivery, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 123, 17-21, 2005	Study design not relevant to protocol for twin pregnancy. Single-centre retrospective cohort assessing potential relationship between outcomes in twin gestations and planned mode of birth
Hage,M.L., Helms,M.J., Dudley,A., Stead,W.W., Hammond,W.E., Neyland,C., Hammond,C.B., Acute childbirth morbidity: its measurement using hospital charges, American Journal of Obstetrics and Gynecology, 166, 1853-1859, 1992	Retrospective analysis of maternal and infant hospital outcomes for caesarean versus vaginal births. Does not state whether twin or triplet pregnancy
Haloob, R. K., Kalaivani, R., Bagtharia, S., Comparison of morbidity among twins and triplets, Journal of Obstetrics & GynaecologyJ Obstet Gynaecol, 23, 367-8, 2003	Comparison not relevant to protocol. Retrospective, observational study comparing morbidity among twins and triplets (all caesarean section)
Hamou, B., Wainstock, T., Mastrolia, S. A., Beer-Weisel, R., Staretz-Chacham, O., Dukler, D., Rafaeli-Yehudai, T., Mazor, M., Erez, O., Induction of labor in twin gestation: lessons from a population based study, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 29, 3999-4007, 2016	Study design not relevant to protocol for twin pregnancy; retrospective population based cohort study assessing the role of induction of labour in twin gestations

Study	Reason for exclusion
Hartley, R. S., Hitti, J., Please exit safely: maternal and twin pair neonatal outcomes according to delivery mode when twin A is vertex, Journal of Maternal-Fetal & Neonatal Medicine, 30, 54-59, 2017	Study design not relevant to protocol for twin pregnancy; retrospective population-based study
Heluin,G., Papiernik,E., Berardi,J.C., Frydman,R., Delivery of twin pregnancy, Acta Geneticae Medicae et Gemellologiae, 28, 361-362, 1979	Study design not relevant to protocol for twin pregnancy - retrospective case series
Hengst,P., Aedtner,O., Kokott,T., Twins--results after changing the management in pregnancy and labor, Journal of Perinatal Medicine, 21, 303-308, 1993	Study design not relevant to protocol for twin pregnancy. Retrospective analysis
Herbst,A., Kallen,K., Influence of mode of delivery on neonatal mortality in the second twin, at and before term, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 1512-1517, 2008	Study design not relevant to protocol for twin pregnancy; Swedish Medical Birth Registry
Hoffmann, E., Oldenburg, A., Rode, L., Tabor, A., Rasmussen, S., Skibsted, L., Twin births: cesarean section or vaginal delivery?, Acta Obstetricia et Gynecologica Scandinavica, 91, 463-9, 2012	Study design not relevant to protocol for twin pregnancy; population-based retrospective cohort study
Hofmeyr, G Justus, Barrett, Jon F, Crowther, Caroline A, Planned caesarean section for women with a twin pregnancy, Cochrane Database of Systematic Reviews, 2015	Cochrane review of twin pregnancy. Included studies relevant to this protocol have been assessed (Barrett 2013; Rabinovici 1987)
Hogle, K. L., Hutton, E. K., McBrien, K. A., et al.,, Cesarean delivery for twins: a systematic review, American Journal of Obstetrics and Gynecology, 188, 220-227, 2003	Systematic review of twin pregnancy. Relevant included RCTs identified and assessed for this protocol (Rabinovici 1987)
Jhaveri, R. R., Nadkarni, T. K., Perinatal Outcome of Second Twin with Respect to Mode of Delivery: An Observational Study, Journal of Clinical and Diagnostic Research JCDRJ Clin Diagn Res, 10, QC26-QC28, 2016	Study design not relevant to protocol for twin pregnancy; retrospective analysis from hospital birth records
Jonsdottir, F., Henriksen, L., Secher, N. J., Maaloe, N., Does internal podalic version of the non-vertex second twin still have a place in obstetrics? A Danish national retrospective cohort study, Acta Obstetricia et Gynecologica Scandinavica, 94, 59-64, 2015	Study design not relevant to protocol for twin pregnancy; retrospective cohort study
Jonsson, M., Induction of twin pregnancy and the risk of caesarean delivery: a cohort study, BMC Pregnancy & Childbirth, 15, 136, 2015	Study design not relevant to protocol for twin pregnancy; cohort study
Kaplan, B., Peled, Y., Rabinerson, D., Goldman, G. A., Nitzan, Z., Neri, A., Successful external version of B-twin after the birth of A-twin for vertex--non-vertex twins, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 58, 157-60, 1995	Study design not relevant to protocol for twin pregnancy; retrospective review
Keith, L. G., Ameli, S., Depp, O. R., Hobart, J., Keith, D. M., The Northwestern University Triplet Study. II: Fourteen triplet pregnancies delivered between 1981 and 1986, Acta Geneticae Medicae et Gemellologiae, 37, 65-75, 1988	Study design not relevant to protocol; retrospective, non-comparative, chart review of triplet pregnancy
Kessous, R., Friedler-Mashiach, Y., Sheiner, E., Risk factors predicting an emergency cesarean section for second twin	Abstract of a retrospective study in twin pregnancy

Study	Reason for exclusion
after vaginal delivery of the first twin, American Journal of Obstetrics and Gynecology, 208, S290, 2013	
Khandelwal, M., Revanasiddappa, V. B., Moreno, S. C., Simpkins, G., Weiner, S., Westover, T., Monoamniotic monochorionic twins-can they be delivered safely via vaginal route?, Obstetrics and Gynecology, 127, 3S, 2016	Abstract of Retrospective cohort study of twin pregnancy
Ko, H. J., Jun, J. K., Clinical factors associated with failed trials of labor in late preterm and term twin pregnancies, Journal of Perinatal Medicine, 42, 449-55, 2014	Study design not relevant to protocol for twin pregnancy; consecutive case series
Ko, H. J., Jun, J. K., Park, C. W., Park, J. S., Yoon, B. H., Neonatal outcomes of trials of labor in twin pregnancies, American Journal of Obstetrics and Gynecology, 210, S320-S321, 2014	Abstract of retrospective cohort study of twin pregnancies
Kong, C. W., To, W. W. K., The predicting factors and outcomes of caesarean section of the second twin, Journal of Obstetrics and Gynaecology, 1-5, 2017	Study design not relevant to protocol for twin pregnancy; retrospective review
Kontopoulos,E.V., Ananth,C.V., Smulian,J.C., Vintzileos,A.M., The impact of route of delivery and presentation on twin neonatal and infant mortality: a population-based study in the USA, 1995-97, Journal of Maternal-Fetal and Neonatal Medicine, 15, 219-224, 2004	Study design not relevant to protocol for twin pregnancy; population-based retrospective cohort study based on the matched multiple births
Kurzel, R. B., Claridad, L., Lampley, E. C., Cesarean section for the second twin, Journal of Reproductive Medicine, 42, 767-70, 1997	Study design not relevant to protocol for twin pregnancy; retrospect case series
Kwon, J. Y., Yoon, W. S., Lee, G. S., Kim, S. J., Shin, J. C., Park, I. Y., Umbilical arterial blood gas and perinatal outcome in the second twin according to the planned mode of delivery, International Journal of Medical Sciences, 8, 643-8, 2011	Study design not relevant to protocol for twin pregnancy; retrospective analysis of medical records
Laajili, H., Chioukh, F. Z., Hajji, A., Toumi, D., Korbi, E., Monastiri, K., Sakouhi, M., Delivery mode in twin pregnancies with first twin in breech: A retrospective study in a Tunisian maternity level III over a period of 12 years, Journal of Maternal-Fetal and Neonatal Medicine, 27, 423, 2014	Study design not relevant to protocol for twin pregnancy; retrospective single-centre study of 815 twin pregnancies
Laube, D. W., Multiple pregnancy, operative delivery, anesthesia, and analgesia, Current Opinion in Obstetrics & GynecologyCurr Opin Obstet Gynecol, 2, 40-4, 1990	Narrative review
Lee, Y. M., Delivery of twins, Seminars in Perinatology, 36, 195-200, 2012	A review on the optimal length of gestation for twins and consideration regarding the mode of birth
Lee,H.C., Blumenfeld,Y.J., Randomised controlled trial: Caesarean delivery for twin gestation at 32-38 weeks does not lead to improved clinical outcomes for neonates or mothers, Evidence-Based Medicine, 19, 119-, 2014	Commentary on Barrett et al. A randomised trial of planned caesarean or vaginal birth for twin pregnancy. NEJM 2013; 369:1295–305
Leeker, M., Beinder, E., Twin pregnancies discordant for anencephaly - Management, pregnancy outcome and review of literature, European Journal of Obstetrics Gynecology and Reproductive Biology, 114, 15-18, 2004	The paper describes 6 cases of twin pregnancies discordant for anencephaly and gives a short review on this topic

Study	Reason for exclusion
Liu,S., Benirschke,K., Scioscia,A.L., Mannino,F.L., Intrauterine death in multiple gestation, Acta Geneticae Medicae et Gemellologiae, 41, 5-26, 1992	The paper describes 41 cases of intrauterine death that occurred in women with multiple gestation and examines the aetiology of neurological and other damage in the surviving infants
Machtinger,R., Sivan,E., Maayan-Metzger,A., Moran,O., Kuint,J., Schiff,E., Perinatal, postnatal, and maternal outcome parameters of triplet pregnancies according to the planned mode of delivery: results of a single tertiary center, Journal of Maternal-Fetal and Neonatal Medicine, 24, 91-95, 2011	A case-control study where each vaginal birth case was matched with caesarean section cases based on certain characteristics (gestational age etc.); study design is not according to the protocol
Mei-Dan, E., Asztalos, E. V., Melamed, N., Willan, A. R., Barrett, J. F. R., Cesarean versus vaginal delivery for women in spontaneous labor of twin pregnancy: A secondary analysis of the Twin Birth Study, American Journal of Obstetrics and Gynecology, 1), S164, 2016	Conference abstract
Mei-Dan, E., Dougan, C., Melamed, N., Asztalos, E. V., Aviram, A., Willan, A. R., Barrett, J. F. R., Planned cesarean or vaginal delivery for women in spontaneous labor with a twin pregnancy: A secondary analysis of the Twin Birth Study, BirthBirth, 02, 02, 2018	A subgroup analysis (women in spontaneous labour only) from Barrett et al. 2013 which is already included in the review
Monson, M., Silver, R. M., Multifetal Gestation: Mode of Delivery, Clinical Obstetrics & Gynecology, 58, 690-702, 2015	A review on mode of birth for multiple gestations. Studies from this review were assessed for a potential inclusion
Morikawa, M., Cho, K., Yamada, T., Yamada, T., Sato, S., Minakami, H., Clinical features and short-term outcomes of triplet pregnancies in Japan, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 121, 86-90, 2013	Non relevant comparison
Murray-Davis, B., McVittie, J., Barrett, J. F., Hutton, E. K., Exploring Women's Preferences for the Mode of Delivery in Twin Gestations: Results of the Twin Birth Study, Birth (Berkeley, Calif.), 43, 285-292, 2016	Non relevant outcomes
Mutihir,J.T., Triplet pregnancy as seen in the Jos University Teaching Hospital, Nigerian Postgraduate Medical Journal, 14, 281-284, 2007	A retrospective review of the triplet pregnancies in a Obstetrics and Gynecology department in Nigeria
Olofsson,P., Triplet and quadruplet pregnancies--a forthcoming challenge also for the 'general' obstetrician, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 35, 159-171, 1990	Mixed population, that is triplet and quadruplet pregnancies
Pons,J.C., Charlemaine,C., Dubreuil,E., Papiernik,E., Frydman,R., Management and outcome of triplet pregnancy, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 76, 131-139, 1998	A retrospective study comparing triplet births (the obstetrical follow-up parameters) from 2 different time periods
Pratt,S.D., Anesthesia for breech presentation and multiple gestation, Clinical Obstetrics & Gynecology, 46, 711-731, 2003	The paper describes breech presentation in general, risks associated with this presentation, physiological changes in multiple pregnancy and complications associated with that

Study	Reason for exclusion
Robinson,C., Chauhan,S.P., Intrapartum Management of Twins, Clinical Obstetrics and Gynecology, 47, 248-262, 2004	Review describes the intrapartum management of multiple gestations, with emphasis on twin pregnancies
Rodrigues, F., Vale-Fernandes, E., Teixeira, N., Miranda, A., Gil, B., Barros, J., Optimal delivery route for cephalic-noncephalic twins, Journal of Perinatal Medicine, 41, 2013	Conference abstract
Rossi, A. C., Mullin, P. M., Chmait, R. H., Neonatal outcomes of twins according to birth order, presentation and mode of delivery: a systematic review and meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 118, 523-32, 2011	A systematic review of observational studies on mode of birth in twin pregnancy
Saccone, G., Berghella, V., Planned delivery at 37 weeks in twins: a systematic review and meta-analysis of randomized controlled trials, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 29, 685-9, 2016	Studies included in this review were assessed for a potential inclusion
Sato, Y., Emoto, I., Maruyama, S., Taga, A., Fujii, T., Twin vaginal delivery is associated with lower umbilical arterial blood pH of the second twin and less intrapartum blood loss, Journal of Maternal-Fetal and Neonatal Medicine, 29, 3067-3071, 2016	Retrospective cohort study
Shinwell,E.S., Blickstein,I., Lusky,A., Reichman,B., Excess risk of mortality in very low birthweight triplets: A national, population based study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 88, F36-F40, 2003	Non relevant comparison
Shub, Alexis, Walker, Susan P, Planned early delivery versus expectant management for monoamniotic twins, Cochrane Database of Systematic Reviews, 2015	No trials were identified for this review
Simoes, T., Queiros, A., Goncalves, M. R., Periquito, I., Silva, P., Blickstein, I., Perinatal outcome of dichorionic-triamniotic as compared to trichorionic triplets, Journal of Perinatal Medicine, 44, 875-879, 2016	Non relevant comparison, that is dichorionic-triamniotic triplets versus trichorionic triplets
Smith, G. C. S., Shah, I., White, I. R., et al.,, Mode of delivery and the risk of delivery-related perinatal death among twins at term: a retrospective cohort study of 8073 births, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1139-1144, 2005	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study
Smith,G.C., Pell,J.P., Dobbie,R., Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study, BMJ, 325, 1004-, 2002	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study
Smith,G.C., Fleming,K.M., White,I.R., Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland, and Wales, 1994-2003: retrospective cohort study, BMJ, 334, 576-, 2007	Retrospective cohort study
Steins Bisschop, C. N., Vogelvang, T. E., May, A. M., Schuitemaker, N. W., Mode of delivery in non-cephalic presenting twins: a systematic review, Archives of Gynecology & Obstetrics, 286, 237-47, 2012	Studies from this review were assessed for a potential inclusion
Suzuki, S., Yoneyama, Y., Sawa, R., Takeuchi, M., Shin, S., Araki, T., Fetal position associated with an increased risk of cesarean delivery in nulliparous twin gestations, Acta	Retrospective cohort study

Study	Reason for exclusion
Obstetricia et Gynecologica Scandinavica, 80, 273-274, 2001	
Suzuki,S., Risk factors for emergency cesarean delivery of the second twin after vaginal delivery of the first twin, Journal of Obstetrics & Gynaecology Research, 35, 467-471, 2009	Case-control study
Thiery,M., Kermans,G., Derom,R., Triplet and higher-order births: what is the optimal delivery route?, Acta Geneticae Medicae et Gemellologiae, 37, 89-98, 1988	Mixed population, which is triplets, quadruplets and sextuplets. Case series
Varner, M. W., Thom, E., Spong, C. Y., Landon, M. B., Leveno, K. J., Rouse, D. J., Moawad, A. H., Simhan, H. N., Harper, M., Wapner, R. J., Sorokin, Y., Miodovnik, M., Carpenter, M., Peaceman, A., O'Sullivan M, J., Sibai, B. M., Langer, O., Thorp, J. M., Ramin, S. M., Mercer, B. M., National Institute of Child, Health, Human Development Maternal-Fetal Medicine Units, Network, Trial of labor after one previous cesarean delivery for multifetal gestation, Obstetrics & GynecologyObstet Gynecol, 110, 814-9, 2007	Non relevant comparison, that is women with a prior multifetal caesarean birth versus those with a prior singleton caesarean birth
Vintzileos, A. M., Ananth, C. V., Kontopoulos, E., Smulian, J. C., Mode of delivery and risk of stillbirth and infant mortality in triplet gestations: United States, 1995 through 1998, American Journal of Obstetrics and Gynecology, 192, 464-469, 2005	Mode of birth is an outcome and not a comparison
Weissman, A., Talmon, R., Jakobi, P., The outcome of abdominally delivered triplets and twins: a matched case-control study, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 79, 123-5, 1998	A case-control study of matched twin and triplet births
Weissman, A., Yoffe, N., Jakobi, P., Brandes, J. M., Paldi, E., Blazer, S., Management of triplet pregnancies in the 1980s--are we doing better?, American Journal of Perinatology, 8, 333-7, 1991	Case series
Welsh, A., Clements, S., Henry, A., Bisits, A., Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: The Twins Timing of Birth Randomised Trial, BJOG: An International Journal of Obstetrics and Gynaecology, 119, 1675-1676, 2012	Letter to the editor
Wen, S. W., Demissie, K., Yang, Q., Walker, M. C., Maternal morbidity and obstetric complications in triplet pregnancies and quadruplet and higher-order multiple pregnancies, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 191, 254-8, 2004	Non relevant comparison
Wildschut, H. I., van Roosmalen, J., van Leeuwen, E., Keirse, M. J., Planned abdominal compared with planned vaginal birth in triplet pregnancies, British Journal of Obstetrics & Gynaecology, 102, 292-6, 1995	Non relevant comparison
Wong,L.F., Holmgren,C.M., Silver,R.M., Varner,M.W., Manuck,T.A., Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks, American Journal of Obstetrics and Gynecology, 212, 215-215, 2015	No data for the relevant comparison (planned vaginal birth versus planned caesarean section) were reported

Study	Reason for exclusion
Yang, Q., Wen, S. W., Chen, Y., Krewski, D., Fung Kee Fung, K., Walker, M., Neonatal mortality and morbidity in vertex-vertex second twins according to mode of delivery and birth weight, Journal of Perinatology, 26, 3-10, 2006	Study design not relevant to protocol for twin pregnancy. Retrospective cohort study
Zafarmand, Mh, Goossens, Sm, Tajik, P, Bossuyt, Pm, Asztalos, Ev, Gardener, G, Willan, Ar, Roumen, Fj, Mol, Bw, Barrett, Jy, Personalizing twin delivery management: a secondary analysis of a randomized clinical trial comparing planned caesarean or planned vaginal delivery, American journal of obstetrics and gynecology. Conference: 38th annual meeting of the society for maternal-fetal medicine: the pregnancy meeting. United states, 218, S146, 2018	Conference abstract
Ziadeh, S. M., Perinatal outcome in 41 sets of triplets in Jordan, Birth (Berkeley, Calif.), 27, 185-188, 2000	The same population and results as in Ziadeh S.M. Gynecologic and Obstetric Investigation, Gynecologic and Obstetric Investigation 162-165

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Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal mode of birth to improve outcomes for mothers and babies in twin and triplet pregnancy?

No research recommendation was made for this review.