National Institute for Health and Care Excellence

Draft for consultation

Twin and Triplet Pregnancy

[B2] Evidence review for interventions for the prevention of spontaneous preterm birth

NICE guideline tbc

Evidence reviews

March 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Interventions to prevent spontaneous preterm birth in twins and triplets

Review question

What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Introduction

Spontaneous preterm birth and iatrogenic preterm birth that are secondary to other complications occur more frequently in twin and triplet pregnancies than in singleton pregnancies. Preterm birth (even near-term birth) is associated with increased morbidity and use of healthcare resources, with many preterm babies being admitted to neonatal units. Extremely preterm birth (at less than 28 weeks' gestation) is associated with even greater morbidity and mortality and greater use of healthcare resources. It is, therefore, relevant to identify treatments which prevent spontaneous preterm birth without causing adverse effects (AEs) in the woman or babies.

Summary of the protocol

Table 1 summarises the Population, Intervention, Comparator, and Outcome (PICO) characteristics of this review.

Table 1: Summary of protocol (PICO table)

Population	Monochorionic / dichorionic twin and all triplet pregnancies identified by the 11 – 13 week ultrasound scan (not symptomatic, not in labour). **Setting: Any setting**

Intervention	• Bed rest at home or in hospital during the antenatal period
	• Intramuscular or vaginal micronised progesterone
	• Arabin cervical pessary
	• Cervical cerclage
	• Oral tocolytics:
	  ○ beta mimetics
	  ○ ritodrine
	  ○ magnesium sulphate
	  ○ nifedipine
	• Sexual abstinence
	Studies examining combinations of eligible interventions will be included.

Comparator	• Placebo • No intervention • Head-to-head comparisons of eligible interventions
Outcomes	**Critical** **For the woman:** • Mortality **For the baby:** • Gestational age at birth • Perinatal mortality **Important** **For the woman:** • Woman's satisfaction (validated scales)

	• Adverse events, such as infection, haemorrhage, drug effects: hypotension, anaphylaxis, venous thromboembolism **For the baby:** • Perinatal morbidity (birth injuries, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis)

For full details see the review protocol in appendix A.

Methods and process

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

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

Clinical evidence

Included studies

The included studies were divided into the different interventions of interest, as listed in the protocol (Table 1).

For each intervention, twin and triplet pregnancies were separated, and different comparisons were made for each subset of an intervention (type of progesterone, type of oral tocolytic, type of pessary), or different comparators.

Some outcomes were not available for analysis. These were most often outcomes affecting the woman: maternal mortality, woman's satisfaction, AEs (for the woman).

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

Progesterone

Comparison 1. Vaginal progesterone versus placebo for twin pregnancy:

One systematic review of individual patient data (IPD) (Romero 2017) was included which comprised 6 RCTs (Brizot 2015, Cetingoz 2011, El-Rafaie 2016, Fonseca 2007, Rode 2011/PREDICT, Serra 2013) which was restricted to women who have a short cervical length (CL) (defined as ≤25 mm) treated with daily vaginal progesterone pessary/suppository/gel. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Two further RCTs were included comprising an unselected sample of women with twin pregnancy (Norman 2009/STOPPIT, and Wood 2012) treated with daily vaginal progesterone. The following outcome was not available for analysis: woman's satisfaction.

One systematic review (Jarde 2017) was not fully included for all outcomes as it included the same RCTs listed in the IPD analysis by Romero 2017. However, the review was checked for additional outcomes and the data of the review were only used for 1 further outcome not reported previously (maternal mortality).

Comparison 2. Intramuscular progesterone versus placebo for twin pregnancy:

One systematic review of IPD (Schuit 2015) included 6 RCTs (Awwad 2015/PROGESTWIN, Briery 2009, Combs 2011, Lim 2011/AMPHIA, Rouse 2007, Senat 2013) comprising an unselected sample of women with twin pregnancy treated with intramuscular progesterone. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Comparison 3. Intramuscular progesterone versus placebo for triplet pregnancy:

One systematic review of IPD (Combs 2016) included 3 RCTs (Caritis 2009, Combs 2010, Lim 2011/AMPHIA) comprising an unselected sample of women with triplet pregnancy. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Arabin pessary

Comparison 4. Arabin pessary versus no pessary (control) for twin pregnancy:

One systematic review (Jarde 2017) included 3 RCTs (Goya 2016, Liem 2013, Nicolaides 2016) comprising an unselected sample of women with twin pregnancy treated using Arabin Pessary. The following outcomes were not available for analysis: woman's satisfaction, AEs (for the woman).

The included systematic review (Jarde 2017) also performed a subgroup analysis for those women who had a short cervix (defined as a CL≤25 mm). The following outcomes were not available for this analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Comparison 5. Bioteque pessary versus no pessary (control) for twin pregnancy:

One RCT (Berghella 2017) of twin pregnancies with a short cervical (CL≤30mm) treated using Bioteque Pessary was included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Bedrest

Comparison 6. Inpatient bedrest versus no bedrest/normal activity (control) for twin pregnancy:

Two RCTs (Saunders 1985 and Crowther 1989) were included and combined in a meta-analysis comprising an unselected sample of women with twin pregnancy, treated with inpatient bedrest (compared to normal activity). The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman), perinatal morbidity.

Comparison 7. Inpatient bedrest versus no bedrest/normal activity (control) for triplet pregnancy:

One RCT (Crowther 1991) and 1 retrospective cohort study (Skrablin 2002) reporting on an unselected sample of women with triplet pregnancy, treated with inpatient bedrest (compared to normal activity) were included in this review. Some outcomes were not available for analysis from the RCT: maternal mortality, woman's satisfaction, AEs (for the woman), perinatal morbidity. The following outcomes were not available for analysis from the cohort study: maternal mortality, woman's satisfaction, AEs (for the woman).

Comparison 8. Inpatient bedrest versus home bedrest (control) for triplet pregnancy:

One cohort study (Adams 1998) reporting on an unselected sample of women with triplet pregnancy, treated with inpatient bedrest (compared to outpatient/home bedrest) was included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Cervical cerclage

Comparison 9. Cerclage versus no cerclage (control) for twin pregnancy:

One RCT (Dor 1982) comprising an unselected sample of women with twin pregnancy, treated with cervical cerclage was included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman), perinatal morbidity.

One systematic review of IPD (Saccone 2015) included 3 RCTs (Althuisius 2001, Berghella 2004, Rust 2001) reporting on women with twin pregnancy who have a short cervix (defined as CL<25 mm), treated with cervical cerclage, was included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Comparison 10. Cerclage versus no cerclage (control) for triplet pregnancy:

Seven cohort studies (Bernasko 2009, Elimian 1999, Mordel 1993, Obeidat 2017, Rebarber 2005, Sumners 2011, Young 2013) comprising an unselected sample of women with triplet pregnancy were included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman).

Only 1 of these cohort studies examined women who have a short cervix (defined as CL≤25 mm, Young 2013). The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman), perinatal mortality, perinatal morbidity.

Oral tocolytics

Comparison 11. Ritodrine (oral tocolytic) versus placebo for twin pregnancy:

One RCT (O'Connor 1979) reporting on twin pregnancies with unselected CL, treated with Ritodrine compared to placebo, was included in this review. The following outcomes were not available for analysis: maternal mortality, woman's satisfaction, AEs (for the woman), perinatal morbidity.

Sexual abstinence

No clinical studies were found for this intervention.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

Table 2 to Table 6 provides a brief summary of the included studies (Table 2 Progesterone; Table 3 Arabin pessary; Table 4 Bedrest; Table 5 Cervical cerclage; Table 6 Oral tocolytics).

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

Study	Population	Intervention	Comparator	Outcomes
Combs 2016 SR with MA of IPD	Triplet pregnancies (unselected) • Initiated at: range 15-24 weeks' (all studies 16-19 weeks' GA)	Intramuscular progesterone (17OHPC) • 250mg/week	Placebo	• PTB <34 weeks • PTB <32 weeks • PTB <28 weeks • Perinatal mortality • Perinatal morbidity

Study	Population	Intervention	Comparator	Outcomes
USA , Netherlands, Australia RCTs included: • Caritis 2009 • Combs 2010 • Lim 2011	• N=232 (696 infants) • PROG N=136; • PLACEBO N=96			
Norman 2009 (STOPPIT trial) RCT UK	Twin pregnancies (unselected) Randomisation at 22 weeks' GA • 500 enrolled and randomised (N=250 progesterone, N=250 placebo) • Analysed N=247 per group (3 lost to follow up per group)	vPROG • daily 90mg 8% PROG gel	Placebo (same applicator, no progesterone)	• Maternal mortality • GA at birth • PTB <34weeks ○ MCDA ○ DCDA • Perinatal mortality • Maternal infection
Romero 2017 SR with MA of IPD International (multi-site) RCTs included: • Brizot 2015 • Cetingoz 2011 • El-Rafaie 2016 • Fonseca 2007 • Rode 2011 • Serra 2013	Twin pregnancies (with short cervical length ≤25 mm) 6 RCTs included: N=303 women (606 fetuses/infants) from 6RCTs • Vaginal progesterone (vPROG) N=159 • Placebo/no treatment (CONT) N=144	vPROG • 100-400 mg per day • from 20-24 weeks' GA to 34-37 weeks' GA	• Placebo • No treatment	• PTB<28 weeks • PTB<32 weeks • PTB<34 weeks • PTB<37 weeks • Perinatal mortality • Perinatal morbidity
Schuit 2015 SR with MA of IPD International (multi-site) RCTs included: • Awwad 2015	Twin pregnancies (unselected) mPROG (6 RCTs) vPROG (7 RCTs) • total N=3768 women, with 7536 babies; from 13 trials • mPROG (17PC) trials: mPROG N=1089; CONTROL	*Only using data from mPROG:* intramuscular (17PC) progesterone	• Placebo • No treatment	• PTB <28 weeks • PTB <32 weeks • PTB <37 weeks • Perinatal mortality • Perinatal morbidity

Study	Population	Intervention	Comparator	Outcomes
• Aboulghar 2012 • Briery 2009 • Cetingoz 2011 • Combs 2011 • Fonseca 2007 • Lim 2011 • Norman 2009 • Rode 2011 • Rouse 2007 • Senat 2013 • Serra 2013 • Wood 2012	N=944; from 6 studies • vPROG trials: vPROG N=917; CONTROL N=818; from 7 studies			
Wood 2012 RCT Canada	Twin gestation (unselected) Randomisation from 16 weeks' GA • total N=84 (PROG N=42; PBO N=42)	vPROG • 90 mg PROG 8% gel • Daily gel from randomisation to 35^{+6} weeks' GA, or until birth	Placebo (same applicator, no progesterone)	• GA at birth • PTB <37 weeks • Perinatal mortality • Maternal postpartum haemorrhage • Perinatal morbidity

DCDA: dichorionic diamniotic; GA: gestational age; IPD: individual patient data; MA: meta-analysis; MCDA: monochorionic diamniotic; mPROG: intramuscular progesterone; N: number of women (unless specified as infants); PROG: progesterone; PTB: preterm birth; RCT: randomised controlled trial; SR: systematic review; vPROG: vaginal progesterone; wks: weeks

Table 3: Summary of included studies for twin and triplet pregnancy: Arabin pessary

Study	Population	Intervention	Comparator	Outcomes
Berghella 2017 RCT USA	Twin pregnancies (CL≤30mm before 28^{+0} weeks' GA) N=46 agreed to randomisation • Pessary N=23 • Control/no pessary N=23	Bioteque Pessary	No pessary	• GA at birth • PTB <28 weeks • PTB <34 weeks • PTB <37 weeks • Neonatal death • Perinatal morbidity
Jarde 2017 SR with MA Canada RCTs included: • Aboulghar 2012	Twin pregnancies (unselected) Randomisation at 16-29 weeks' GA • 4 studies of 17OHPC assessed short cervix • 3 studies of pessary, with subgroup analysis for CL ≤25 mm	• vPROG • mPROG • Cerclage • Arabin pessary	• Placebo • No intervention	• Maternal mortality • GA at birth • Perinatal mortality • Perinatal morbidity

Study	Population	Intervention	Comparator	Outcomes
• Awwad 2015 • Briery 2009 • Brizot 2015 • Cetingoz 2011 • Combs 2011 • Dor 1982 • El-rafaie 2016 • Fonseca 2007 • Goya 2015 • Hartikainen-Sorru 1980 • Liem 2013 • Lim 2011 • Nicolaides 2016 • Norman 2009 • Rode 2011 • Rouse 2007 • Senat 2013 • Serra 2013 • Wood 2012 • Berghella 2004 - excluded at study level • NacNaughton 1993 - excluded at study level • Rust 2001 - excluded at study level				

DCDA: dichorionic diamniotic; GA: gestational age; IPD: individual patient data; MA: meta-analysis; MCDA: monochorionic diamniotic; mPROG: intramuscular progesterone; N: number of women (unless specified as infants); PROG: progesterone; PTB: preterm birth; RCT: randomised controlled trial; SR: systematic review; vPROG: vaginal progesterone; wks: weeks

Table 4: Summary of included studies for twin and triplet pregnancy: Bedrest

Study	Population	Intervention	Comparator	Outcomes
Adams 1998 Retrospective cohort USA	Triplet pregnancies • N=66 triplet pregnancies • Outpatient bedrest [all triplets receiving care 1993-1996] N=32;	Inpatient bedrest from 24 weeks' GA	Outpatient bedrest	• GA at birth • Perinatal mortality • Perinatal morbidity

Study	Population	Intervention	Comparator	Outcomes
	• Inpatient bedrest [all triplets receiving care 1985-1993] N=34			
Crowther 1989 RCT Zimbabwe	Twin pregnancies of high risk (scored by CL minus cervical dilation) • Measured at ≤34 weeks' N=139 twin pregnancies • N=70 hospitalised (bedrest) group, • N=69 nomal activity (control group)	Inpatient bedrest	Normal activity	• GA at birth • PTB <34 weeks • PTB <37 weeks • Perinatal mortality
Crowther 1991 RCT Zimbabwe	Triplet pregnancies • N=19 triplet pregnancies • Inpatient bedrest N=10; • Outpatient management (normal activity [control]) N=9	Inpatient bedrest	Normal activity	• GA at birth • PTB <34weeks • PTB<37 weeks • Perinatal mortality
Saunders 1985 RCT Zimbabawe	Twin pregnancies • N=212 twin pregnancies randomised to BEDREST in hospital (N=105) or CONTROL (N=107)	Inpatient bedrest • From 32 weeks' GA until onset of labour	Normal activity • Hospital admission used selectively (average 5 weeks later than intervention group)	• GA at birth • PTB <37 weeks • Perinatal mortality
Skrablin 2002 Retrospective cohort (patient selected grouping) Croatia	Triplet pregnancies • Patient selected grouping • group 1 (complete bedrest) selected by N=55 • group 2 (standard outpatient protocol) selected by N=24	Inpatient bedrest • From the start of the second trimester • All women hospitalised from 28 weeks' GA	Normal outpatient protocol • All women hospitalised from 28 weeks' GA	• GA at birth • Perinatal mortality • Perinatal morbidity

DCDA: dichorionic diamniotic; GA: gestational age; IPD: individual patient data; MA: meta-analysis; MCDA: monochorionic diamniotic; mPROG: intramuscular progesterone; N: number of women (unless specified as infants); PROG: progesterone; PTB: preterm birth; RCT: randomised controlled trial; SR: systematic review; vPROG: vaginal progesterone; wks: weeks

Table 5: Summary of included studies for twin and triplet pregnancy: Cervical cerclage

Study	Population	Intervention	Comparator	Outcomes
Bernasko 2006 Retrospective cohort USA	Triplet pregnancies • Cerclage N=55, • No cerclage N=40	Cervical cerclage (McDonald)	No cerclage (or only when cervical change noticed in US)	• GA at birth • PTB <28 weeks • PTB <32 weeks
Dor 1982 RCT Israel	Twin pregnancies • N=50 randomised (N=25 offered suture/cerclage) • N=45 analysed (Cerclage N=22; No cerclage N=23)	Cerclage (McDonald) • Placed at 13 weeks' GA • Removed at 37 weeks' GA; abortion; premature contractions; PROM	No cerclage	• GA at birth • Perinatal mortality
Elimian 1999 Retrospective cohort USA	Triplet pregnancies • N= 59 (N=20/59 cerclage)	Cerclage (McDonald) • Placed at 14.1±0.9 weeks GA	No cerclage	• GA at birth • PTB <32 weeks • GA >37 weeks • Perinatal mortality • Perinatal morbidity
Mordel 1993 Retrospective cohort Israel	Triplet pregnancies • N=35 • 12 elected to have cerclage, remaining 23 served as controls (no cerclage)	Cervical cerclage • Suture placed at 12-14 weeks' GA • Removed at onset of labour • All women hospitalised at 28 weeks'GA	No cerclage • All women hospitalised at 28 weeks' GA	• GA at birth • Perinatal mortality
Obeidat 2017 Retrospective cohort Jordan & Saudi Arabia	Triplet and higher order pregnancies (~90% triplets) N=146 (cerclage N=94; control/no cerclage N=52)	Cervical cerclage • Placed at 11-15 weeks GA • Removed electively ~36wks GA or in emergency	No cerclage	• GA at birth • PTB <28 weeks • PTB <34 weeks • GA >34 weeks • Perinatal mortality
Rebarber 2005 Retrospective cohort USA	Triplet pregnancies • Cerclage N=248; • No cerclage N=3030	Cerclage	No cerclage	• GA at birth • PTB <28 weeks • PTB <32 weeks • Perinatal mortality
Saccone 2015 SR with MA of IPD	Twin pregnancies (CL<25 mm) N=49 twin pregnancies (CERCLAGE N=24,	Cervical cerclage	No cerclage	• GA at birth • PTB <28 weeks • PTB <32 weeks • PTB<34 weeks • PTB <37 weeks

Study	Population	Intervention	Comparator	Outcomes
USA, Italy, Aruba RCTS included: • Althuisius 2001 • Berghella 2004 • Rust 2001	NO CERCLAGE N=25)			• Perinatal mortality • Perinatal morbidity
Sumners 2011 Retrospective cohort USA	Triplet pregnancies • N=141 triplet pregnancies met inclusion criteria • CERCLAGE (transvaginal) TVC N=31 • CERCLAGE (transabdominal) TAC N=60 • NO CERCLAGE (control) N=50	Cerclage: • Transabdominal cerclage (TAC) • Transvaginal cerclage (TVC) TAC was recommended until 2002 for specific cases, then offered to all triplet cases	No cerclage	• GA at birth • PTB<28 weeks • PTB <32 weeks • PTB <37 weeks • Perinatal mortality • Perinatal morbidity
Young 2014 Retrospective cohort USA	Triplet pregnancies (CL<25 mm before 24 weeks' GA) • N=24 (CERCLAGE N=16; NO CERCLAGE N=8)	Cerclage	No cerclage (managed expectantly)	• GA at birth • PTB <28 weeks • PTB <32 weeks • GA >32 weeks

DCDA: dichorionic diamniotic; GA: gestational age; IPD: individual patient data; MA: meta-analysis; MCDA: monochorionic diamniotic; mPROG: intramuscular progesterone; N: number of women (unless specified as infants); PROG: progesterone; PTB: preterm birth; RCT: randomised controlled trial; SR: systematic review; vPROG: vaginal progesterone; wks: weeks

Table 6: Summary of included studies for twin and triplet pregnancy: Oral tocolytics

Study	Population	Intervention	Comparator	Outcomes
O'Connor 1979 RCT Ireland	Twin pregnancies • Treatment started ~28 weeks' GA • Continued until 37 weeks' GA; induced 38-40 weeks • N=50 randomised (25 per group) • N=48 analysed (Ritrodrine N=25; Placebo N=23	Oral tocolytic (Ritodrine) • 100 tablets (supply refreshed each month) • Each tablet: 10 mg ritodrine • Take before means every 6 hours	Placebo	• GA at birth • PTB <37 weeks • Perinatal mortality

DCDA: dichorionic diamniotic; GA: gestational age; IPD: individual patient data; MA: meta-analysis; MCDA: monochorionic diamniotic; mPROG: intramuscular progesterone; N: number of women (unless specified as infants); PROG: progesterone; PTB: preterm birth; RCT: randomised controlled trial; SR: systematic review; vPROG: vaginal progesterone; wks: weeks

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

One cost effectiveness analysis (Liem 2014) was included in this review. This analysis evaluated the cost effectiveness of a cervical pessary to prevent preterm birth in women with a multiple pregnancy.

See also the economic evidence study selection chart in appendix G.

Table 7 provides a brief summary of the included study.

Table 7: Summary of included studies (economic evidence)

Study	Population	Intervention/Comparison	Perspective and cost year	Comments
Liem 2014 Cost effectiveness conducted alongside an RCT Netherlands	Women with a multiple pregnancy	Cervical pessary inserted at a gestational age of 16-20 weeks versus no cervical pessary	Societal 2011 prices	Four univariate sensitivity analyses performed to explore the influence of assumptions and unit cost estimates

Excluded studies

One full-text copy of an article was requested for this review and was included. Therefore, there is no excluded studies list.

Summary of studies included in the economic evidence review

A Dutch study (Liem 2014) reported on an economic evaluation conducted alongside a clinical trial using a societal perspective to assess the cost effectiveness of a cervical pessary to prevent preterm birth in women with a multiple pregnancy. Women allocated to the intervention group (n=403) had the pessary inserted between a gestational age of 16 to 20 weeks. The control group was women without a pessary (n=410) but who otherwise received the same level of obstetric care. Effectiveness was measured using the primary composite outcome of poor perinatal outcome, which comprised stillbirth, periventricular leukomalacia, respiratory distress syndrome, broncho-pulmonary dysplasia, intraventricular haemorrhage, proven sepsis, necrotising enterocolitis and neonatal death before discharge. Costs were collected from the time of randomisation to 6 weeks postpartum and included direct medical costs and patient costs pertaining to travel and lost productivity. Analysis was also undertaken for a subgroup of women whose cervical length was less than the 25th centile (< 38 mm). Costs were denominated in Euros and for a 2011 price year.

Analysis was undertaken on an intention to treat basis with the non-parametric Mann-Whitney U-test used to assess any difference in the use of resources. Uncertainty around

differences in mean costs and the incremental cost effectiveness ratio (ICER) was assessed through non-parametric bootstrapping.

In the results the authors reported that the pessary group had a very small mean reduction in total societal costs per woman of -€94 (95% confidence interval -€5,975 to €5,609), but the difference was not statistically significant at the 5% level. In the subgroup of women with a cervical length < 38 mm a bigger difference in costs was observed, favouring pessary, -€5,436 (95% confidence interval -€11,001 to €1,456), but again this difference was not found to be statistically significant. However, the authors report that the ICERs were difficult to interpret because the study did not demonstrate a treatment benefit with a risk ratio of 0.98 (confidence interval: 0.69 to 1.40) for poor perinatal outcome. However, in probabilistic analysis the results suggested that there was a 98% probability that the pessary was cost effective in women with a cervical length < 38 mm at a cost effectiveness threshold of €15,000 per poor perinatal outcome case avoided. This analysis also suggested that there was a 94% probability the pessary would be cost saving from a societal perspective in this subgroup. The authors conclude that treatment with a cervical pessary in this subgroup appears highly cost effective whilst acknowledging that the small sample for the subgroup analysis was a limitation of the study.

Economic model

An original model was developed to reflect the new clinical evidence identified in this review. The model compared the cost effectiveness of screening to predict the risk of preterm birth, undertaken by measurement of cervical length using transvaginal ultrasound, and a daily dose of micronised vaginal progesterone to delay or prevent spontaneous preterm birth in those pregnancies identified as being at higher risk of preterm birth by screening. The model is summarised below with full details available in appendix J.

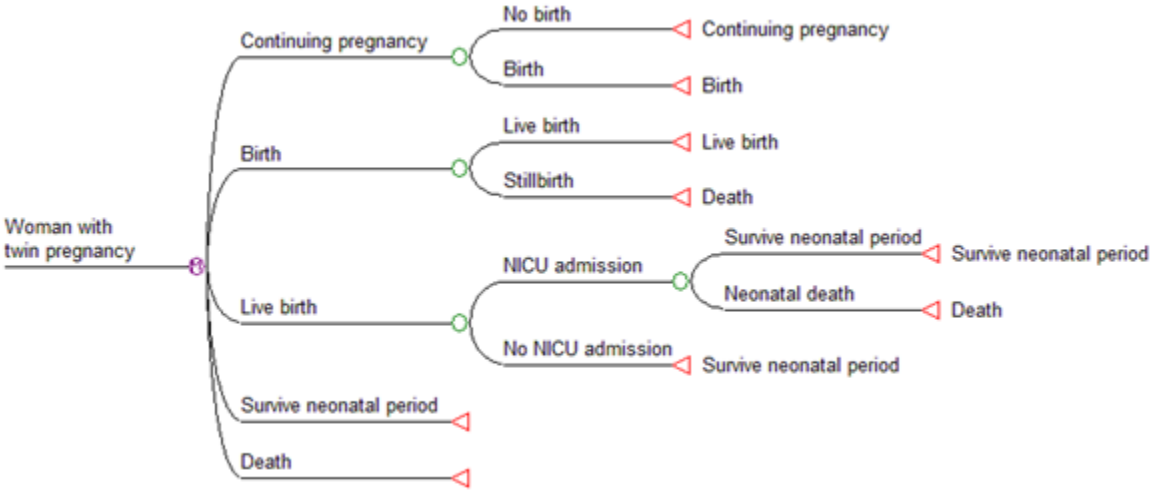
The model took the form of a cost utility analysis and evaluated the following 6 screening strategies for twin pregnancies in an NHS setting:

1. no screening
2. cervical length ≤5mm
3. cervical length ≤10mm
4. cervical length ≤15mm
5. cervical length ≤20mm
6. cervical length ≤25 mm

If a pregnancy was identified as being at higher risk of spontaneous preterm birth by the screening strategy, the woman would be treated with daily vaginal progesterone until birth.

A Markov approach was used to model the pregnancy from a gestational age of 24 weeks to a maximum of 37 weeks. Pregnant women with twins enter the model in the state of 'continuing pregnancy' but for each week of gestational age they can transition to the state of 'birth'. From the 'birth' state, transitions are possible to 'live birth', and subsidiary states reflecting implications for longer term outcome and cost, or 'stillbirth'. This approach is illustrated in Figure 1 below. The transition probabilities to different states vary with gestational age.

Figure 1: Schematic to illustrate Markov approach across pregnancy and the neonatal period



In order to estimate the proportion of pregnancies that would be identified as being at higher risk of spontaneous preterm birth the model factored in a distribution of cervical length at the time of screening. In the base case analysis this was estimated from personal communication (Liem, 2018[a]). Data from Kindinger (2016), included in [B1] Evidence review for ultrasound screening for prediction of the risk of spontaneous preterm birth, was then used to estimate the baseline risk of spontaneous preterm birth by gestational age for twin pregnancies according to their cervical length at the time of screening. Data from an individual patient data meta-analysis (Romero 2017) was then used to modify these baseline risk for pregnancies identified by screening as being at higher risk of preterm birth and treated with vaginal progesterone, using the relative risks reported for <28 weeks, <32 weeks and <36 weeks.

In order to estimate the impact of screening and intervention on health related quality of life and "downstream" costs related to neonatal mortality and morbidity the model included the following clinical outcomes for babies related to preterm birth:

- Stillbirth
- Neonatal death
- Post neonatal death
- Neonatal intensive care unit admission
- Cerebral palsy
- Intraventricular haemorrhage
- Respiratory distress syndrome

For each of these outcomes the analysis modelled a relationship between the risk and gestational age at birth. Depending on the outcome, costs and quality adjusted life years (QALYs) were assigned to these outcomes.

The results of the analysis suggested that it was cost effective to screen for the risk of spontaneous preterm birth using a cervical length threshold of 25 mm and to treat those

[a] The communication was by e-mail correspondence between the guideline topic advisor and Dr Sophie Liem, an obstetrician, who has published on cervical length distribution (https://www.ajog.org/article/S0002-9378(17)32042-2/pdf)

pregnancies identified at being at higher risk of preterm birth. Probabilistic sensitivity analysis showed that using a screening strategy with a cervical length threshold of 25 mm as a basis for treatment had an incremental net monetary benefit (NMB) of £1,013 when compared to the no screening strategy with a 98.5% probability of being the most cost effective strategy. In the probabilistic analysis, screening using a cervical length threshold of 25 mm and treating those pregnancies identified as being at a higher risk of spontaneous preterm birth had a small incremental cost of £35 relative to no screening when savings from averted neonatal mortality and morbidity were taken into account. However, the deterministic analysis suggested that this strategy could be cost saving overall, with the reduction in costs from fewer adverse outcomes more than offsetting the costs of screening and intervention. The costs of daily dose vaginal progesterone accounted for an insignificant part of the overall costs of intervention. This is because vaginal progesterone is inexpensive and because the number of pregnancies identified as being at higher risk of spontaneous preterm is a small proportion of all twin pregnancies.

Sensitivity analysis indicated that the cost effectiveness of screening for spontaneous preterm birth using a cervical length threshold of 25 mm and treatment of those pregnancies identified at being at higher risk of preterm birth was not particularly sensitive to changes in model input parameters. Therefore, the committee considered that a recommendation to offer daily vaginal progesterone to women whose pregnancy had been identified as being at higher risk of preterm birth would be cost effective to the NHS.

Evidence statements

Progesterone

Comparison 1a: Vaginal progesterone versus placebo in twin pregnancy with short cervical length (≤25 mm)

Outcomes for the baby

Gestational age at birth

Moderate quality evidence from 6 RCTs (N=303) showed a clinically important difference in preterm birth before 28 weeks' gestation with a lower: risk associated with the intervention group.

High quality evidence from 6 RCTs (N=303) showed a clinically important difference in preterm birth before 32 weeks' gestation with a lower incidence associated with the intervention group.

Moderate quality evidence from 6 RCTs (N=303) showed a clinically important difference in the incidence of preterm birth before 34 weeks' gestation with a lower risk associated with in the intervention group.

High quality evidence from 6 RCTs (N=303) showed a clinically important difference in incidence of preterm birth before 37 weeks' gestation with a lower risk associated with the intervention group.

Perinatal mortality

All analyses for this outcome within this comparison assumed independence between twins.

High quality evidence from 6 RCTs (N=606 infants) showed a clinically important difference for incidence of any perinatal death with a lower incidence in the intervention group.

Low quality evidence from a subgroup of 6 RCTs (N=606 infants) showed a clinically significant difference for incidence of fetal death with a lower incidence in the intervention group.

High quality evidence from a subgroup of 6 RCTs (N=606 infants) showed a clinically important difference for incidence of neonatal death with a lower incidence in the intervention group.

Perinatal morbidity

Moderate quality evidence from 6 RCTs (N=591) showed a clinically important difference for incidence of respiratory distress syndrome (RDS):with a lower incidence in the intervention group.

Low quality evidence from 5 RCTs (N=148) showed no clinically important difference for incidence of intraventricular haemorrhage (IVH) between the intervention and control groups.

Low quality evidence from 5 RCTs (N=150) showed no clinically important difference for incidence of necrotising enterocolitis (NEC) between the intervention and control groups.

Comparison 1b: Vaginal progesterone versus placebo in twin pregnancy (unselected)

Outcomes for the woman:

Mortality

Moderate quality evidence from 1 RCT (N=494) reported no clinically important difference for incidence of maternal death between intervention and control groups.

Adverse effects

Moderate quality evidence from 1 RCT (N=494) showed no clinically important difference for incidence of infection as an AE for the woman between intervention and control groups.

Very low quality evidence from 1 RCT (N=84) showed no clinically important difference for incidence of haemorrhage as an AE for the woman between intervention and control groups.

Outcomes for the baby:

Gestational age at birth

Moderate quality evidence from 1 RCT (N=494) reported no clinically important difference for mean GA at birth (weeks) between intervention and control groups.

Low quality evidence from 1 RCT (N=84) showed no clinically important difference for median and range for GA at birth (could not be meta-analysed) between intervention and control groups.

Moderate quality evidence from 1 RCT (N=494) showed no clinically important difference for incidence of preterm birth (or intrauterine death) before 34 weeks' gestation between intervention and control. The RCT stratified for chorionicity:

- Low quality evidence from 1 RCT (N=91/494) showed no clinically important difference for incidence of preterm birth/death (<34 weeks) in MCDA twins between intervention and control groups.
- Moderate quality evidence from 1 RCT (N=403/494) showed a clinically important difference for incidence of preterm birth/death (<34 weeks) in DCDA twins with a higher incidence in the intervention group.

Very low quality evidence from 1 RCT (N=494) showed no clinically important difference for incidence of preterm birth (or intrauterine [IU] death) before 37 weeks' gestation between intervention and control groups.

Perinatal mortality

Low quality evidence from 1 RCT (N=171 infants) reported no clinically important difference for incidence of any perinatal death between intervention and control groups.

Low quality evidence from 1 RCT (N=494) reported no clinically important difference for incidence of intrauterine death between intervention and control groups.

Low quality evidence from 1 RCT (N=494) reported no clinically important difference for incidence of neonatal death between intervention and control groups.

Perinatal morbidity

Moderate quality evidence from 1 RCT (N=171 infants) showed no clinically important difference for incidence of RDS between intervention and control groups.

Low quality evidence from 1 RCT (N=171 infants) showed no clinically important difference for incidence of IVH between intervention and control groups.

Low quality evidence from 1 RCT (N=171 infants) showed no clinically important difference for incidence of NEC between intervention and control groups.

Comparison 2: Intramuscular progesterone versus placebo in twin pregnancy (unselected)

Outcomes for the woman:

Mortality

Data was not available for this comparison (maternal mortality was included in one systematic review, but found no included studies reporting it).

Outcomes for the baby:

Gestational age at birth

Low quality evidence from 6 RCTs (N=2033 pregnancies) showed no clinically important difference for incidence of preterm birth before 28 weeks' gestation between the intervention and control groups.

Low quality evidence from 6 RCTs (N=2033 pregnancies) showed no clinically important difference for incidence of preterm birth before 32 weeks' gestation between the intervention and control groups.

High quality evidence from 6 RCTs (N=2033 pregnancies) showed no clinically important difference for incidence of preterm birth before 37 weeks' gestation between the intervention and control groups.

Perinatal mortality

Very low quality evidence from 6 RCTs (N=4066 infants) showed no clinically important difference for incidence of any perinatal death between the intervention and control groups.

Perinatal morbidity

Low quality evidence from 6 RCTs (N=4066 infants) showed no clinically important difference for incidence of RDS between the intervention and control groups.

Low quality evidence from 6 RCTs (N=4066 infants) showed no clinically important difference for incidence of IVH between the intervention and control groups.

Low quality evidence from 6 RCTs (N=4066 infants) showed no clinically important difference for incidence of NEC between the intervention and control groups.

Comparison 3: Intramuscular progesterone (17OHPC) versus placebo in triplet pregnancy (unselected) – IPD data

Outcomes for the baby:

Gestational age at birth

Low quality evidence from 3 RCTs (N=232) showed no clinically important difference for incidence of preterm birth before 28 weeks' gestation between the intervention and placebo groups.

Very low quality evidence from 3 RCTs (N=232) showed no clinically important difference for incidence of preterm birth before 32 weeks' gestation between the intervention and placebo groups.

Moderate quality evidence from 3 RCTs (N=232) showed no clinically important difference for incidence of preterm birth before 34 weeks' gestation between intervention and placebo groups.

Perinatal mortality

Very low quality evidence from 3 RCTs (N=696 infants) showed no clinically important difference for incidence of any perinatal death between intervention and placebo groups.

Low quality evidence from 3 RCTs (N=696 infants) showed a clinically important difference for incidence of neonatal death with a lower incidence in the intervention group.

Low quality evidence from 3 RCTs (N=696 infants) showed a clinically important difference for incidence of fetal death with a lower incidence in the intervention group.

Perinatal morbidity

Low quality evidence from 3 RCTs (N=673 infants) showed no clinically important difference for incidence of RDS between the intervention and placebo groups.

Low quality evidence from 3 RCTs (N=669 infants) showed no clinically important difference for incidence of IVH (Grade 3-4) between the intervention and placebo groups.

Low quality evidence from 3 RCTs (N=672 infants) showed no clinically important difference for incidence of NEC between the intervention and placebo groups.

Arabin pessary

Comparison 4a: Pessary (Arabin) versus no pessary (control) in twins (unselected CL)

Outcomes for the woman:

Mortality

Low quality evidence from 1 RCT (N=795) showed no clinically important difference for incidence of maternal death between intervention and control groups.

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from 2 RCTs (N=929) showed no clinically important difference for mean GA at birth (weeks) between intervention and control groups.

Low quality evidence from 3 RCTs (N=2106) showed no clinically important difference for incidence of preterm birth before 28 weeks' gestation between intervention and control groups.

Moderate quality evidence from 2 RCTS (N=1972) showed no clinically important difference for incidence of preterm birth before 32 weeks' gestation between intervention and control groups.

Very low quality evidence from 2 RCTs (N=1311) showed no clinically important difference for incidence of preterm birth before 34 weeks' gestation between intervention and control groups.

High quality evidence from 2 RCTs (N=929) showed no clinically important difference for incidence of preterm birth before 37 weeks' gestation between intervention and control groups.

Perinatal mortality

Low quality evidence from one RCT (N=2354 infants) showed no clinically important difference for incidence of any perinatal death between intervention and control groups.

Low quality evidence from 3 RCTs (N=4210 infants) showed no clinically important difference for incidence of neonatal death between intervention and control groups.

Low quality evidence from one RCT (N=1590 infants) showed no clinically important difference for incidence of stillbirth between intervention and control groups.

Perinatal morbidity

Moderate quality evidence from 2 RCTs (N=2559) showed no clinically important difference for incidence of respiratory distress syndrome (RDS) between intervention and control groups.

Low quality evidence from 3 RCTs (N=4149) showed no clinically important difference for incidence of intraventricular haemorrhage (IVH grades 1-4) between intervention and control groups.

Low quality evidence from 3 RCTs (N=4149) showed no clinically important difference for incidence of nectrotising enteroolitis (NEC) between intervention and control groups.

Comparison 4b: Pessary (Arabin) versus no pessary (control) in twins (subgroup CL≤25 mm)

Outcomes for the baby:

Gestational age at birth

Low quality evidence from one RCT (N=134) showed a clinically important difference for mean gestational age at birth (weeks) with a mean difference of 2.2 weeks higher in the intervention group.

Low quality evidence from one RCT (N=134) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation between intervention and control groups.

Very low quality evidence from 2 RCTs (N=348) showed no clinically important difference for incidence of preterm birth before 34 weeks gestation between intervention and control groups.

Moderate quality evidence from one RCT (N=134) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

Perinatal mortality

Moderate quality evidence from one RCT (N=428 infants) showed no clinically important difference for incidence of any perinatal death between intervention and control groups.

Low quality evidence from one RCT (N=266) showed no clinically important difference for incidence of neonatal death between intervention and control groups.

Perinatal morbidity

Low quality evidence from one RCT (N=266) showed no clinically important difference for incidence of Respiratory Distress Syndrome (RDS) between intervention and control groups.

Low quality evidence from one RCT (N=266) showed no clinically important difference for incidence of intraventricular haemorrhage (IVH grades 1-4) between intervention and control groups.

Low quality evidence from one RCT (N=266) showed no clinically important difference for incidence of Necrotising Enterocolitis (NEC) between intervention and control groups.

Comparison 5: Pessary (Bioteque) versus no pessary (control) in twins (CL≤30mm)

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from one RCT (N=46) for mean gestational age at birth (weeks) showed a difference of 0.9 weeks (higher in intervention group), however it could not be assessed whether this was clinically important due to lack of variation data (SD or CI).

Very low quality evidence from one RCT (N=46) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation between intervention and control groups.

Very low quality evidence from one RCT (N=46) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation between intervention and control groups.

Very low quality evidence from one RCT (N=46) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

Perinatal mortality

Very low quality evidence from one RCT (N=92 infants) showed no clinically important difference for incidence of neonatal death between intervention and control groups

Perinatal morbidity

Very low quality evidence from one RCT (N=92 infants) showed no clinically important difference for Respiratory Distress Syndrome (RDS) between intervention and control groups.

Very low quality evidence from one RCT (N=92 infants) showed no clinically important difference for intraventricular haemorrhage (IVH) between intervention and control groups.

Very low quality evidence from one RCT (N=92 infants) showed no clinically important difference for Necrotising Enterocolitis (NEC) between intervention and control groups.

Bedrest

Comparison 6: Inpatient bedrest versus no bedrest/normal activity (control) in twins

Outcomes for the baby:

Gestational age at birth

High quality evidence from 2 RCTs (N=351) showed no clinically important difference for mean gestational age at birth (weeks) between intervention and control groups.

Low quality evidence from one RCT (N=139) showed no clinically important difference for incidence of preterm birth before 34 weeks gestation between intervention and control groups.

Very low quality evidence from 2 RCTs (N=351) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

Perinatal mortality

Moderate quality evidence from 2 RCTS (N=424 infants) showed no clinically important difference for incidence of any perinatal death between intervention and control groups.

Low quality evidence from 2 RCTS (N=702 infants) showed no clinically important difference for incidence of stillbirth between intervention and control groups.

Low quality evidence from 2 RCTs (N=702 infants) showed no clinically important difference for incidence of neonatal death between intervention and control groups.

Comparison 7a: Inpatient bedrest versus no bedrest/normal activity (control) in triplets (RCTs)

Outcomes for the baby:

Gestational age at birth

Low quality evidence from one RCT (N=19) showed no clinically important difference for mean gestational age at birth (Weeks) between intervention and control groups.

Low quality evidence from one RCT (N=19) showed no clinically important difference for incidence of preterm before 34 weeks gestation between intervention and control groups.

Moderate quality evidence from one RCT (N=19) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

Perinatal mortality

Moderate quality evidence from one RCT (N=57 infants) showed no clinically important difference for incidence of stillbirth between intervention and control groups.

Moderate quality evidence from one RCT (N=57 infants) death showed no clinically important difference for incidence of neonatal between intervention and control groups.

Comparison 7b: Inpatient bedrest versus no bedrest/normal activity (control) in triplets (cohort studies)

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from one cohort study (N=99) showed no clinically important difference for mean gestational age at birth (weeks) between intervention and control groups.

Perinatal mortality

Very low quality evidence from one cohort study (N=198 infants) showed no clinically important difference for incidence of perinatal death between intervention and control groups.

Perinatal morbidity

Very low quality evidence from one cohort study (N=198 infants) showed no clinically important difference for incidence of intraventricular haemorrhage (IVH grades 1-4) between intervention and control groups.

Very low quality evidence from one cohort study (N=198 infants) showed no clinically important difference for incidence of IVH (grades 3-4) between intervention and control groups.

Low quality evidence from one cohort study (N=198 infants) showed no clinically important difference for incidence of necrotising enterocolitis (NEC) between intervention and control groups.

Comparison 8: Inpatient bedrest versus home bedrest (control) in triplets (cohort studies)

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from one cohort study (N=79) showed a clinically important mean difference for mean gestational age at birth (weeks) of 3.8 weeks higher in the intervention group.

Perinatal mortality

Low quality evidence from one cohort study (N=237 infants) showed a clinically important difference for incidence of any perinatal death with fewer deaths in the intervention group.

Low quality evidence from one cohort study (N=237 infants) showed a clinically important difference for incidence of intrauterine death with fewer deaths in the intervention group compared to the control group.

Low quality evidence from one cohort study (N=212 infants) showed a clinically important difference for incidence of neonatal death with fewer deaths in the intervention group compared to the control group.

Perinatal morbidity

Very low quality evidence from one cohort study (N=212 infants) showed no clinically important difference for incidence of intraventricular haemorrhage (IVH) between intervention and control groups.

Cervical cerclage

Comparison 9a: Cerclage versus no cerclage (control) in twins (unselected CL)

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from one RCT (N=45) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

Perinatal mortality

Very low quality evidence from one RCT (N=90 infants) showed no clinically important difference for incidence of neonatal death between intervention and control groups.

Comparison 9b: Cerclage versus no cerclage (control) in twins (CL<25 mm) – IPD data

Outcomes for the baby:

Gestational age at birth

Moderate quality evidence from 3 RCTs (N=49) for mean gestational age at birth (weeks) showed a mean difference of 3.87 weeks in favour of the control group, though due to lack of variation data (SD and CI) it cannot be assessed whether this is clinically important.

Low quality evidence from 3 RCTs (N=49) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation between intervention and control groups.

Moderate quality evidence from 3 RCTs (N=49) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation between intervention and control groups.

Low quality evidence from 3 RCTs (N=49) showed no clinically important difference for incidence of preterm birth before 34 weeks between intervention and control groups.

Perinatal mortality

Moderate quality evidence from 3 RCTs (N=98 infants) showed no clinically important difference for perinatal mortality between intervention and control groups.

Perinatal morbidity

High quality evidence from 3 RCTs (N=98 infants) showed a clinically important difference for Respiratory Distress Syndrome (RDS) between groups with a higher incidence in the intervention group.

Low quality evidence from 3 RCTs (N=98 infants) showed no clinically important difference for intraventricular haemorrhage (IVH) between intervention and control groups.

Comparison 10a: Cerclage versus no cerclage (control) in triplets (unselected CL) – cohort studies

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from 5 cohort studies (N=3613) showed no clinically important difference for mean gestational age at birth (weeks) between intervention and control groups.

- Very low quality evidence from 4 cohort studies (N=335) showed no clinically important difference for mean gestational age at birth (weeks), with the intervention (cervical cerclage) performed before 18 weeks gestation, between intervention and control groups.
- Very low quality evidence from one cohort study (N=3278) showed no clinically important difference for mean gestational age at birth (weeks), with the intervention

(cervical cerclage) performed before 32 weeks (average 23 weeks) gestation, between intervention and control groups.

Very low quality evidence from one cohort study (N=141) for median gestational age at birth (weeks) showed lower age in cerclage groups compared to control group, though clinical significance could not be determined due to lack of variation data (SD or CI).

Very low quality evidence from 4 cohort studies (N=3660) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation between intervention and control group.

- Very low quality evidence from 3 cohort studies (N=382) showed a clinically important difference for incidence of preterm birth before 28 weeks gestation, with cervical cerclage performed before 18 weeks gestation, with a higher rate of preterm birth in the intervention compared to control groups.
- Very low quality evidence from one cohort study (N=3278) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation, with cervical cerclage performed before 32 weeks (average 23 weeks) gestation, between intervention and control groups.

Very low quality evidence from 4 cohort studies (N=3573) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation between intervention and control group.

- Very low quality evidence from 3 cohort studies (N=295) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation, with cervical cerclage performed before 18 weeks gestation, between intervention and control groups.
- Very low quality evidence from one cohort study (N=3278) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation, with cervical cerclage performed before 32 weeks (average 23 weeks) gestation, between intervention and control groups.

Very low quality evidence from one cohort study (N=146) showed a clinically important difference for incidence of preterm birth before 34 weeks gestation with a higher incidence of preterm birth in the intervention.

Low quality evidence from 2 cohort studies (N=180) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and control groups.

<u>Perinatal mortality</u>

Very low quality evidence from 3 cohort studies (N=10116 infants) showed no clinically important difference for incidence of any perinatal death between intervention and control groups.

- Very low quality evidence from 2 cohort studies (N=282 infants) showed no clinically important difference for incidence of any perinatal death, with cervical cerclage performed before 18 weeks gestation, between intervention and control groups.
- Very low quality evidence from one cohort study (N=9834 infants) showed no clinically important difference for incidence of any perinatal death, with cervical cerclage performed before 32 weeks (average 23 weeks) gestation, between intervention and control groups.

Very low quality evidence from one cohort study (N=423 infants) showed no clinically important difference for incidence of intrauterine death between intervention and control groups.

<u>Perinatal morbidity</u>

Very low quality evidence from one cohort study (N=177 infants) showed no clinically important difference for incidence of respiratory distress syndrome (RDS) between intervention and control groups.

Very low quality evidence from two cohort studies (N=600 infants) showed a clinically important difference for incidence of intraventricular haemorrhage (IVH) with a lower incidence in the intervention group.

- Very low quality evidence from one cohort study (N=177 infants) showed no clinically important difference for incidence of IVH (any grade) between intervention and control groups.
- Very low quality evidence from one cohort study (N=423 infants) showed no clinically important difference for incidence of IVH (Grades 3-4) between intervention and control groups.

Comparison 10b: Cerclage versus no cerclage (control) in triplets (CL≤25 mm) – cohort studies

Outcomes for the baby:

Gestational age at birth

Very low quality evidence from one cohort study (N=24, total 72 infants) for median gestational age at birth (weeks) showed a difference of 1.5 weeks higher in the intervention group, though clinical significance could not be determined due to lack of data on variation (SD or CI data).

Very low quality evidence from one cohort study (N=24) showed no clinically important difference for incidence of preterm birth before 28 weeks gestation between intervention and control groups.

Very low quality evidence from one cohort study (N=24) showed no clinically important difference for incidence of preterm birth before 32 weeks gestation between intervention and control groups.

Oral tocolytics

Comparison 11: Ritodrine (oral tocolytic) versus placebo in twins

Outcomes for the baby:

Gestational age at birth

Moderate quality evidence from one RCT (N=48) showed no clinically important difference for mean gestational age at birth (weeks) between intervention and placebo groups.

Moderate quality evidence from one RCT (N=48) showed no clinically important difference for incidence of preterm birth before 37 weeks gestation between intervention and placebo groups.

Perinatal mortality

Moderate quality evidence from one RCT (N=98 infants) showed no clinically important difference for incidence of perinatal mortality between intervention and placebo groups.

Sexual abstinence

No data available for this intervention.

Economic evidence

One cost effectiveness analysis undertaken in the Netherlands found no statistically significant differences in costs or poor perinatal outcomes in women when using a cervical pessary to prevent preterm birth in multiple pregnancy. The economic analysis is partially applicable to the NICE decision-making context, and is characterised by potentially serious limitations.

One cost effectiveness analysis undertaken in the Netherlands found there was a 94% probability that cervical pessary to prevent preterm birth in multiple pregnancy was cost saving in a subgroup of women with a cervical length of < 38 mm measured at a gestation of 16 to 22 weeks. The economic analysis is partially applicable to the NICE decision-making context, and is characterised by potentially serious limitations.

Evidence from the guideline economic analysis suggested that screening for spontaneous preterm birth using a cervical length threshold of 25 mm and daily vaginal progesterone for women whose pregnancies were identified as being at higher risk of spontaneous birth was cost effective compared to screening thresholds using a shorter cervical length and to no screening, with an incremental NMB of £952 and a 98.5% probability of being the most cost effective strategy. The economic analysis is directly applicable to the NICE decision-making context, and is characterised by minor limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal and perinatal mortality were prioritised as critical outcomes because these give the highest level of concern to the women and their families during the pregnancy. These outcomes, if they occur, are also associated with the long term psychological, physical, and financial impact on the woman and/or her family.

Gestational age at birth was chosen as a critical outcome because it is the single most significant and independent predictor of perinatal mortality and morbidity.

Woman's satisfaction was prioritised as an important outcome because it measures the effectiveness of the intervention from the woman's perspective.

Adverse events such as infection, haemorrhage, drug effects for example hypotension, anaphylaxis, and venous thromboembolism were prioritised as important outcomes because of the effect on the woman's health, recovery after giving birth, and ability to interact with the baby following the birth.

Perinatal morbidities such as birth injuries, respiratory distress syndrome, intraventricular haemorrhage, and necrotising enterocolitis were identified as important outcomes by the committee because although some of the above outcomes may be transient, they may go on to have a long-term impact on the child's health.

The quality of the evidence

The quality of the evidence for this review was assessed with GRADE. Risk of bias was assessed using the method stated in the protocol.

The committee agreed that where evidence was used from individual patient data meta-analyses, additional outcomes from the original paper were not sought because they were content that the number of outcomes reported in these studies were sufficient for decision making and they considered findings of them to be more robust than those of other types of meta-analysis.

Progesterone

The quality of the evidence for the outcomes reported in the included IPD examining twin pregnancies was rated as very low to high. When downgraded, this was due to imprecision and inconsistency. The quality of the evidence for the outcomes reported in the included IPD examining triplets was rated as very low to moderate. It was often downgraded due to imprecision and inconsistency.

The quality of the evidence from the included RCTs in twins was rated as very low to high. When downgraded, this was due to imprecision and indirectness (includes non-twin pregnancies; <5% triplets).

Arabin pessary

The quality of the evidence for the outcomes reported in the included SR was rated as very low to high. The quality of the evidence was downgraded due to imprecision and inconsistency.

The quality of the evidence from the included RCT was rated as very low. The quality of the evidence was downgraded due to imprecision and risk of bias (unclear in allocation concealment, attrition bias, reporting bias, high in performance bias – unable to blind participants and personnel).

Bedrest

The quality of the evidence for the outcomes reported in the included RCTs was rated as very low to high. The quality of the evidence was downgraded due to imprecision.

The quality of the evidence for the outcomes reported in the included cohort study was rated as very low to low. The quality of the evidence was downgraded due to imprecision (already low due to being an observational study).

Cervical cerclage

The quality of the evidence for the outcomes reported in the included RCT was rated as very low. The quality of the evidence was downgraded due to imprecision and risk of bias (unclear selection bias, and high performance bias).

The quality of the evidence for the outcomes reported in the included IPD was rated as low to high. The quality of the evidence was downgraded due to imprecision.

The quality of the evidence for the outcomes reported in the included cohort study was rated as very low to low. The quality of the evidence was downgraded due to imprecision, indirectness (includes one study where 10% of population had higher order pregnancies; quadruplets and quintuplets), and risk of bias (comparability at baseline) (already low due to being observational studies).

Oral tocolytics

The quality of the evidence for the outcomes reported in the included RCT was rated as low to moderate. The quality of the evidence was downgraded due to imprecision.

Benefits and harms

Intramuscular progesterone

The committee discussed the evidence for intramuscular progesterone in the prevention of spontaneous preterm birth, and agreed that it showed no clinical benefit, and in some

instances had negative or unpleasant side-effects, and decided to not recommend the use of intramuscular progesterone in the prevention of spontaneous preterm birth, in any group.

Intramuscular progesterone showed some clinical benefit in triplet pregnancies for perinatal mortality (neonatal death, fetal death). However, the evidence was rated as low quality, and due to the lack of information reported within the published source data (IPD analysis) to assess imprecision and inconsistency, the committee felt they could not make a recommendation to change routine practices to use intramuscular progesterone in all women with a triplet pregnancy.

Arabin Pessary, Bedrest, Cervical Cerclage, Oral Tocolytics

Although the committee noted that increased GA by a mean of 2.2 weeks was seen with the use of arabin pessary in women with a short cervix (<25 mm), they concluded that the evidence did not support routine use (low quality, small sample size, no evidence of clinical benefit in a number of outcomes) with no improvement in neonatal outcomes, and no reduction in preterm birth before 28 or 34 weeks' gestation. Bioteque pessary was grouped under the title Arabin pessary due to the clinical and physical similarity in design. Therefore the committee decided there was no evidence of a valuable clinical effect to support the use of Arabin (and Bioteque) pessary.

The committee discussed cervical cerclage in twin pregnancies in women, and in women with a cervical length < 25mm, utilising the findings of the IPD meta-analysis. They noted that there was no clinical benefit reported for any of the outcomes for the unselected population (any length cervix), and the only clinical benefit was noted for RDS, which was based on a very small sample of women with a short cervix.

The evidence for cervical cerclage in triplets (women with any cervical length) showed some clinical benefit for very preterm birth (before 28 weeks gestation), preterm birth less than 34 weeks, and IVH. However, the quality was very low and came from observational cohort studies, and so the committee did nto feel it was strong enough to make a recommendation to routinely use, but suggested triplet pregnancies were treated on a case by case basis. Women with a short cervix (less than 25mm) showed no clinical benefit from cervical cerclage, and again evidence was very low quality.

In the absence of convincing evidence for effectiveness the committee decided to retain the 2011 recommendation not to use Arabin pessary or cervical cerclage to prevent spontaneous preterm birth.

The committee discussed ongoing trials they were aware of examining the use of the Arabin pessary and targeted cervical cerclage as interventions for the prevention of spontaneous preterm birth in twins and triplets. They noted that the results of these trials may change recommendations following completion and publication of their findings.

The committee also discussed whether hospital bedrest for triplets was indicated. They noted that the evidence to support a reduction in perinatal loss, which appeared to occur without a reduction in preterm birth was of low quality. Additionally they discussed the potential for confounding effects within the cohort studies included in the evidence, as often hospital bedrest is advised when there are additional clinical/medical needs that are being addressed. The implication to NHS costs, and restriction to women with recommended bedrest would prove unpopular and could potentially increase the risk of maternal morbidity through an increase in thromboembolic risk and psychological stress. There was very little evidence regrading bedrest for twin pregnancies, of which there was no evidence of clinical benefit.

The committee agreed that the use of oral tocolytics for prevention of spontaneous preterm birth in twin and triplet pregnancies would not be recommended due to insufficient evidence for twin pregnancies (one study of 48 twin pregnancies showed evidence of no clinical

benefit for any of the listed outcomes available). There was no evidence assessing triplet pregnancies.

Ultimately, the committee retained the existing 2011 recommendation that arabin pessary, bed rest, cervical cerclage and oral tocolytics should not be used routinely to prevent spontaneous preterm birth because there was still no evidence to support their use.

Vaginal progesterone

Based on the evidence presented at the time, the committee agreed based on the evidence that administration of micronised vaginal progesterone could potentially decrease the risk of preterm birth in women with twin pregnancy with short cervical length ≤25 mm measured transvaginally by 18^{+0} to 20^{+6} weeks. This gestational window was a pragmatic decision taken by the committee to align the transvaginal cervical length scan with the mid trimester fetal anomaly scan. This could potentially reduce the risks of extreme prematurity.

Based on the experience and expertise of the committee, it was assessed that the side effects of administering daily micronised vaginal progesterone in this high risk subgroup (women with short cervix: CL ≤25 mm) were likely to be minimal. The committee agreed that the benefits of daily micronised vaginal progesterone (200-400 mg) used in women with twin pregnancy and short cervix (≤25 mm) outweighed the potential disadvantages.

The committee recognised that the evidence on the effectiveness of daily micronised vaginal progesterone came from selected populations of women, specifically with a twin pregnancy and a cervical length ≤25 mm.

Despite the evidence suggesting a potential benefit of using vaginal progesterone for subgroups of women with twin pregnancy and short cervix, the committee chose not to make a recommendation on the use of progesterone. They knew of emerging evidence related to progesterone in subgroups of women with a short cervix which may change the conclusion about its effectiveness. With uncertainty about the effectiveness of progesterone to prevent preterm birth, the committee preferred not to comment on cervical length screening (see also the related evidence review B1 screening for spontaneous preterm birth).

Research recommendations

Despite the limited evidence for some of the listed interventions in twins and triplets, the committee decided not to make a research recommendation because theu retained the 2011 recommendations (because there was no further evidence to the contrary). The committee agreed that some of these interventions were now outdated and decided that further research would not lead to a change in practice. They did not make a research recommendation for vaginal progesterone for triplets because further research is already in progress.

Cost effectiveness and resource use

An original model was developed for the guideline which jointly assessed the cost effectiveness of both screening to predict the risk of spontaneous preterm birth, undertaken by measurement of cervical length using transvaginal ultrasound, and intervention with micronised vaginal progesterone to delay or prevent preterm birth. The committee considered this analysis when making recommendations on screening to predict the risk of preterm and the use of vaginal interventions to prevent or delay spontaneous preterm birth.

The analysis demonstrated that it was cost effective to screen using a cervical length threshold of 25 mm when compared with other cervical length thresholds as it identified more pregnancies that would benefit from treatment without incurring any additional cost of identification when compared to lower cervical length thresholds. However, screening was only cost effective relative to no screening because the benefits of vaginal progesterone in

preventing spontaneous preterm birth were large relative to the combined costs of screening and intervention, especially in the context of “downstream” savings from reduced perinatal mortality and morbidity. The results of the economic analysis suggested that screening to predict the risk of spontaneous preterm birth using a cervical length threshold of 25 mm, measured by transvaginal ultrasound, and a daily dose of micronised vaginal progesterone for women whose pregnancies were identified as being at higher risk of preterm birth would represent a cost effective use of NHS resources. However, the committee was aware of new evidence that would be emerging on the use of progesterone that could alter their conclusions about its effectiveness. Given this uncertainty with respect to treatment effectiveness, the committee decided they could not change current practice and recommend vaginal progesterone to prevent preterm birth.

Whilst the committee noted there was economic evidence that suggested that cervical pessary could be cost effective to prevent preterm birth in multiple pregnancy in women with a cervical length less than 38 mm they noted that this was based on a small sample and that the clinical evidence was too weak to support the use of this pessary.

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1 Appendices

2 Appendix A – Review protocols

3 Review protocol – review question: What interventions are effective in preventing
4 spontaneous preterm birth in twin and triplet pregnancy?

5 **Table 8: Review protocol for interventions in preventing spontaneous preterm**
6 **birth**

Field (based on PRISMA-P)	Content
Review question	What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?
Type of review question	Intervention
Objective of the review	To assess the effectiveness in twin and triplet pregnancy of interventions in general use to prevent spontaneous preterm birth.
Eligibility criteria – population/disease/condition/issue/domain	All women confirmed as having a twin or triplet pregnancy by the 11 to 13-week ultrasound scan (not symptomatic, not in labour, membranes intact, not requiring imminent birth for maternal or fetal indications): 1. Twin pregnancy 2. Triplet pregnancy Setting: any setting

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**For twin and triplet pregnancy:**
	• Bed rest at home or in hospital during the antenatal period
	• Intramuscular or vaginal micronised progesterone
	• Arabin cervical pessary
	• Cervical cerclage
	• Oral tocolytics:
	  ○ beta mimetics
	  ○ ritodrine
	  ○ magnesium sulphate
	  ○ nifedipine
	• Sexual abstinence
	Studies examining combinations of eligible interventions will be included

Eligibility criteria – comparator(s)/control or reference (gold) standard	**For twin and triplet pregnancy:** • No intervention • Head-to-head comparisons of eligible interventions Pairwise analysis will be performed Studies examining within class comparisons will be excluded
Outcomes and prioritisation	**For twin and triplet pregnancy:** ***Critical outcomes*** For the woman: • Mortality For the baby: • Gestational age at birth • Perinatal mortality ***Important outcomes***:

Field (based on PRISMA-P)	Content
	For the woman: • Woman's satisfaction (validated scales) • Adverse events such as infection, haemorrhage, drug effects e.g. hypotension, anaphylaxis, venous thromboembolism For the baby: • perinatal morbidity (birth injuries, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis)
Eligibility criteria – study design	• Systematic reviews of randomised controlled trials (RCTs) for twin and triplet pregnancy • Individual RCTs • Cohort studies for triplets (prospective cohort studies will be prioritised over retrospective) Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions Conference abstracts will not be considered.
Other inclusion exclusion criteria	Exclusions: • Women with a quadruplet or higher-order pregnancy as per scope • Studies that do not report results specifically for twin and/or triplet pregnancies • Women with known structural and chromosomal anomalies • Studies that include <5 pregnancies • Studies in which interventions are given to women in labour or women requiring imminent birth • Studies examining preterm birth in entire populations of women with a complication (e.g. gestational diabetes or hypertension)
Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following population subgroups for which data will be reviewed and analysed separately if available: **1. For twin pregnancy:** • dichorionic diamniotic • monochorionic diamniotic • monochorionic monoamniotic • Cephalic, non-cephalic **2. For triplet pregnancy**: • trichorionic triamniotic • dichorionic triamniotic • dichorionic diamniotic • monochorionic triamniotic • monochorionic monoamniotic • Cephalic, non-cephalic 3. Gestational age for twin and triplet pregnancy (weeks): • <28 • 28 – <32 • 32 – <34 • 34 – 36/37

Field (based on PRISMA-P)	Content
	Important confounders: • Parity (for triplets)
Selection process – duplicate screening/selection/analysis	This review question was selected as a high priority for health economic analysis and so will be subject formal dual sifting of 10% of search results. Discrepancies will be discussed between reviewers with resolution of any disputes by discussion with the senior reviewer. Hard copies of retrieved papers will be read by 2 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
Data management (software)	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists. Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
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 • Limit year of publication to 2010 (date of previous guideline searches) Supplementary search techniques: No supplementary search techniques will be used.
Identify if an update	This is an update of a review performed in 2011. Question: What interventions are effective in preventing spontaneous preterm delivery in twin and triplet pregnancy? Chapter 8.2 of full guideline Recommendations: 1.5.2 Preventing preterm birth 1.5.2.1 Do not use the following interventions (alone or in combination) routinely to prevent spontaneous preterm birth in twin or triplet pregnancies: • bed rest at home or in hospital; • intramuscular or vaginal progesterone; • cervical cerclage; • oral tocolytics. RR13 What interventions are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?
Author contacts	Developer: National Guideline Alliance. https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.

Field (based on PRISMA-P)	Content
Search strategy – for one database	For details please see appendix F
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables)
Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • ROBIS for systematic reviews of Individual Patient Data • Cochrane risk of bias for RCTs • Newcastle-Ottawa scale for cohort studies For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
Methods for analysis – combining studies and exploring (in)consistency	A full description of this is provided in the methods in supplementary material C
Meta-bias assessment – publication bias, selective reporting bias	For details please see the methods chapter of the full guideline and section 6.2 of Developing NICE guidelines: the manual 2014 If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline
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. For details please see the methods chapter of the full guideline
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists

Field (based on PRISMA-P)	Content
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
PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; ROBIS: Risk of Bias in Systematic Reviews

Appendix B – Literature search strategies

Literature search for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Clinical Searches

Date of initial search: 22/03/2018

Database(s): Embase 1980 to 2018 Week 12, 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: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, 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 emez
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or dichorionic or monochorionic or trichorionic).tw.
5	or/1-4
6	bed rest/
7	(bed adj2 rest).tw.
8	progesterone/
9	gestagen/ use emez
10	(gestagen* or progesterone or progestagen* or progestin*).tw.
11	uterine cervix cerclage/ use emez or cerclage, cervical/ use ppez
12	((cervical or cervix) adj2 (cerclage or stitch*)).tw.
13	uterus spasmolytic agent/ use emez
14	tocolysis/ or tocolytic agents/ use ppez
15	(tocolysis or tocolytic*).tw.
16	exp beta adrenergic receptor stimulating agent/ use emez or exp adrenergic beta-agonists/ use ppez
17	(beta* adrenergic receptor agonist* or beta* adrenergic agonist* or beta* receptor agonist* or beta* agonist* or betamimetic* or beta mimetic*).tw.
18	ritodrine/
19	ritodrine.tw.
20	magnesium sulfate/
21	(magnesium adj (sulfate or sulphate)).tw.
22	nifedipine/

#	Searches
23	nifedipine.tw.
24	sexual abstinence/
25	(sex* adj2 (abstin* or abstain*)).tw.
26	pessary/ use ppez
27	vaginal pessary/ use emez
28	((cervical or cervix) adj2 pessar*).tw.
29	or/6-28
30	5 and 29
31	limit 30 to (english language and yr="2010-Current")
32	Letter/ use ppez
33	letter.pt. or letter/ use emez
34	note.pt.
35	editorial.pt.
36	Editorial/ use ppez
37	News/ use ppez
38	exp Historical Article/ use ppez
39	Anecdotes as Topic/ use ppez
40	Comment/ use ppez
41	Case Report/ use ppez
42	case report/ or case study/ use emez
43	(letter or comment*).ti.
44	or/32-43
45	randomized controlled trial/ use ppez
46	randomized controlled trial/ use emez
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	animals/ not humans/ use ppez
51	animal/ not human/ use emez
52	nonhuman/ use emez
53	exp Animals, Laboratory/ use ppez
54	exp Animal Experimentation/ use ppez
55	exp Animal Experiment/ use emez
56	exp Experimental Animal/ use emez
57	exp Models, Animal/ use ppez
58	animal model/ use emez
59	exp Rodentia/ use ppez
60	exp Rodent/ use emez
61	(rat or rats or mouse or mice).ti.
62	or/49-61

#	Searches
63	31 not 62
64	remove duplicates from 63

Date of initial search: 22/03/2018

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

Date of updated search: 06/09/2018

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) adj3 (birth* or pregnan* or gestation* or foetus* or foetal or fetus* or fetal)) .tw.
#3	(chorionicity or monochorionic* or dichorionic* or trichorionic*)
#4	{or #1-#3}
#5	MeSH descriptor: [Bed Rest] this term only
#6	(bed near/2 rest) .tw
#7	MeSH descriptor: [Progesterone] this term only
#8	MeSH descriptor: [Progestins] this term only
#9	(gestagen* or progesterone or progestagen* or progestin*) .tw.
#10	MeSH descriptor: [Cerclage, Cervical] this term only
#11	((cervical or cervix) adj2 (cerclage or stitch*)) .tw.
#12	MeSH descriptor: [Tocolysis] this term only
#13	MeSH descriptor: [Tocolytic Agents] this term only
#14	(tocolysis or tocolytic*) .tw.
#15	MeSH descriptor: [Adrenergic beta-Agonists] explode all trees
#16	(beta* adrenergic receptor agonist* or beta* adrenergic agonist* or beta* receptor agonist* or beta* agonist* or betamimetic* or beta mimetic*) .tw.
#17	MeSH descriptor: [Ritodrine] this term only
#18	ritodrine.tw
#19	MeSH descriptor: [Magnesium Sulfate] this term only
#20	(magnesium adj (sulfate or sulphate)) .tw.
#21	MeSH descriptor: [Nifedipine] this term only
#22	nifedipine.tw
#23	MeSH descriptor: [Sexual Abstinence] this term only
#24	(sex* adj2 (abstin* or abstain*)) .tw.
#25	MeSH descriptor: [Pessaries] this term only
#26	((cervical or cervix) adj2 pessar*) .tw.
#27	{or #5-#26}

ID	Search
#28	#4 and #27 Publication Year from 2010 to 2018

Health economics searches

Date of initial search: 22/03/2018

Database(s): Embase 1980 to 2018 Week 12, 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: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, 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 emez
3	((multiple* or twin* or triplet* or monozygotic or dizygotic or trizygotic) adj3 (birth* or pregnan* or gestation* or f?etus* or f?etal)).tw.
4	(chorionicity or dichorionic or monochorionic or trichorionic).tw.
5	or/1-4
6	bed rest/
7	(bed adj2 rest).tw.
8	progesterone/
9	gestagen/ use emez
10	(gestagen* or progesterone or progestagen* or progestin*).tw.
11	uterine cervix cerclage/ use emez or cerclage, cervical/ use ppez
12	((cervical or cervix) adj2 (cerclage or stitch*)).tw.
13	uterus spasmolytic agent/ use emez
14	tocolysis/ or tocolytic agents/ use ppez
15	(tocolysis or tocolytic*).tw.
16	exp beta adrenergic receptor stimulating agent/ use emez or exp adrenergic beta-agonists/ use ppez
17	(beta* adrenergic receptor agonist* or beta* adrenergic agonist* or beta* receptor agonist* or beta* agonist* or betamimetic* or beta mimetic*).tw.
18	ritodrine/
19	ritodrine.tw.
20	magnesium sulfate/
21	(magnesium adj (sulfate or sulphate)).tw.
22	nifedipine/

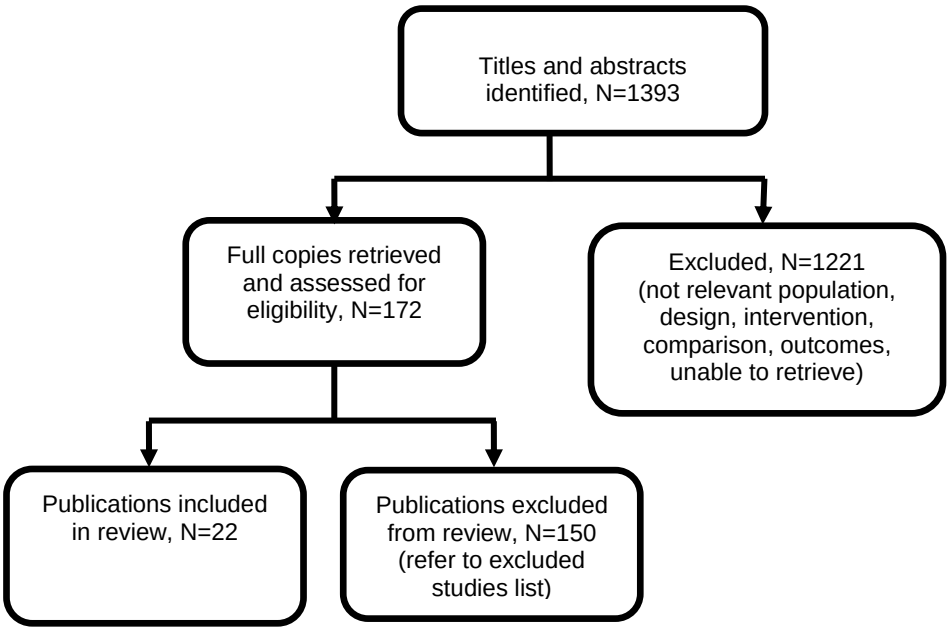
#	Searches
23	nifedipine.tw.
24	sexual abstinence/
25	(sex* adj2 (abstin* or abstain*)).tw.
26	pessary/ use ppez
27	vaginal pessary/ use emez
28	((cervical or cervix) adj2 pessar*).tw.
29	or/6-28
30	5 and 29
31	limit 30 to (english language and yr="2010-Current")
32	Letter/ use ppez
33	letter.pt. or letter/ use emez
34	note.pt.
35	editorial.pt.
36	Editorial/ use ppez
37	News/ use ppez
38	exp Historical Article/ use ppez
39	Anecdotes as Topic/ use ppez
40	Comment/ use ppez
41	Case Report/ use ppez
42	case report/ or case study/ use emez
43	(letter or comment*).ti.
44	or/32-43
45	randomized controlled trial/ use ppez
46	randomized controlled trial/ use emez
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	animals/ not humans/ use ppez
51	animal/ not human/ use emez
52	nonhuman/ use emez
53	exp Animals, Laboratory/ use ppez
54	exp Animal Experimentation/ use ppez
55	exp Animal Experiment/ use emez
56	exp Experimental Animal/ use emez
57	exp Models, Animal/ use ppez
58	animal model/ use emez
59	exp Rodentia/ use ppez
60	exp Rodent/ use emez
61	(rat or rats or mouse or mice).ti.
62	or/49-61

#	Searches
63	31 not 62
64	Economics/
65	Value of life/
66	exp "Costs and Cost Analysis"/
67	exp Economics, Hospital/
68	exp Economics, Medical/
69	Economics, Nursing/
70	Economics, Pharmaceutical/
71	exp "Fees and Charges"/
72	exp Budgets/
73	(or/64-72) use ppez
74	health economics/
75	exp economic evaluation/
76	exp health care cost/
77	exp fee/
78	budget/
79	funding/
80	(or/74-79) use emez
81	budget*.ti,ab.
82	cost*.ti.
83	(economic* or pharmaco?economic*).ti.
84	(price* or pricing*).ti,ab.
85	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
86	(financ* or fee or fees).ti,ab.
87	(value adj2 (money or monetary)).ti,ab.
88	or/81-87
89	73 or 80 or 88
90	63 and 89
91	remove duplicates from 90

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Figure 2: Flow diagram of clinical article selection for: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Adams, D. M., Sholl, J. S., Haney, E. I., Russell, T. L., Silver, R. K., Perinatal outcome associated with outpatient management of triplet pregnancy, American Journal of Obstetrics and Gynecology, 178, 843-847, 1998 **Ref Id** 742684 **Country/ies where the study was carried out** USA **Study type**	**Sample size** n=66 triplet pregnancies (outpatient bedrest [1993-1996] n=32 ; inpatient bedrest [1985-1993] n=34) **Characteristics** **mean±SD, n (%)** Maternal age: INPATIENT 31.3±4.7 years; OUTPATIENT 32.1±3.9 years prior PTB: n=0 in both groups, prior spontaneous abortion: INPATIENT n=8/34 (24%); OUTPATIENT n=14/32 (44%)	**Interventions** INPATIENT BEDREST: hospital admission (inpatient) for bedrest from 24 weeks gestation OUTPATIENT BEDREST/CONTROL: outpatient bedrest All other aspects the same between groups including: education, rest period advised, discontinuation of vaginal intercourse, ultrasound survey, serial scanning, weekly non-stress testing	**Details** • patient education regarding signs and symptoms of premature labour • lateral recumbent rest (4-6hours/day) beginning at 16 weeks gestation, increasing to 6-8 hours at 20 weeks, progressing to complete bedrest at 24 weeks gestation • discontinuation of vaginal intercourse at 20 weeks • detailed ultrasonographic survey of the fetal anatomy at 18-20 weeks gestation • weekly cervical examination from 22-24 weeks onwards • serial scanning to evaluate fetal growth	**Results** **mean±SD, n (%)** Gestational age at birth: INPATIENT BEDREST 33.5±2.8 weeks (range 26.3 - 37.4 weeks); OUTPATIENT BEDREST/CONTROL 32.5±2.8 weeks (range 26.0 - 36.1 weeks) Perinatal mortality: INPATIENT BEDREST n=1/102 (0.9%) infants; CONTROL n=1/96 (1%) infants Perinatal morbidity: • IVH 1-4: INPATIENT BEDREST n=1/102 (0.9%); CONT n=1/96 (1%)	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (inpatient bedrest)** *somewhat representative (one star)* 2. **Selection of the non-exposed cohort (outpatient bedrest/control)** *drawn from the same community as the exposed cohort (but different era) (one star)* 3. **Ascertainment of exposure** *by secure medical records (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (2/2)**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
retrospective cohort study **Aim of the study** To compare length of hospitalisation and perinatal outcomes of triplet pregnancies managed as outpatients or inpatients (3rd trimester bedrest), to determine anticipated savings in hospital days due to change in perinatal outcome. **Study dates** April 1993 - April 1996 (outpatient bedrest cohort) compared with cohort from Jan 1985 - March 1993 (routine hospitalisation/inpatient bedrest cohort)	**Inclusion criteria** All triplets receiving care from Division of Maternal-Fetal Medicine at Evanston Hospital between Jan 1985 and April 1996 **Exclusion criteria** Birth before 24 weeks gestation (as bedrest is implemented from this GA) Empiric cervical cerclage, prophylactic tocolysis, home uterine monitoring.		• and amniotic fluid volume during the third trimester • weekly non-stress testing beginning at 32 weeks gestation, or earlier if required.	• IVH 3-4: INPATIENT BEDREST n=0/102; CONT n=1/96 (1%) • NEC: INPATIENT BEDREST n=0/102; CONT n=0/96	1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *cohorts are comparable based on : age, nulliparity, prior PTB, prior spontaneous abortion, fertility therapy, incidence of pregestational diabetes or chronic hypertension (two stars)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - until discharge from hospital postnatally (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up, all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding not reported					
Full citation Berghella, V, Dugoff, L, Ludmir, J, Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial, Ultrasound in Obstetrics & Gynecology, 49, 567-572, 2017 **Ref Id** 809506 **Country/ies where the study was carried out** USA **Study type**	**Sample size** N=421 twin pregnancies screened; N=85 had TVS-CL≤30mm (transvaginal sonography - cervical length) only N=46 agreed to randomisation (PESSARY N=23; CONTROL/no pessary N=23) **Characteristics** **Median (IQR) or n (%) PESSARY N=23; CONTROL N=23** Maternal age: PESSARY 27.0 (23.4-33.0) years; CONTROL 32.9 (26.2-36.8) years	**Interventions** BIOTEQUE PESSARY (similar to Arabin pessary - image appears almost identical)	**Details** Pessary routinely removed in 36th week of gestation, or before this due to: patient request, preterm prelabour rupture of membranes (PPROM), labour, and vaginal bleeding. Randomised centrally using random blocks of two, four, and six women. Stratified by gestational age (18+0 to 23+6 weeks, 24+0 to 27+6 weeks); study site, chorionicity (mono versus dichorionic). No other treatment was recommended. Size of pessary determined by pelvic examination. **Sample size** Based on reduction in rate of PTB<34weeks from 40% to 20%. With 80% power to detect 5% significance,	**Results** **Median (IQR), n (%)** Gestational age at birth: PESSARY 35.9 (28.9-36.9) weeks, CONTROL 35.0 (33.0-36.7) • GA<28 weeks: PESSARY n=4/23 (17%); CONTROL n=4/23 (17%); RR=1.0[0.28-3.52] • PTB<34weeks PESSARY n=9/23 (39%); CONTROL n=8/23 (35%); RR=1.13[0.53-2.40] • PTB<37weeks: PESSARY n=19/23 (83%);	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** • **Random sequence generation** *random number generator with random block sizes of 2, 4, or 6, consenting participants were randomly allocated to pessary or placebo. Randomisation was stratified: gestational age, study site, chorionicity (LOW)* • **Allocation concealment** *Not reported (**UNCLEAR**)* **Performance bias - blinding of participants and personnel:** *unable to blind participants and personnel (**HIGH**)* **Detection bias - Blinding of outcome assessment:** *Not possible to affect outcomes (LOW)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** Evaluate whether cervical pessary (Bioteque) prevent preterm birth in twin gestation with short cervix (≤30mm at mid-trimester transvaginal sonography scan - before 28 weeks) **Study dates** 2nd April 2014 - 30th June 2016 **Source of funding** Not reported	GA at randomisation: PESSARY 21.0 (20.1-24.2) weeks; CONTROL 21.2 (20.1-24.3) weeks CL at randomisation: PESSARY 16.7 (10.7-27.8) mm; CONTROL 22.9 (15.9-25.6) mm Nulliparous: PESSARY n=11/23 (48%); CONTROL n=15/23 (65%) Prior PTB<37wks: PESSARY n=0; CONTROL n=3/23 (13%) **Inclusion criteria** Asymptomatic women, age 18-50 years with dichorionic or monochorionic twin gestation Transvaginally measured cervical length ≤30mm before 28+0 weeks gestation		required n=164. Recruitment stopped before this at advice of Data and Safety Monitoring Committee due to trouble recruiting (overlap with another study at 2 sites).	CONTROL n=19/23 (83%); RR=1.0[0.76-1.30] Perinatal mortality: neonatal death: PESSARY n=4/46 infants (9%); CONTROL n=3/46 infants (7%); RR=1.33[0.32-5.63] Perinatal morbidity: • RDS: PESSARY n=11/46 infants (24%); CONTROL n=8/46 infants (17%); RR=1.38[0.61-3.10] • IVH: PESSARY n=2/46 infants (24%); CONTROL n=1/46 infants (2%); RR=2.0[0.19-21.3] • NEC: PESSARY n=1/46 infants (2%); CONTROL	**Attrition bias - Incomplete outcome data:** *Not reported - appears to be intention to treat (**UNCLEAR**)* **Reporting bias - Selective reporting:** *Not reported - appears to report all outcomes and participants (**UNCLEAR**)* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Monoamniotic twins • Single, triplet, or higher • twin-twin transfusion syndrome • early selective intrauterine growth restriction (IUGR) • ruptured membranes • lethal fetal structural anomaly • fetal chromosomal abnormality • present or planned cerclage • vaginal bleeding • suspicion of chorioamnionitis • ballooning of membranes outside the cervix into the vagina • TVS-CL of 0mm			n=0/46 infants (0%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• painful regular uterine contractions • placenta previa				
Full citation Bernasko,J., Lee,R., Pagano,M., Kohn,N., Is routine prophylactic cervical cerclage associated with significant prolongation of triplet gestation?, Journal of Maternal-Fetal and Neonatal Medicine, 19, 575-578, 2006 **Ref Id** 222466 **Country/ies where the study was carried out** USA **Study type**	**Sample size** Cerclage n=55, no cerclage n=40 **Characteristics** Maternal age: CERCLAGE 33.6±3.7 years; CONTROL 33.85±3.3 years Nulliparous: CERCLAGE n=38/55 (69.1%); CONTROL n=27/40 (67.5%) History of cervical insufficiency: CERCLAGE n=1/55 (1.8%); CONTROL n=0 History of PTB or PPROM in previous pregnancy:	**Interventions** CERCLAGE: McDonald type suture performed under regional anaesthesia Non cerclage group/CONTROL: no cerclage, or underwent cerclage only after cervical change was detected by ultrasound	**Details** CONTROL group: n=13 women met criteria for emergency cerclage, and elected to have procedure **Statistical power -** Based on the sample sizes of the two groups, and the observed standard deviations, the study had 80% power to detect an effect size of 0.6 (approximately 1.4 weeks gestational age at birth). Average gestational age for emergency cerclage (part of CONTROL group): 17 weeks Emergency cerclage women (within CONTROL group) delivered ~2 weeks earlier than those who either did not require emergency cerclage (CONTROL group) or had planned cerclage	**Results** Gestational age at birth: CERCLAGE 33.6±2.4 weeks; CONTROL 33.7±2.3 weeks • GA<28 weeks: CERCLAGE n=1/55 (1.8%); CONTROL n=0/40 • GA 28-<32 weeks: PTB<32wks CERCLAGE n=11/55 (20%); CONTROL n=9/40 (22.5%)	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (planned cerclage)** *Truly representative (one star)* 2. **Selection of the non-exposed cohort (no or emergency cerclage/control)** *Drawn from same community as exposed cohort (one star)* 3. **Ascertainment of exposure** *Secure records (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *Yes (one star)* **COMPARABILITY (2/2)** 1. **Comparability of cohorts on the basis of the design or**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Retrospective cohort **Aim of the study** Determine if routine prophylactic cervical cerclage is associated with prolonging triplet pregnancy **Study dates** July 1999 - Dec 2003 **Source of funding** Not reported	CERCLAGE n=2/55; CONTROL n=0 **Inclusion criteria** Triplet pregnancy beyond 13 weeks gestational age **Exclusion criteria** None reported		(CERCLAGE group) (not statistically significant).		**analysis controlled for confounders** *states no difference in maternal age, nulliparity, history of or current STDs, history of cervical insufficiency. Analysed as intention to treat (emergency cerclage in CONTROL group) (two stars)* **OUTCOME (3/3)** 1. **Assessment of outcome** *Record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *Yes - until hospital discharge after birth (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up - all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Combs, C. A., Schuit, E., Caritis, S. N., Lim, A. C., Garite, T. J., Maurel, K., Rouse, D., Thom, E., Tita, A. T., Mol, B., Global Obstetrics Network, collaboration, 17-Hydroxyprogesterone caproate in triplet pregnancy: an individual patient data meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 123, 682-90, 2016 **Ref Id** 660254 **Country/ies where the study was carried out** USA, Netherlands, Australia	**Sample size** n=232 pregnancies (696 infants) PROGESTERONE n=136; PLACEBO n=96 **Characteristics** PROG n=136; PLA n=96 **mean±SD, n (%)** Maternal age: PROG 32.0±5.4 years; PLA 32.0±5.0 years Nulliparous: PROG n=76 (56%); PLA n=49 (51%) GA at randomisation: PROG 19.1±2.0 weeks; PLA 19.1±1.9 weeks Trichorionic: PROG n=112 (85%); PLA n=76 (89%) Dichorionic: PROG n=12 (9%); PLA n=9 (11%) Monochorionic: PROG n=7 (5%); PLA n=0	**Interventions** intramuscular progesterone (17-hydroxyprogesterone caproate (17OHPc)) 250mg weekly initiated at: range 15-24weeks (all studies 16-19weeks GA) median (IQR) time from randomisation to birth: PROG 97 (79-109) days; PLA 95 (78-106) days; HR=0.96[0.72-1.3, p=0.78]	**Details** Followed IPD protocol of Schuit 2015 (progesterone use in twins) • Caritis 2009 (NICHD-MFMU trial) • Combs 2010 (Obstetrix trial) • Lim 2011 (AMPHIA trial)	**Results** **PROG n=136; PLA n=96 pregnancies** PTB<34weeks: PROG n=86/136 (63%); PLA n=64/96 (67%), I2=4%; RR=0.95[0.78-1.2] PTB<32weeks: PROG n=48/136 (35%); PLA n=36/96 (38%), I2=63%; RR=0.92[0.55-1.56] PTB<28weeks: PROG n=15/136 (11%); PLA n=12/96 (12%), I2=0%; RR=0.88[0.43-1.8] **Perinatal outcomes: PROG n=408, PLA n=288 infants** Perinatal death: PROG n=25/408 (6.1%), PLA 14/288 (4.9%), I2=72%, RR=1.3[0.37-4.2] • Fetal death (≥20 weeks): PROG n=3 (0.7%), PLA n=6 (2.1%)	**Limitations** Systematic reviews using IPD are assessed using ROBIS criteria **Domain 1: Concerns regarding specification of study eligibility: LOW** Reason for concern: no concerns - reason for exclusion of one study given and valid **Domain 2: Concerns regarding methods used to identify and/or select studies: LOW** Reason for concern: no concerns **Domain 3: Concerns regarding methods used to collect data and appraise studies: LOW** Reason for concern: no concerns **Domain 4: Concerns regarding the synthesis and findings: LOW** Reason for concern: no concerns **RISK OF BIAS IN THE REVIEW** A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? yes B. Was the relevance of identified studies to the review's research question appropriately considered? yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? yes **Risk of bias in the review: LOW**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Systematic Review with meta-analysis of Individual Patient Data (IPD) **Aim of the study** To determine whether the outcome of triplet pregnancy is affected by prophylactic administration of 17-hydroxyprogesterone caproate (17OHPc) **Study dates** Literature search to November 2014 **Source of funding** No funding	**Inclusion criteria** RCTs including women with triplet pregnancies randomly allocated to treatment with progestogens (including micronised progesterone and 17OHPc) versus control in the second or third trimester with the intention of preventing preterm birth **Exclusion criteria** Excluded when: • investigator(s) decline to provide data; • more than 10% attrition or exclusion of women after randomisation;			• Neonatal death (≥20 weeks): PROG n=19 (4.7%), PLA n=4 (1.3%) Perinatal morbidity: • RDS: PROG 115/395 (29%); PLA 83/278 (30%), I2=44%, RR=0.99[0.65-1.5] • IVH3-4: PROG 6/391 (1.5%), PLA 7/278 (2.5%), I2=0%, RR=0.37[0.089-1.5] • NEC 2-3: PROG 10/394 (3.1%), PLA 8/278 (2.9%), I2=23%, RR=0.94[0.31-2.8]	Quality assessment by Review authors (NGA have not returned to primary studies to re-assess ROB) Individual studies included used Cochrane ROB table: Caritis 2009 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *NONE* Combs 2010 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• incomplete reporting of reasons for withdrawals and protocol violations; • imbalance in drop-outs across groups; • incomplete reporting of all the study's pre-specified outcomes; • outcomes of interest not made available for analysis Authors decided to exclude the only trial using vaginal progesterone (Wood 2012) instead of intramuscular, as only the trial had only 3 triplet pregnancies that could have been included.				**Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *NONE* Lim 2011 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *NONE* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Crowther,C.A., Neilson,J.P., Verkuyl,D.A., Bannerman,C., Ashurst,H.M., Preterm labour in twin pregnancies: can it be prevented by hospital admission?, British Journal of Obstetrics and Gynaecology, 96, 850-853, 1989 **Ref Id** 246765 **Country/ies where the study was carried out** Zimbabwe **Study type** RCT **Aim of the study** Examine whether bedrest in hospital	**Sample size** n=139 twin pregnancies (n=70 hospitalised (BEDREST) group, n=69 control group); n=278 infants (BEDREST n=140; CONT n=138) all analysed as intention to treat **Characteristics** **Mean±SD or n (%)** maternal age: BEDREST 27.1±5.9 years; control 27.0±5.7 years GA at study entry: BEDREST 33.3±1.8 weeks; control 33.5±1.8 weeks previous PTB: BEDREST 12/70 (17%; control 11/69 (16%) **Inclusion criteria**	**Interventions** BEDREST in hospital	**Details** **<u>Power calculation:</u>** It was estimated that a trial size of 44 would have an 80% chance (beta error 0-20) of detecting a statistically significant difference at the 5% level (alpha error 0.05) if the preterm birth rate was reduced from 80% to 40%. But no data in high risk group - lead to decision to recruit as many women as possible.	**Results** **Mean±SD or n (%)** Gestational age at birth: BEDREST 35.8±1.9 weeks; CONT 35.8±1.9 weeks • GA 32-<34 weeks: PTB<34 weeks: BEDREST 11/70 (15.7%); CONT 12/69 (17.4%) • GA 34-<36/37 weeks: PTB<37 weeks: BEDREST 51/70(72.9%); CONT 55/69 (79.7%) Perinatal mortality: • stillbirths: BEDREST 1/140; CONT 1/138 • neonatal death: BEDREST	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** *LOW* • **Random sequence generation** *Used block randomisation - series of consecutively numbered opaque enveloped, and woman allocated according to enclosed instructions (LOW)* • **Allocation concealment** *Researchers involved in randomisation were not involved in allocation to treatment (LOW)* **Performance bias - blinding of participants and personnel:** *Not possible to blind participants (HIGH)* **Detection bias - Blinding of outcome assessment:** *All newborn infants were examined by a paediatrician who was unaware to which group the mother had been allocated (LOW)* **Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(for women with specific cervical findings that put them at high risk of preterm birth) improves twin pregnancy outcome **Study dates** "from 1984" **Source of funding** University of Zimbabwe and the Sims Black Trust	high risk twin pregnancies determined by cervical measurements: cervical score was calculated by cervical length (cm) minus cervical dilatation. Score of ≤-2 (i.e. -2, -3, -4, ..) measured at GA≤34weeks **Exclusion criteria** • labour at study entry • use of tocolytic drugs			1/140; CONT 1/138	*compliance with treatment. Compliance reported as high (n=2/70 in BEDREST did not report to ward) for both groups (LOW)* **Reporting bias - Selective reporting:** *(UNCLEAR)* **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Crowther, C. A., Verkuyl, D. A., Ashworth, M. F., Bannerman, C., Ashurst, H. M., The effects of hospitalization for bed rest on duration	n=19 triplet pregnancies (Inpatient BEDREST n=10; outpatient management/CONT n=9) All analysed as intention to treat	INPATIENT HOSPITALISED BEDREST: women asked to come into antenatal ward as soon after recruitment as possible. All were encourage to rest in bed,	**<u>Power calculation:</u>** No estimation of study size was used. Sample expected to be small due to low incidence of triplets, but aimed to recruit as many women as possible in study period.	Gestational age at birth: BEDREST: 34.4±2.2 weeks; CONTROL 33.7±2.5 weeks	**Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** • **Random sequence generation** *Block randomisation was used ...*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of gestation, fetal growth and neonatal morbidity in triplet pregnancy, Acta Genet Med Gemellol (Roma), 40, 63-8, 1991 **Ref Id** 867286 **Country/ies where the study was carried out** Zimbabwe **Study type** RCT **Aim of the study** To compare routine hospitalisation for bed rest with conventional outpatient management in triplet pregnancy	**Characteristics** **Mean±SD or n (%)** Maternal age: BEDREST 25.2±5.5 years; CONT 29.3±7.4 years previous PTB: BEDREST n=0/10; CONT n=1/9 GA at study entry: BEDREST 29.0±4.7 weeks; CONT 29.4±3.0 weeks **Inclusion criteria** Women with confirmed triplet pregnancy from 24 weeks gestation onwards attending multiple pregnancy clinic at Harare Maternity Hospital. **Exclusion criteria**	ambulation was allowed. Women had a normal hospital diet and antenatal assessments were weekly OUTPATIENT ROUTINE CARE/control: encourage to continue normal activity at home, and seen weekly in the antenatal clinic. Admitted to hospital if complications arose such as preterm labour, hypertension, or preterm rupture of membranes	**<u>Hospital admission and length of stay</u>** BEDREST group: all were admitted and none required absence from hospital (100% compliance). Mean antenatal stay: 38.3±29.3 days. CONTROL group: n=6/9 required admission to hospital due to complications. Mean GA at admission: 32.9±2.6 weeks (~4 weeks later than INPATIENT BEDREST group). Mean antenatal stay: 7±8.5 days	• GA 32-<34 weeks: PTB<34 weeks: BEDREST n=3/10; CONT n=4/9; OR=0.56 [0.09-3.42] • GA 34-<36/37 weeks: PTB<37 weeks BEDREST n=8/10; CONT n=9/9; OR=0.13 [0.01-2.33] Perinatal mortality: • stillbirths: BEDREST n=1/30 infants; CONT n=0/27 infants; OR=0.31 [0.04-2.33] • early neonatal death: BEDREST n=0/30 infants; CONT n=3/27 infants; OR=0.11 [0.01-1.13]	*consecutively numbered, opaque, sealed envelopes, and woman allocated according to the enclosed instructions (LOW)* • **Allocation concealment** *Researchers involved in treatment allocation were not involved in preparing the randomisation schedule (LOW)* **Performance bias - blinding of participants and personnel:** *Unable to participants to allocation (HIGH)* **Detection bias - Blinding of outcome assessment:** *All newborn infants were examined by a paediatrician who was unaware to which group the mother had been allocated (LOW)* **Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of compliance with treatment. Compliance reported for both groups (LOW)* **Reporting bias - Selective reporting:** *UNCLEAR*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1984-1986 **Source of funding** University of Zimbabwe and the Sims Black Trust	• women with uncertain gestational age • cervical suture • hypertension • caesarean section scar • antepartum haemorrhage				**Other information**
Full citation Dor,J., Shalev,J., Mashiach,S., Blankstein,J., Serr,D.M., Elective cervical suture of twin pregnancies diagnosed ultrasonically in the first trimester following induced ovulation, Gynecologic and Obstetric Investigation, 13, 55-60, 1982 **Ref Id** 222590	**Sample size** n=50 randomised (n=25 offered suture/cerclage) n=45 analysed (CERCLAGE n=22, CONT n=23) **Characteristics** Maternal (mean) age: CERCLAGE 28.1 years; CONT 30.4 years **Inclusion criteria** Infertile women who had confirmed twin	**Interventions** CERCLAGE: at 13 weeks gestation, McDonald suture using double silk stitches, removed after: 37th week, inevitable abortion, premature contractions, or premature rupture of membranes	**Details** Sutures (cerclage) made at 13 weeks gestational age. In the sutured group. 3 women (12%) aborted in the 14th, 16th, and 17th gestational week, while in the non-sutured group 2 of 25 women (8%) aborted in the 15th and 16th week.	**Results** Gestational age at birth: GA 34-<36/37 weeks: PTB<37wks CERCLAGE n=10/22 (45.4%), CONT n=11/23 (47.8%) Perinatal mortality: neonatal death: CERCLAGE n=8/44 infants (18.2%); CONT n=7/46 infants (15.2%)	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** *UNCLEAR* • **Random sequence generation** *not reported (UNCLEAR)* • **Allocation concealment** *Not reported (UNCLEAR)* **Performance bias - blinding of participants and personnel:** *not possible (HIGH)* **Detection bias - Blinding of outcome assessment:** *Independent study nurse extracted data from hospital records (LOW)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Israel **Study type** RCT **Aim of the study** Examine cervical suture versus non suture in first trimester twin gestation **Study dates** Not reported **Source of funding** Not reported	gestation (ultrasound 6-10weeks) from induced ovulation "two or more gestational sacs with fetal tissue and heart beats in each sac" **Exclusion criteria**				**Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of compliance with treatment. Compliance reported for both groups (LOW)* **Reporting bias - Selective reporting:** *UNCLEAR* **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Elimian,A., Figueroa,R.,	n= 59 (n=20/59 cerclage)	Prophylactic cerclage at 14.1±0.9 weeks	Uniform/standard guideline for management/care of	CERCLAGE n=20 (60 infants);	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nigam,S., Verma,U., Tejani,N., Kirshenbaum,N., Perinatal outcome of triplet gestation: does prophylactic cerclage make a difference?, Journal of Maternal-Fetal Medicine, 8, 119-122, 1999 **Ref Id** 153174 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** To compare perinatal outcomes of triplet pregnancies with and without	**Characteristics** Maternal age: CERCLAGE 31.1±3.3 years, CONTROL 30.7±5.2 years Nulliparous: CERCLAGE n=13/20 (65%); CONTROL n=26/39 (66.7%) **Inclusion criteria** • women with triplet pregnancy • initiated prenatal care before 15 weeks gestation • no sign of previous or current cervical insufficiency **Exclusion criteria** None reported	gestation (McDonald cerclage)	triplet pregnancies, except for use of cerclage or not. Emphasis on bedrest at home in the recumbent position. Hospitalisation only used for maternal, obstetric, or medical conditions or fetal indications	CONTROL n=39 (117 infants) Gestational age at birth: CERCLAGE 32.8± 2.4 weeks; CONTROL 31.5±3.6 weeks • PTB 31-37wks: CERCLAGE n=18/20 (90%); CONTROL n=24/39 (62%) • GA 32-<34 weeks: PTB 32-37wks CERCLAGE n=16/20 (80%); CONTROL n=21/39 (54%) • No births GA>37wks • PTB<32weeks: CERCLAGE n=4/20; CONTROL n=18/39 Perinatal mortality: CERCLAGE n=0/60; CONTROL n=5/117 (4%) Perinatal morbidity:	Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (cerclage)** *truly representative (one star)* 2. **Selection of the non-exposed cohort (no cerclage/control)** *drawn from the same community as the exposed cohort (one star)* 3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (1/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *Reported as no differences between groups in maternal age, parity, preterm labour rate, comorbidities. However possible self-selection of*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prophylactic cerclage **Study dates** January 1988 - June 1997 **Source of funding** Not reported				• RDS: CERCLAGE n=11/60 infants (18%); CONTROL n=32/117 (27%) • IVH: CERCLAGE n=6/60 infants; CONTROL n=19/117 infants	*cerclage/no cerclage may have biased sample (one star)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - until hospital discharge (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up of cohorts - all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**
Full citation Jarde, A., Lutsiv, O., Park, C. K., Barrett, J., Beyene, J., Saito, S., Dodd, J. M., Shah, P. S., Cook, J. L., Biringer, A. B.,	**Sample size** Across all interventions (cerclage, pessary, progesterone): 23 RCTs including 6626 twin pregnancies	**Interventions** • vaginal/local progesterone • intramuscular/systemic progesterone • cervical pessary	**Details** Included 16 RCTs of TWINS ONLY assessing vaginal progesterone (vPROG) and mPROG (analysed separately) compared to	**Results** **<u>PROGESTERONE -</u>** Only reporting single outcome for vPROG and mPROG as remaining outcomes from	**Limitations** Systematic reviews are assessed using AMSTAR2 (Shea et al 2017) criteria (12/16) 1. **Did the research questions and inclusion criteria for the**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Giglia, L., Han, Z., Staub, K., Mundle, W., Vera, C., Sabatino, L., Liyanage, S. K., McDonald, S. D., Preterm birth prevention in twin pregnancies with progesterone, pessary, or cerclage: a systematic review and meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 124, 1163-1173, 2017 **Ref Id** 660272 **Country/ies where the study was carried out** Canada **Study type** Systematic Review with meta-analysis	**Characteristics** randomisation at 16-29wks gestation • 4 studies of 17OHPC assessed short cervix • 3 studies of pessary, with subgroup analysis for CL≤25 mm **Inclusion criteria** Women with twin pregnancy randomised to intervention versus placebo/no intervention, one intervention versus another intervention, or combination. **Exclusion criteria**	• cerclage (MacDonald-type)	placebo/no treatment in meta-analysis: • Aboulghar 2012 • Awwad 2015 • Brizot 2015 • Briery 2009 • Cetingoz 2011 • Combs 2011 • El-rafaie 2016 • Fonseca 2007 • Hartikainen-Sorru 1980 • AMPHIA trial (Lim 2011) • STOPPIT trial (Norman 2009) • PREDICT trial (Rode 2011) • Rouse 2007 • Senat 2013 • Serra 2013 • Wood 2012 included 3 RCTs of TWINS ONLY assessing Arabin pessary in meta-analysis: • Liem 2013 • Goya 2015 • Nicolaides 2016	included RCTs have been reported in Romero 2017 (vPROG) and Schuit 2015 (mPROG) - both higher quality SR due to use of individual patient data **VAGINAL PROGESTERONE (vPROG) -** Maternal mortality: N=1, n=0 cases (reported by Norman 2009/STOPPIT, so reported in primary analysis) **INTRAMUSCULAR PROGESTERONE (mPROG) -** Maternal mortality: N=0 (no included studies report maternal mortality for mPROG) **<u>ARABIN PESSARY</u>** ***Pooled data from 3 studies (pessary v control/no pessary: N=number of studies, n=number of participants)***	**review include the components of PICO?** yes 2. **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** Yes 3. **Did the review authors explain their selection of the study designs for inclusion in the review?** Yes 4. **Did the review authors use a comprehensive literature search strategy?** Yes 5. **Did the review authors perform study selection in duplicate?** Yes 6. **Did the review authors perform data extraction in duplicate?** Yes 7. **Did the review authors provide a list of excluded studies and justify the exclusions?** No 8. **Did the review authors describe the included studies in adequate detail?** No 9. **Did the review authors use a satisfactory technique for**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Assess evidence for the effectiveness of progesterone, cerclage, and pessary in twin pregnancies. **Study dates** Literature search until 25 January 2016 **Source of funding** Canadian Institutes of Health Research (CIHR) Knowledge Synthesis Grant (RN281576-362279)	• non-RCTs • cluster-randomised trials • non-peer reviewed literature • studies published as abstracts • studies assessing prevention of preterm birth where contractions had started (e.g. use of tocolytics)		Included 4 RCTs of TWIN ONLY assessing cerclage in meta-analysis: • Dor 1982 • NacNaughton 1993 - excluded at study level • Rust 2001 - excluded at study level • Bergehella 2004 - excluded at study level	Maternal mortality: N=1, n=795, RR=3.05[0.12-74.72] Gestational age at birth (weeks): N=2, n=929, I2=88%, MD=1.17[-0.68 to 3.03] • PTB<28weeks N=3, n=2106, I2=30%, RR=0.84[0.49-1.44] • PTB<32weeks N=2, n=1972, I2=0%, RR=0.91[0.69-1.19] • PTB<34weeks N=2, n=1311, I2=87%, RR=0.71[0.29-1.71] • PTB<37weeks N=2, n=929, I2=0%, RR=0.96[0.86-1.07] Perinatal mortality:	**assessing the risk of bias (RoB) in individual studies that were included in the review?** Yes 10. **Did the review authors report on the sources of funding for the studies included in the review?** No 11. **If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?** Yes 12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** Yes 13. **Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** Yes 14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** No 15. **If they performed quantitative synthesis did**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				• Any perinatal death: N=1, n=2354, RR=0.91[0.55-1.49] • Neonatal death: N=3, n=4210, I2=2%, RR=0.89[0.57-1.38] • Stillbirth: N=1, n=1590, RR=0.70[0.30-1.64] Perinatal morbidity: • RDS: N=2, n=2559, I2=0%, RR=1.08[0.84-1.39] • IVH (1-4): N=3, n=4149, I2=21%, RR=0.99[0.49-2.00] • NEC: N=3, n=4149, I2=0%, RR=1.05[0.51-2.16]	**the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** yes 16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** yes **ARABIN PESSARY** Quality assessment by Review authors (NGA have not returned to primary studies to re-assess ROB) Individual studies included used Cochrane ROB table: Goya 2016 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: UNCLEAR** **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Subgroup analysis for CL≤25 mm Gestational age at birth (weeks): **N=1, n=134, MD=2.20[1.03-3.37]** • PTB<28weeks N=1, n=134, RR=0.43[0.14-1.33] • PTB<34weeks N=2, n=348, I2=87%, RR=0.74[0.27-2.00] • PTB<37weeks N=1, n=134, RR=0.95[0.77-1.18] Perinatal mortality: • Any perinatal death: N=1, n=428, RR=1.70[0.85-3.39] • Neonatal death: N=1, n=266,	**Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* ***OVERALL: LOW*** Liem 2013 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: UNCLEAR** **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* ***OVERALL: LOW*** Nicolaides 2016 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: UNCLEAR**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR=0.19[0.01-3.95] Perinatal morbidity: • RDS: N=1, n=266, RR=0.96[0.37-2.47] • IVH (1-4): N=1, n=266, RR=0.11[0.01-1.95] • NEC: N=1, n=266, RR=0.19[0.01-3.95]	**Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* ***OVERALL: LOW*** **Other information**
Full citation Mordel,N., Zajicek,G., Benshushan,A., Schenker,J.G., Laufer,N., Sadovsky,E., Elective suture of uterine cervix in triplets, American	**Sample size** n=35 (12 elected to have cerclage, remaining 23 served as controls) **Characteristics** Not reported	**Interventions** Elective cervical suture - at 12-14 weeks gestation. Decision to perform suture was arbitrarily made by consultant/attending physician	**Details** All women were routinely hospitalised from 28 wks gestation due to diagnosis of triplets. Sutures removed when labour started, all women delivered by caesarean section.	**Results** Gestational age at birth: (mean±SD) CERCLAGE 33.0±5.1 weeks; CONTROL 34.7±2.8 weeks Perinatal mortality: CERCLAGE n=3/36 newborns (83/1000);	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (elective cerclage)** *truly representative (one star)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Perinatology, 10, 14-16, 1993 **Ref Id** 223002 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort **Aim of the study** evaluate the efficacy of elective cervical suture at 12-14 weeks gestation in prolonging gestation of triplets **Study dates** January 1978-December 1987	**Inclusion criteria** Triplet gestation. Decision to perform suture was arbitrarily made by consultant/attending physician. Woman elected to undergo procedure. **Exclusion criteria** None reported		Data retrieved retrospectively from patient files. Statistical evaluation by analysis of variance.	CONTROL n=6/69 newborns (87/1000)	2. **Selection of the non-exposed cohort (no cerclage/control)** *drawn from the same community as the exposed cohort (one star)* 3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (0/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *(not enough information to determine comparability - stated no difference in mean maternal age, infertility, tocolytic use). However self-selection of cerclage/no cerclage will have biased sample (NO stars)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes -*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported					*birth and neonatal period (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up - all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: POOR QUALITY** **Other information**
Full citation Norman,J.E., Mackenzie,F., Owen,P., Mactier,H., Hanretty,K., Cooper,S., Calder,A., Mires,G., Danielian,P., Sturgiss,S., MacLennan,G., Tydeman,G., Thornton,S., Martin,B., Thornton,J.G., Neilson,J.P., Norrie,J., Progesterone for the	**Sample size** 500 enrolled and randomised (n=250 progesterone, n=250 placebo) Analysed n=247 per group (3 lost to follow up per group) **Characteristics** **Continuous data as mean±SD (range)** Maternal age: VPROG 33±5 (range	**Interventions** Randomisation at 22wks GA, intervention began at 24+0 wks gestation for 10 weeks. Supplied with single use applicators (one per day) containing gel for intravaginal insertion. • Progesterone group: daily 90mg 8% progesterone gel administered vaginally	**Details** Primary outcome was birth or IU death before 34wks. Birth of first twin defined time of birth. One twin death in utero before 34wks classed as death before 34wks (even if 2nd twin born after 34wks). **<u>Statistical analysis:</u>** Intention to treat analysis based on pre-specified plan. Adjusted for chorionicity for primary outcome (<34wk birth/IU death). No formal interim analyses performed, so no	**Results** **continuous data presented as mean±SD** Maternal mortality: VPROG n=0/247; PLA n=0/247 Gestational age at birth: vPROG 35.4±3.5 weeks; PLA 35.7±3 weeks; MD=-0.3[-0.9 to 0.3]; p=0.31 • GA 32-<34 weeks: *all preterm birth or*	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias: LOW** • **Random sequence generation** *randomisation schedule with permuted blocks of randomly mixed sizes; used interactive telephone voice response randomisation service (LOW)* • **Allocation concealment** *drugs supplied in sealed opaque covering (LOW)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis, Lancet, 373, 2034-2040, 2009 **Ref Id** 221842 **Country/ies where the study was carried out** UK **Study type** Double-blind, placebo controlled trial **Aim of the study** Assess (vaginal) progesterone gel in preventing preterm (before 34 weeks)	18-44) yrs; PLA 33±6 (19-50) yrs Monochorionic twins: VPROG n=46/247; PLA n=45/247 **Inclusion criteria** Women with twin pregnancy: gestation and chorionicity established by 20 wks GA by ultrasound any cervical length (unselected) **Exclusion criteria** • pregnancy complicated by recognised structural or chromosomal fetal abnormality at recruitment • any contraindications to progesterone • planned cervical suture	• Placebo group: same applicator, no progesterone	adjustments made during the study. **<u>Power calculation:</u>** Based on 20% of twin deliveries before 34wks. n=250 per group gave 85% power for 5% significance to reduce preterm birth <34wks to 10% in treatment group.	*IU death<34wks: vPROG n=61/247 (24.7%); PLA n=48/247 (19.4%); OR=1.36[0.89-2.09]* Perinatal mortality: • intrauterine death: vPROG n=6/247; PLA n=4/247; p=0.52 • neonatal death: vPROG n=8/247; PLA n=6/247; p=0.59 Woman's satisfaction: *not validated scale* Adverse effects (for mother): • infection: vPROG n=0/247; PLA n=0/247; p=1.00	**Performance bias - Blinding of participants and personnel:** *all personnel and participants were masked to treatment assignment for study duration. Trial statistician and Oversight Committee had access to unblinded data but had no contact with participants (LOW)* **Detection bias - Blinding of outcome assessment:** *outcomes recorded from hospital notes by a trained clinician (UNCLEAR)* **Attrition bias - Incomplete outcome data:** *Analyses by intention-to-treat, followed pre-specified plan. No missing data were imputed - 3 mothers lost to follow up per group so excluded from analysis (LOW)* **Reporting bias - Selective reporting:** *reported outcomes despite in contradiction to hypothesis (LOW)* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
birth or intrauterine death **Study dates** 1 Dec 2004 - 30 April 2008 **Source of funding** Research grant CZH/4/200 from the Chief Scientist Office of the Scottish Government Health Directorate	• planned elective birth before 34 wks GA • planned intervention for twin to twin transfusion before 22wks GA • Higher multiple pregnancy			<u>Stratification by chorionicity: birth or IU death <34wks</u> Monochorionic: VPROG n=10/46 (21.7%)l PLA n=14/45 (31.1%); OR=0.62[0.24-1.58] Dichorionic: vPROG n=51/201 (25.4%); PLA n=34/202 (16.8%); OR=1.73[1.06-2.83]	
Full citation Obeidat, N., Alchalabi, H., Obeidat, M., Sallout, B., Hamadneh, S., Hamadneh, J., Khader, Y., Amarin, Z., Effectiveness of Prophylactic Cervical Cerclage in Prolonging Higher-Order Multiple Pregnancies, Sultan	**Sample size** n=146 (cerclage n=94; control/no cerclage n=52) **Characteristics** Maternal age: CERCLAGE 30.9±5.1 years; CONTROL 30.6±4.6 years	**Interventions** Suture placed at 11-16 weeks gestation, removed electively around 36 weeks, or in case of emergency.	**Details** Suture was McDonald type using 5mm polyester tape. Inserted under general anaesthetic. Discharged the same day. Advised to avoid demanding physical activities, but not assigned to bedrest. **<u>Statistical power -</u>** sample size gave a power of >80% to detect 5% difference between groups.	**Results** Gestational age at birth: CERCLAGE 31.7±2.9 weeks; CONTROL 32.9±2.7 weeks • GA<28 weeks: 24-<32 weeks CERCLAGE n=50/94 (53.2%);	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (cerclage)** *truly representative (one star)* 2. **Selection of the non-exposed cohort (no cerclage/control)** *drawn from*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Qaboos University Medical JournalSultan Qaboos Univ Med J, 17, e314-e318, 2017 **Ref Id** 758035 **Country/ies where the study was carried out** Jordan & Saudi Arabia **Study type** Retrospective cohort **Aim of the study** Determine the effect of cervical cerclage to prolong higher order multiple pregnancies (~90% triplets, ~10% quadruplets and quintuplets)	**Inclusion criteria** Women with triplet or higher order pregnancy beyond 24 weeks gestation in study period. Patient files reviewed **Exclusion criteria** None reported			CONTROL n=19/52 (36.5%) • GA 32-<34 weeks: CERCLAGE n=30/94 (31.9%); CONTROL n=12/52 (23.1%) • GA 34-<36/37 weeks: >34weeks CERCLAGE n=14/94 (14.9%); CONTROL n=21/52 (40.4%) Perinatal mortality (neonatal death/stillbirths): CERCLAGE "none" n=87/94 (92.6%), "at least one" n=7/94 (7.4%); CONTROL "none" n=46/52 (88.5%) "at least one" n=6/52 (11.5%)	*the same community as exposed cohort (one star)* 3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (1/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *states no differences (and adjustments made for) ART, number of fetuses, parity, maternal age. however self-selection of cerclage/no cerclage will have biased sample (ONE star)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - to hospital discharge (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up -*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Feb 2014 - Jan 2015 **Source of funding** No funding received for the study					*all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**
Full citation Rebarber,A., Roman,A.S., Istwan,N., Rhea,D., Stanziano,G., Prophylactic cerclage in the management of triplet pregnancies, American Journal of Obstetrics and Gynecology, 193, 1193-1196, 2005 **Ref Id** 223113 **Country/ies where the study was carried out**	**Sample size** cerclage n=248; no cerclage n=3030 total n=3278 met inclusion criteria **Characteristics** Maternal age: CERCLAGE 33.1±2.6 year; CONTROL 32.1±4.6 years History of PTB: CERCLAGE 5.6%; CONTROL 3.1% GA at start of outpatient surveillance: CERCLAGE 23.1±3.0	**Interventions** prophylactic cerclage	**Details** The study had 80% power to detect a 30% reduction in the primary outcome (incidence of PTB<32weeks)	**Results** CERCLAGE n=248 (744 infants); CONTROL n=3030 (9090 infants) Gestational age at birth: CERCLAGE 33.1±2.6 weeks; CONTROL 33.0±2.5 weeks • GA<28 weeks: PTB<28weeks CERCLAGE 4% (~10/248); CONTROL 4.5% (~136/3030) • GA 28-<32 weeks: PTB<32weeks CERCLAGE	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (cerclage)** *truly representative (one star)* 2. **Selection of the non-exposed cohort (no cerclage/control)** *drawn from the same community (one star)* 3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** Retrospective cohort **Aim of the study** Determine if (elective) prophylactic cerclage improves pregnancy outcomes in women with triplet pregnancies (without history of cervical insufficiency) **Study dates** January 1990 - May 2004 **Source of funding** Not reported	weeks; CONTROL 23.5±3.3 weeks **Inclusion criteria** Carrying a triplet gestation and enrolled for preterm labour surveillance before 32 weeks for at least one day **Exclusion criteria** • outcome data unavailable • diagnosis of cervical insufficiency in the index, or previous pregnancy			27.4% (~68 out of n=248); CONTROL 27.5% (~833 out of n=3030) Perinatal mortality: live birth CERCLAGE n=9028/9090 (99.1%); CONTROL n=737/744 (99.3%)* *reported as described, but suspect the values are reversed based on number cerclage/control cases	**COMPARABILITY (0/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *study comparable in maternal age, marriage, nulliparity, bleeding in index pregnancy before surveillance; different baseline characteristics described for history of PTB, enrolment in outpatient surveillance, prevalence of smoking during pregnancy. however self-selection of cerclage/no cerclage will have biased sample (NO star)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - to hospital discharge (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up - all subjects accounted for (one star)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					OVERALL QUALITY ASSESSMENT: POOR QUALITY **Other information**
Full citation O'Connor,M.C., Murphy,H., Dalrymple,I.J., Double blind trial of ritodrine and placebo in twin pregnancy, British Journal of Obstetrics and Gynaecology, 86, 706-709, 1979 **Ref Id** 194526 **Country/ies where the study was carried out** Ireland **Study type** RCT	**Sample size** n=50 randomised (25 per group) n=48 analysed (RITODRINE n=25; PLA n=23) n=1 excluded due to hospital admission for prolonged hypertension; n=1 excluded from analyses due to uncertainty over GA (based on menstruation dates) **Characteristics** Not reported **Inclusion criteria**	**Interventions** RITODRINE: 100 tablets. Each tablet contained 10mg ritodrine hydrochloride or placebo.	**Details** One tablet before meals, every 6 hours (supply refreshed every month). Weekly routine antenatal care given by an obstetrician. Treatment continued until GA of 37 complete weeks, induced between 38-40 weeks if not already given birth. Mean time for initiating treatment: RITODRINE: 28.4 ±3.1 weeks, PLA: 27.6±3.1 weeks	**Results** **mean±SD, n(%): RITODRINE n=25, PLACEBO n=24 (n=23 for GA due to lack of data for accurate gestational age to be calculated by authors)** Gestational age at birth: RITODRINE 37.7±1.4 weeks; PLA 36.7±2.1 weeks (based on last menstrual period) • GA 34-<36/37 weeks: PTB<37weeks RITODRINE n=5/25; PLA n=10/23 (based	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** • **Random sequence generation** *not reported (UNCLEAR)* • **Allocation concealment** *used a coded bottle of tablets, sealed envelopes containing code were available for emergency use, but was not necessary (LOW)* **Performance bias - blinding of participants and personnel:** *women and treating clinicians did not know the group of allocation - used a coded bottle of tablets, sealed envelopes containing code were available for emergency use, but was not necessary. (LOW)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Assess the prophylactic effect of oral ritodrine on twin pregnancy outcomes **Study dates** Not reported **Source of funding** Not reported	Twin pregnancy diagnosed by ultrasound 20-34 weeks gestation. **Exclusion criteria** Women who required hospital admission for hypertension or antepartum haemorrhage were excluded			on last menstrual period) Perinatal mortality: PLA: 1/48 infants	**Detection bias - Blinding of outcome assessment:** *Double blind trial - outcome measurements performed by paediatrician who were unaware of the prenatal therapy (LOW)* **Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of compliance with treatment - n=2 excluded from PLA, clear reasons given (LOW)* **Reporting bias - Selective reporting:** *(UNCLEAR)* **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Romero, R., Conde-Agudelo, A., El-Refaie, W., Rode, L., Brizot, M. L., Cetingoz, E., Serra, V., Da Fonseca, E., Abdelhafez, M. S., Tabor, A., Perales, A., Hassan, S. S., Nicolaides, K. H.,	n=303 women (606 fetuses/infants) from 6RCTs Vaginal progesterone (vPROG) n=159 Placebo/no treatment (CONT) n=144 **Characteristics**	Vaginal progesterone capsule/pessary/suppository: 100-400mg per day from 20-24weeks GA to 34-37weeks	Included 6RCTs of TWINS ONLY assessing vaginal progesterone (vPROG) compared to placebo/no treatment in meta-analysis: • Brizot 2015 • Cetingoz 2011 • El-Rafaie 2016 • Fonseca 2007	SR main outcome: Preterm birth <33 weeks: vPROG n=50/159; CONT n=62/144; RR=0.69[0.51-0.93] I2=0%, z=2.44, p=0.01 (favours vPROG)	Systematic reviews using IPD are assessed using ROBIS criteria **Domain 1: Concerns regarding specification of study eligibility: LOW** Reason for concern: no concerns **Domain 2: Concerns regarding methods used to identify and/or select studies: LOW** Reason for concern: no concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data, Ultrasound in Obstetrics & Gynecology, 49, 303-314, 2017 **Ref Id** 660296 **Country/ies where the study was carried out** USA, UK, Egypt, Denmark, Brazil, Turkey, Spain **Study type** Systematic review with meta-analysis of Individual Patient Data (IPD)	**Median (IQR) or n (%)** Maternal age: vPROG 27 (25-30) years; CONT 28 (25-31) years Monochorionic pregnancy: vPROG n=8 (5%); CONT n=6 (4.2%) Gestational age at randomisation: vPROG 21.7 (20.6-23.1) weeks; CONT n=22.1 (21.1-23.3) weeks Cervical length at randomisation: vPROG 22 (20-23)mm; CONT 22 (20-23)mm Cephalic/non-cephalic: *not reported* **Inclusion criteria** RCTs with asymptomatic women with twin gestation and short cervix (<25 mm) in mid-trimester, who were randomly allocated to receive		• PREDICT trial (Rode 2011) • Serra 2013	Gestational age at birth: • GA<28 weeks: vPROG 9/159; CONT 12/144; pooled RR=0.51 [0.24-1.08]; I2=0% • GA 28-<32 weeks: vPROG 20/159; CONT 34/144; pooled RR (for all <32wks)=0.51[0.34-0.77]; I2=0%; NNT=6[5-14] • GA 32-<34 weeks: vPROG 34/159; CONT 32/144; pooled RR (for all <34wks)=0.71[0.56-0.91]; I2=0%; NNT=6[4-21] • GA 34-<36/37 weeks: vPROG 44/159; CONT 53/144; pooled RR (for all <37wks)=0.94[0.86-1.02]; I2=0%	**Domain 3: Concerns regarding methods used to collect data and appraise studies: LOW** Reason for concern: no concerns **Domain 4: Concerns regarding the synthesis and findings: LOW** Reason for concern: no concerns **RISK OF BIAS IN THE REVIEW** A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? yes B. Was the relevance of identified studies to the review's research question appropriately considered? yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? yes **Risk of bias in the review: LOW** Quality assessment by Review authors (NGA have not returned to primary studies to re-assess ROB) Individual studies included used Cochrane ROB table: Brizot 2015 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Assess the efficacy of vaginal progesterone to prevent pre-term birth in asymptomatic women with twin gestation and a short cervix (≤25 mm) in mid-trimester **Study dates** Databases searched from inception to 31 December 2016 **Source of funding** Perinatology Research Branch, Program for Perinatal Research & Obstetrics, Eunice Kennedy Shriver National Institute of Child Health and	vaginal progesterone or placebo/no treatment. Primary aim of study was to prevent preterm birth and/or adverse perinatal outcomes. **Exclusion criteria** • Quasi-randomised trials • trials of vaginal progesterone in women with preterm labour, arrested labour, preterm rupture of membranes (PPROM), second trimester bleeding. • trials that assess vaginal progesterone in first trimester to prevent miscarriage • studies that did not report clinical outcomes			Perinatal mortality: vPROG 43/318; CONT 72/288; pooled RR*=0.51 [0.36-0.70]; pooled RR**=0.58 [0.39-0.84]; I2=24%; NNT=7 [5-20] • stillbirths/fetal death: vPROG 9/318; CONT 9/288; RR*=0.57[0.23-1.42]; RR**=0.68[0.26-1.84]; I2=0% • intrauterine/neonatal death: vPROG 34/318; CONT 63/288; RR*=0.5[0.34-0.71]; RR**=0.53[0.35-0.81]; I2=25%; NNT=8[5-19] Perinatal morbidity: • RDS: vPROG 102/311; CONT 131/280; RR*=0.67[0.55-	**Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Cetingoz 2011 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* El-refaie 2016 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Human Development, NIH Federal funds from NICHD/NIH/DHHS contract no. HHSN275201300006C	• Studies published as abstract if additional information was not available.			0.82]; RR**=0.7[0.56-0.89]; I2=0%; NNT=6[4-16] • IVH: vPROG 2/80; CONT 2/68; RR*=0.93[0.15-5.75]; RR**=1.47[0.22-9.63]; I2=0% • NEC: vPROG 1/82; CONT 0/68; RR*=1[0.04-22.43]; RR**=1.07[0.05-22.25]; I2=NA **assuming independence between twins, **adjustment for non-independence between twins*	**Performance bias - Blinding of participants and personnel: HIGH** **Detection bias - Blinding of outcome assessment: HIGH** **Attrition bias - Incomplete outcome data: UNCLEAR** **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Fonseca 2007 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Rode 2011 (PREDICT trial) **Selection bias:** LOW • **Random sequence generation** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					• **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Serra 2013 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Saccone, G., Rust, O., Althuisius, S., Roman, A., Berghella, V., Cerclage for short cervix in twin pregnancies: systematic review and meta-analysis of randomized trials using individual patient-level data, Acta Obstetricia et Gynecologica ScandinavicaActa Obstet Gynecol Scand, 94, 352-8, 2015 **Ref Id** 756448 **Country/ies where the study was carried out** USA, Italy, Aruba **Study type**	**Sample size** n=49 twin pregnancies (CERCLAGE n=24, NO CERCLAGE n=25) **Characteristics** **Mean±SD, and n (%)** Maternal age: CERCLAGE 28.88±5.4 years; CONT 28.08±6.35 years Previous PTB<37weeks: CERCLAGE n=6/24 (25%); CONT n=1/25 (4%) Cervical length: CERCLAGE 18.6±6.1 cm*; CONT 18.3±4.7 cm* - **described as cm in text, suspect typographical error, and actually should use mm* GA at randomisation: CERCLAGE 21.4±3.1 weeks; CONT 23.3±2.1 weeks	**Interventions** CERCLAGE: not described in paper CONTROL: not described in paper	**Details** Data for twin pregnancies with short cervical length (<25 mm) from 3 RCTS: • Althuisius 2001 • Berghella 2004 • Rust 2001	**Results** Gestational age at birth: CERCLAGE 30.33 weeks; CONT 34.2 weeks, p=0.007 • GA<28 weeks: PTB<28wks CERCLAGE n=7/24 (29.2%); CONT n=2/25 (8%); RR=2.62 [0.72-9.51], aOR=1.66 [0.62-4.01] • GA 28-<32 weeks: PTB<32wks CERCLAGE n=11/24 (45.8%); CONT n=4/25 (16%); RR=2.48 [0.96-6.37]; aOR=1.77 [0.88-3.39] • GA 32-<34 weeks: PTB<34wks CERCLAGE n=15/24; CONT n=6/25; RR=2.19	**Limitations** Systematic reviews using IPD are assessed using ROBIS criteria **Domain 1: Concerns regarding specification of study eligibility: LOW** Reason for concern: no concerns **Domain 2: Concerns regarding methods used to identify and/or select studies: LOW** Reason for concern: no concerns **Domain 3: Concerns regarding methods used to collect data and appraise studies: LOW** Reason for concern: no concerns **Domain 4: Concerns regarding the synthesis and findings: UNCLEAR** Reason for concern: lack of information in some areas **RISK OF BIAS IN THE REVIEW** A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? yes B. Was the relevance of identified studies to the review's research question appropriately considered? yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? yes **Risk of bias in the review: LOW**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Systematic review with meta-analysis of Individual Patient Data **Aim of the study** Evaluate the efficacy of cervical cerclage in twin pregnancies with short cervix (<25 mm before 24 weeks) **Study dates** Literature search from inception to September 2014 **Source of funding** Reported as no specific funding	**Inclusion criteria** RCTs of asymptomatic twin gestations screened by transvaginal ultrasound (TVU) in the second trimester of pregnancy, where the mothers were found to have a short cervical length (CL < 25 mm). Eligible women were randomised to cerclage versus no cerclage (control) **Exclusion criteria** • quasi-randomised trials • history-indicated cerclage • twin-only-indicated cerclage • physical examination-			[0.72, 6.63]; I2=36%, Z=1.38 • GA 34-<36/37 weeks: PTB<37wks CERCLAGE n=22/24 (91.7%); CONT n=19/25 (76%); RR=1.18 [0.91-1.53]; aOR=1.13 [0.17-8.66] Perinatal mortality: CERCLAGE n=11/48 infants (22.9%); CONT n=3/50 infants (6%); RR=2.66 [0.83-8.54]; aOR=2.04[0.55-8.32] Perinatal morbidity: • RDS: CERCLAGE n=15/48 infants (31.3%); CONT n=3/50 infants (6%); RR=5.07[1.75-14.7]; aOR=3.88[1.09-21.03]	Quality assessment by Review authors (NGA have not returned to primary studies to re-assess ROB) Individual studies included used Cochrane ROB table: Althuisius 2001 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: HIGH** **Detection bias - Blinding of outcome assessment: HIGH** **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Berghella 2004 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	indicated cerclage • major fetal anomaly			• IVH: CERCLAGE n=3/48 infants (6.3%); CONT n=3/50 infants (6%); RR=1.13[0.27-4.74], aOR=1.09[0.21-4.98] *aOR: OR adjusted for confounders (previous PTB and gestational age at randomisation)*	**Performance bias - Blinding of participants and personnel: HIGH** **Detection bias - Blinding of outcome assessment: HIGH** **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Rust 2001 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: HIGH** **Detection bias - Blinding of outcome assessment: UNCLEAR** **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Saunders, M. C., Dick, J. S., Brown, I. M., McPherson, K., Chalmers, I., The effects of hospital admission for bed rest on the duration of twin pregnancy: a randomised trial, Lancet, 2, 793-5, 1985 **Ref Id** 867307 **Country/ies where the study was carried out** Zimbabwe **Study type** RCT **Aim of the study** To evaluate the policy of advising all mothers with a diagnosis of twin	**Sample size** n=212 twin pregnancies randomised to BEDREST in hospital (n=105) or CONTROL (n=107) **Characteristics** **Mean±SD or n (%)** Maternal age: BEDREST 26.6±6.7 years; CONT 27.3±6.0 SBP: BEDREST 114.4±12.4 mmHg; CONT 115.5±15.1mmHg DBP: BEDREST 70±102.9* mmHg; CONT 71.7±7.6 mmHg *suspected typographical error in document **Inclusion criteria**	**Interventions** BEDREST: hospitalised from 32 weeks gestation until onset of labour CONTROL: hospital admission used only selectively (on average 5 weeks later)	**Details** **<u>Power calculation:</u>** It was estimated that a trial with 100 subjects in each arm would have a 40% chance of detecting a reduction in the risk of preterm birth before 37 weeks by one-third, from 30% to 20%.	**Results** Gestational age at birth: BEDREST 37.3±2.2 weeks; CONT 37.9±2.5 weeks • GA 34-<36/37 weeks: PTB<37 weeks BEDREST 32/105 (30.4%); CONT 20/107 (18.7%) Perinatal mortality*: BEDREST n=8/210 infants (rate per 1000: 38.1); CONTROL n=2/214 infants (rate per 1000: 23.4) • stillbirths*: BEDREST 5/210; CONT 3/214 • early neonatal death*: BEDREST 3/210; CONT 2/214	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** • **Random sequence generation** *consecutively num bered series of sealed envelopes (LOW)* • **Allocation concealment** *Not reported (UNCLEAR)* **Performance bias - blinding of participants and personnel:** *Unable to blind participants to allocation. (HIGH)* **Detection bias - Blinding of outcome assessment:** *Data were collected from the standard clinical case records and abstracted for analysis after birth. Assessment of duration of gestation at birth was made by labour-ward staff who were unaware of the group to which individual women had been assigned. (LOW)* **Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of compliance with*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy to come into hospital for bed rest at 32 weeks' gestation **Study dates** Not reported **Source of funding** Sims Black Lectureship & DHSS project grant	Women with twin pregnancy at last scheduled antenatal visit before 32 weeks gestations (usually 30wks) **Exclusion criteria** None reported			*excluding death due to lethal malformations	*treatment. Compliance reported for both groups [BEDREST group n=92/105 were admitted before onset of labour - 11 declined admission, 2 delivered before admission; CONTROL group n=58/107 were admitted before labour ~5 weeks later, n=1 delivered before 32 weeks] (LOW)* **Reporting bias - Selective reporting:** *(UNCLEAR)* **Other information**
Full citation Schuit, E., Stock, S., Rode, L., Rouse, D. J., Lim, A. C., Norman, J. E., Nassar, A. H., Serra, V., Combs, C. A., Vayssiere, C., Aboulghar, M. M., Wood, S., Cetingoz, E., Briery, C. M., Fonseca, E. B., Worda, K., Tabor, A., Thom, E. A., Caritis, S. N.,	**Sample size** total n=3768 women, with 7536 babies; from 13 trials mPROG (17PC) trials: mPROG n=1089; CONTROL n=944; from 6 studies vPROG trials: vPROG n=917; CONTROL n=818; from 7 studies	**Interventions** • intramuscular (17PC) progesterone (mPROG) • vaginal progesterone (vPROG)	**Details** Included 13 RCTs of TWINS ONLY assessing vaginal progesterone (vPROG) or intramuscular progesterone (mPROG) compared to placebo/no treatment in meta-analysis (data for vPROG and mPROG analysed separately): Intramuscular Progesterone studies:	**Results** **Only data from mPROG to be used in review to avoid double counting with Romero 2017** **Intramuscular progesterone (mPROG)** Gestational age at birth: • GA<28 weeks: mPROG	**Limitations** Systematic reviews using IPD are assessed using ROBIS criteria **Domain 1: Concerns regarding specification of study eligibility: LOW** Reason for concern: no concerns **Domain 2: Concerns regarding methods used to identify and/or select studies: LOW** Reason for concern: no concerns **Domain 3: Concerns regarding methods used to collect data and appraise studies: LOW** Reason for concern: no concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Awwad, J., Usta, I. M., Perales, A., Meseguer, J., Maurel, K., Garite, T., Aboulghar, M. A., Amin, Y. M., Ross, S., Cam, C., Karateke, A., Morrison, J. C., Magann, E. F., Nicolaides, K. H., Zuithoff, N. P. A., Groenwold, R. H. H., Moons, K. G. M., Kwee, A., Mol, B. W. J., Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: An individual participant data meta-analysis, BJOG: An International Journal of Obstetrics and Gynaecology, 122, 27-37, 2015 **Ref Id** 809670	**Characteristics** **mPROG: mean (SD) or n (%)** Maternal age: mPROG 31.6(5.6)yrs; CONT 31.4(5.8)yrs Monochorionic pregnancy: mPROG n=139/1089 (14%); CONT n=120/944 (14%) Gestational age at randomisation: mPROG 19.0 (3.0)wks; CONT 19.0 (2.9)wks Cervical length at randomisation: 2.3(1.5)cm; 2.5(1.4)cm Cephalic/non-cephalic: *not reported* **vPROG: mean (SD) or n (%)** Maternal age: vPROG 32.2 (5.0)yrs; CONT 32.2 (5.0)yrs Monochorionic pregnancy: vPROG n=97/917 (11%);		• PROGESTWIN trial (Awwad 2015) • Briery 2009 • Combs 2011 • AMPHIA trial (Lim 2011) • Rouse 2007 • Senat 2013 Vaginal Progesterone studies (covered in another IPD SR, or meta-analysed separately): • Aboulghar 2012 • Cetingoz 2011 • Fonseca 2007 • STOPPIT trial (Norman 2009) • PREDICT trial (Rode 2011) • Serra 2013 • Wood 2012	n=60/1089 (6%); CONT n=50/944 (5%); RR=0.94[0.58-1.5]; p=0.81; I2=0[0-73] • GA 28-<32 weeks: n=103/1089 (9%); n=65/944 (7%); RR (for all<32wks)=1.3[0.87-1.8]; p=0.22; I2=59[0-83] • GA 34-<36/37 weeks: n=330/1089 (31%); n=275/944 (30%); RR (for all<37wks)=1.1[0.94-1.2]; p=0.4; I2=0[0-69] Perinatal mortality: mPROG n=78/2178 (4%); CONT n=78/1888 (4%); RR=0.8[0.33-1.9]; p=0.54; I2=70[31-87] Perinatal morbidity:	**Domain 4: Concerns regarding the synthesis and findings: LOW** Reason for concern: no concerns **RISK OF BIAS IN THE REVIEW** A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? yes B. Was the relevance of identified studies to the review's research question appropriately considered? yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? yes **Risk of bias in the review: LOW** Quality assessment by Review authors (NGA have not returned to primary studies to re-assess ROB) Individual studies included used Cochrane ROB table: Awwad 2015 (PROGESTWIN) **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Netherlands, Denmark, USA, Lebanon, Spain, France, Egypt, Canada, turkey, Brazil, Austria, UK, Australia **Study type** Systematic Review with meta-analysis of Individual Patient Data **Aim of the study** Assess the effectiveness of progesterone (PROG) to prevent neonatal morbidity or preterm birth in twin pregnancies. Vaginal progesterone (vPROG) and intramuscular (17PC)	CONT n=111/818 (15%) Gestational age at randomisation: 20.1(3.1)wks; 20.6 (2.7)wks Cervical length at randomisation: 3.8 (0.9)cm; 3.7(0.9)cm Cephalic/non-cephalic: *not reported* **Inclusion criteria** • RCTs that investigated effectiveness of vPROG/mPROG versus a placebo/no treatment for reduction in preterm birth and/or adverse perinatal outcomes • second or third trimester women with			• RDS: mPROG n=330/2178 (15%); CONT n=233/1888 (13%); RR=1.2[0.93-1.6]; p=0.12; I2=50[0-80] • IVH: n=23/2178 (1%); n=12/1888 (1%); RR=1.7[0.73-3.8]; p=0.17; I2=0[0-66] • NEC: n=16/2178 (1%); n=11/1888 (1%); RR=1.2[0.79-2.0]; p=0.26; I2=0[0-19]	**Attrition bias - Incomplete outcome data:** *LOW - based on protocol only* **Reporting bias - Selective reporting:** *LOW - based on protocol only* ***Other bias:*** *LOW - based on protocol only* Briery 2009 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Combs 2011 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
progesterone (mPROG) analysed separately. **Study dates** Literature search to 1 March 2013 **Source of funding** Netherlands Organization for Scientific Research (grants 918.10.615 & 9120.8004)	• twin pregnancy • trials assessing effectiveness in subgroups, also included (e.g. short cervix) **Exclusion criteria** None reported				**Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Lim 2011 (AMPHIA) **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel:** *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Rouse 2007 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Performance bias - Blinding of participants and personnel: *LOW* **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* Senat 2013 **Selection bias:** LOW • **Random sequence generation** *LOW* • **Allocation concealment** *LOW* **Performance bias - Blinding of participants and personnel: HIGH** **Detection bias - Blinding of outcome assessment:** *LOW* **Attrition bias - Incomplete outcome data:** *LOW* **Reporting bias - Selective reporting:** *LOW* ***Other bias:*** *LOW* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Skrablin,S., Kuvacic,I., Jukic,P., Kalafatic,D., Peter,B., Hospitalization versus. outpatient care in the management of triplet gestations, International Journal of Gynaecology and Obstetrics, 77, 223-229, 2002 **Ref Id** 194665 **Country/ies where the study was carried out** Croatia **Study type** retrospective cohort study (patient selected grouping) **Aim of the study**	**Sample size** 79 triplet pregnancies group 1 (complete bedrest) selected by n=55 group 2 (standard outpatient protocol) selected by n=24 **Characteristics** spontaneous triplet gestation n=18; assisted reproductive techniques n=61 "no difference in maternal age, socio-economic background, educational level, assisted reproduction, pre-pregnancy height or weight, or race" **Inclusion criteria** triplet pregnancies that reached 16 weeks gestation were analysed	**Interventions** Women selected home normal activity, or hospital bedrest from start of second trimester. After 28 weeks of gestation, all outpatients were hospitalised until birth, irrespective of symptoms.	**Details** After 28 weeks of gestation, all outpatients were hospitalised until birth, irrespective of symptoms.	**Results** Gestational age at birth: BEDREST 34.1±2.7 weeks; CONT 30.3±4.3 weeks Perinatal mortality: ≥24wks BEDREST n=21/165 (12.7%) (only 157 live births from 55 pregnancies); CONT n=31/72 (43%) (only 55 live births from 24 pregnancies) • intrauterine death: ≥24wks BEDREST n=8/165 (4.8%) (only 157 live births); CONT n=17/72 (only 55 live births) • early neonatal death: ≥24wks BEDREST n=13/157 (8.3%); CONT n=14/55 (25.5%) - based on live births only	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (3/4)** 1. **Representativeness of exposed cohort (inpatient bedrest)** *self-selected group* 2. **Selection of the non-exposed cohort (outpatient management)** *drawn from the same community as the exposed cohort (one star)* 3. **Ascertainment of exposure** *by secure medical records (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (1/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *cohorts are comparable based on: age, socio-economic background, education level, assisted reproduction technology, pre-pregnancy height and weight,*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
"Compare the course and outcome of triplet gestations under a preventive care strategy that includes hospitalization, surveillance, bed rest, and daily specialized care from the beginning of the second trimester, with pregnancies managed according to the Croatian standard outpatient care protocol for multiplets" **Study dates** 1986-2000 **Source of funding** Not reported	**Exclusion criteria** none reported			Perinatal morbidity: • IVH: BEDREST n=0/157 live births; CONT n=1/55 live births (1.8%)	*chorionicity. Not comparable for nulliparity, elective C-section (one star)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - until discharge from hospital postnatally (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up, all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Sumners,J.E., Moore,E.S.,		All cerclage performed between 7.7 weeks and	**Statistical power:** A post-hoc power analysis indicated	Gestational age at birth as median	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ramsey,C.J., Eggleston,M.K., Transabdominal cervical cerclage in triplet pregnancies and risk of extreme prematurity and neonatal loss, Journal of Obstetrics and Gynaecology, 31, 111-117, 2011 **Ref Id** 194690 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** Compare gestational age and incidence of preterm birth among triplet gestation who underwent cerclage	n=141 triplet pregnancies met inclusion criteria CERCLAGE (transvaginal) TVC n=31 CERCLAGE (transabdominal) TAC n=60 NO CERCLAGE (control) n=50 **Characteristics** Maternal age: 31.1±4.8 years 97.9% Caucasian GA at TVC placement: 13.4±2.1 weeks (range 7.7 - 18.4 weeks) GA at TAC placement: 13.0±1.1 weeks (range 10.7 - 17.6 weeks) CERCLAGE groups had higher incidence of nulliparity, infertility intervention.	18.4 weeks gestational age. Transabdominal cerclage (TAC): discharged within 3 days of the procedure. Performed using laparotomy. Transvaginal cerclage (TVC): outpatient procedure only, performed under spinal anaesthesia, using modified McDonald technique "Prior to 2002, TAC was recommended when only classical indications (history indicative of cervical incompetence with either a failed prophylactic TVC or deep cervical laceration or extreme cervical shortening) or non-classical indications (uterine anomaly, UA) or an extremely shortened cervix or deep cervical laceration without cervical incompetence) coexisted with the triplet pregnancy. Beginning in 2002,	that this study attained 72% power at alpha<0.05. A total of 12 more women in the TAC group would have been required, at the same pre-term birth rate, to achieve a statistically significant difference for birth prior to 28 weeks between treatment groups.	(IQR): TAC 33.1 (2.7) weeks; TVC 32.6 (3.6) weeks; CONTROL 33.6 (4.0) weeks • GA<28 weeks: PTB<28wks TAC n=2/60 (3.6%); TVC n=5/31 (16.1%); CONTROL n=6/50 (12.2%) • GA 28-<32 weeks: PTB<32wks TAC n=16/60 (28.6%); TVC n=14/31 (45.2%); CONTROL n=16/50 (32.7%) • GA 34-<36/37 weeks: PTB<37wks TAC n=60/60; TVC n=30/31; CONTROL n=50/50 Perinatal mortality: intrauterine fetal demise: TAC n=2/180 infants (1.1%); TVC	Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (cerclage [TVC or TAC])** *truly representative (one star)* 2. **Selection of the non-exposed cohort (no cerclage/control)** *drawn from the same community (one star)* 3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (1/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *stated very homogeneous sample, except for use of cerclage, however self-selection of cerclage/no cerclage will have biased sample (one star)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(transvaginal cerclage or transabdominal cerclage) compared to no cerclage **Study dates** 1989 - 2009 **Source of funding** Not reported	**Inclusion criteria** • Triplet gestation, all foetuses alive at GA 18 week scan. • 83.5% who had CERCLAGE, elected to have it. **Exclusion criteria** • Planned foetal reduction • Not followed after 24weeks gestation	prophylactic TAC was offered to women with triplets, as a treatment option, after detailed discussion of the operative risks"		n=3/93 infants (3.2%); CONTROL n=2/150 infants (1.3%) Perinatal morbidity: IVH 3-4: TAC n=4/180 infants (2.2%); TVC n=2/93 infants (2.5%); CONTROL n=9/150 (6.3%)	**OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - until hospital discharge (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up - all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: GOOD QUALITY** **Other information**
Full citation Wood,S., Ross,S., Tang,S., Miller,L., Sauve,R., Brant,R., Vaginal progesterone to prevent preterm birth in multiple pregnancy: A	**Sample size** total n=84 (Progesterone group=42; placebo=42) **Characteristics**	**Interventions** Daily gel to be administered vaginally from randomisation to 35+6 weeks GA, or until birth if sooner. Gel provided in single-use applicators, supplied with enough to last until 35+6	**Details** Sample size based on survey of Canadian obstetricians: minimally important clinical difference of 2 weeks GA at birth. Assumed 10% drop out, and 85% power, estimated sample total	**Results** **continuous variables as median (IQR), range, mean difference as they were not normally distributed** Gestational age at birth: VPROG 36+3	**Limitations** **Risk of Bias assessed using Cochrane ROB tool** **Selection bias:** • **Random sequence generation** *random number generator with random block sizes of 2 or 4, consenting*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized controlled trial, Journal of Perinatal Medicine, 40, 593-599, 2012 **Ref Id** 260952 **Country/ies where the study was carried out** Canada **Study type** RCT **Aim of the study** Assess the effect of (vaginal) progesterone on duration of pregnancy for mothers with twin and triplet pregnancy **Study dates**	**median (IQR), and range (as not normally distributed)** **VPROG n=42; PLA n=42** Maternal age: vPROG 34 (IQR 6), 19-43 yrs; PLA 34 (IQR 5), 22-44 years GA at randomisation: VPROG 19+2 (IQR 1+3), 16+3 - 21+1 weeks; PLA 19+6 (IQR 1+3) 14+5 - 21+1 No of twin pregnancies: vPROG n=40/42 (95%); PLA n=41/42 (98%) No of triplets pregnancies: vPROG n=2/42; PLA n=1/42 **Inclusion criteria** • pregnant women with two or more live foetuses at 16-18week ultrasound	weeks GA. All other clinical care for multiples remained as per usual. • Progesterone group: 90mg progesterone 8 % vaginal gel • Placebo group: identical applicators with gel containing no progesterone	n=100. Revised sample size based on no drop out: total n=80 (40 per group). Analysis by intention to treat. Single analysis when all participants were followed up 28 days after birth, and all outcome data had been collected from hospital charts. Cervical length was monitored according to usual practice of the physician.	(IQR 2+6) 20+0 to 38+2 weeks; PLA 36+2 (IQR 3+0) 28+4 to 38+4; p=0.585; Difference=0+1, 95%CI[-0+4 to 1+1) • GA 34-<36/37 weeks: *all<37wks:* vPROG n=25/42 (60%); PLA n= 27/42 (26%); p=0.823; RR=0.87[0.47-1.59] Perinatal mortality: intrauterine death/neonatal death: vPROG n=2/86 infants; PLA n=1/85 infants; RR=1.98[0.18-21.39] Adverse effects (for mother): • postpartum haemorrhage: vPROG n=5/42 (12%); PLA n=3/42 (7%); p=0.247;	*participants were randomly allocated to progesterone or placebo (allocation ratio, 1:1). Randomisation was stratified: primiparous twins, multiparous twins, and triplets and higher-order multiple pregnancies. Sequence generated by the trial statistician was provided to the dispensing pharmacy. Pharmacy dispensed either progesterone or placebo according to allocation (LOW)* • **Allocation concealment** *Not reported (UNCLEAR)* **Performance bias - blinding of participants and personnel:** *women and treating clinicians did not know the group of allocation. (LOW)* **Detection bias - Blinding of outcome assessment:** *Independent study nurse extracted data from hospital records (LOW)* **Attrition bias - Incomplete outcome data:** *Analysis by intention-to-treat, according to allocated group regardless of compliance with*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 2006 - October 2010 **Source of funding** Calgary Health Region Perinatal Funding Competition (peer reviewed funding)	• higher order pregnancies who reduced pre-GA 13wks • any cervical length (unselected) **Exclusion criteria** • women with placenta previa • pre-existing hypertension • known major fetal anomaly detected on ultrasound • monoamniotic or monozygotic multiple pregnancies • maternal seizure disorder • active or history of thromboembolytic disease • maternal liver disease • known or suspected breast			RR=1.67[0.43-6.53] Perinatal morbidity: • RDS: vPROG n=15/86 infants; PLA n=22/85 infants; RR=0.68[0.38-1.22] • IVH: n=3/86; n=1/85; RR=2.93[0.31-27.58] • NEC: n=1/86; 2/85; RR=0.49[0.05-5.28] ***GA at birth (mean±SD could not be calculated as data is described as not having normal distribution)***	*treatment. Compliance reported as 97.8% for both groups (LOW)* **Reporting bias - Selective reporting:** *trial registered with clinicaltrials.gov. Outcomes clearly stated (LOW)* **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	malignancy or pathology • known or suspected progesterone-dependent neoplasia • plans to relocate during pregnancy • previous participation in this trial or other perinatal clinical trials • known sensitivity to progesterone				
Full citation Young, Cm, Stanisic, T, Wynn, Lb, Shrivastava, Vl, Haydon, Ml, Wing, Da, Use of cerclage in triplet pregnancies with an asymptomatic short cervix, Journal of ultrasound in medicine, 33, 343-347, 2014	**Sample size** n=24 (CERCLAGE n=16; CONT n=8) **Characteristics** **Median (IQR), n (%)** Maternal age: CERCLAGE 32.5 (31.0-37.5) years; CONT 30 (20.1-38.6) years	**Interventions** women with short CL managed with cerclage versus managed expectantly	**Details** Transvaginal ultrasound measure of cervical length at 16-24 weeks gestation. Bed rest, tocolysis, and antenatal corticosteroids were used at the discretion of the attending perinatologist.	**Results** **Median (IQR), n (%)** Gestational age at birth: CERCLAGE 31.3 (29.3-32.3) weeks, n=48 infants; CONT 29.8 (27.5-32.4) weeks, n=24 infants • GA<28 weeks: CERCLAGE n=3/16 (19%);	**Limitations** Quality assessment was done using the Newcastle Ottowa scale for cohort studies **SELECTION (4/4)** 1. **Representativeness of exposed cohort (cerclage)** *truly representative (one star)* 2. **Selection of the non-exposed cohort (control)** *drawn from same community (one star)*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 809726 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** Outcomes in triplet pregnancies with cervical shortening (<25 mm before 24 weeks gestation) with and without cervical suture/cerclage **Study dates** 1 Jan 1998 - 31 Dec 2004 **Source of funding**	CL at enrolment: CERCLAGE 1.65 (1.3-1.95) cm; CONT 2.2 (1.76-2.33) cm (p=0.01 sig diff at baseline) **Inclusion criteria** Triplet gestation with cervical length <25 mm before 24 weeks gestation **Exclusion criteria** Pregnancies complicated by multi-fetal pregnancy reduction or those that delivered for maternal or fetal indications before 32 weeks			CONT n=1/8 (13%) • GA 28-<32 weeks: CERCLAGE n=7/16 (445); CONT n=5/8 (63%) • GA 32-<34 weeks: GA>32wks CERCLAGE n=6/16 (36%); CONT n=2/8 (25%) Composite neonatal outcome: CERCLAGE n=8/16 (50%); CONT n=3/8 (38%)	3. **Ascertainment of exposure** *secure record (one star)* 4. **Demonstration that outcome of interest was not present at start of study** *yes (one star)* **COMPARABILITY (0/2)** 1. **Comparability of cohorts on the basis of the design or analysis controlled for confounders** *some confounders controlled for. Other confounders significant different at baseline - cervical length. however self-selection of cerclage/no cerclage will have biased sample (NO star)* **OUTCOME (3/3)** 1. **Assessment of outcome** *record linkage (one star)* 2. **Was follow up long enough for outcome to occur?** *yes - to hospital discharge (to account for neonatal outcomes) (one star)* 3. **Adequacy of follow-up of cohorts** *complete follow up -*

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported					*all subjects accounted for (one star)* **OVERALL QUALITY ASSESSMENT: POOR QUALITY** **Other information**

Appendix E – Forest plots

Forest plots for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

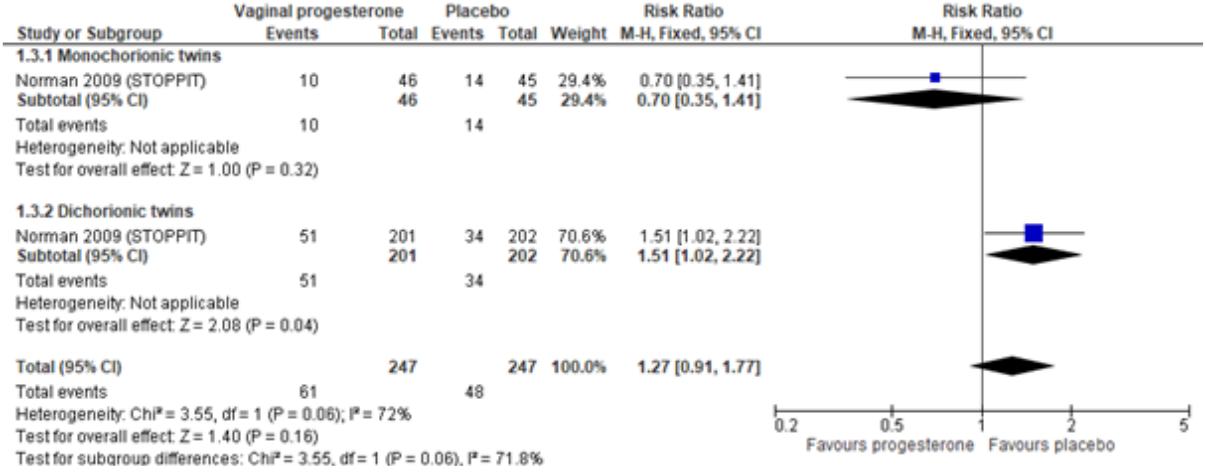
Outcomes with only one study are not represented in forest plots. Please see the GRADE tables for those outcomes.

Data from systematic reviews are not represented in forest plots. Please see GRADE tables for those outcomes.

Comparison 1b: Vaginal progesterone versus placebo in twin pregnancy (unselected)

Vaginal progesterone (daily 90mg gel) versus placebo for prevention of spontaneous preterm birth in TWINS – Meta-analysis from primary studies of UNSELECTED twin pregnancy

Figure 3: Gestational age at birth/ IU death<34wks – stratified by chorionicity



Appendix F – GRADE tables

GRADE profiles for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Progesterone

Comparison 1a: Vaginal progesterone versus placebo in twin pregnancy with short CL (≤25 mm)

Table 9: Clinical evidence profile for Comparison 1a: Vaginal progesterone versus placebo for preventing spontaneous preterm birth in twins – data from a systematic review of IPD of twin pregnancy with short CL (≤25 mm)

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (100-400mg daily)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth <28 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	9/159 (5.7%)	12/144 (8.3%)	RR 0.51 (0.24 to 1.08)	41 fewer per 1000 (from 63 fewer to 7 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Gestational age at birth <32 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	29/159 (18.2%)	46/144 (31.9%)	RR 0.51 (0.34 to 0.77)	157 fewer per 1000 (from 73 fewer to 211 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Gestational age at birth <34 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	63/159 (39.6%)	78/144 (54.2%)	RR 0.71 (0.56 to 0.91)	157 fewer per 1000 (from 49 fewer to	⊕⊕⊕⊖ MODERATE	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (100-400mg daily)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										238 fewer)		
Gestational age at birth <37 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	137/159 (86.2%)	131/144 (91%)	RR 0.94 (0.86 to 1.02)	55 fewer per 1000 (from 127 fewer to 18 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal mortality (any) [5]												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/318 (13.5%)	72/288 (25%)	RR 0.51 (0.36 to 0.58)[3]	123 fewer per 1000 (from 105 fewer to 160 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal mortality (stillbirth/fetal death) [5]												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	9/318 (2.8%)	9/288 (3.1%)	RR 0.57 (0.23 to 1.42)[3]	13 fewer per 1000 (from 24 fewer to 13 more)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal mortality (intrauterine/neonatal death) [5]												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	34/318 (10.7%)	63/288 (21.9%)	RR 0.50 (0.34 to 0.71)[3]	109 fewer per 1000 (from 63 fewer to 144 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal morbidity (RDS) [5]												

Quality assessment							Number of women		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vaginal progesterone (100-400mg daily)**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	102/311 (32.8%)	131/280 (46.8%)	RR 0.67 (0.55 to 0.82)[3]	154 fewer per 1000 (from 84 fewer to 211 fewer)	⨁⨁⨁⨀ MODERATE	IMPORTANT
Perinatal morbidity (IVH) [5]												
5	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	2/80 (2.5%)	2/68 (2.9%)	RR 0.93 (0.15 to 5.75)[3]	2 fewer per 1000 (from 25 fewer to 140 more)	⨁⨁⨀⨀ LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vaginal progesterone (100-400mg daily)**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Perinatal morbidity (NEC) [5]												
5	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	1/82 (1.2%)	0/68 (0%)	RR 1.0 (0.04 to 22.43)[3]	–	⨁⨁⨀⨀ LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MID: minimal important difference; NEC: necrotising enterocolitis; RDS: respiratory distress syndrome; RR: risk ratio
1 Not reported here - included in Jarde 2017, but data came from single study (Norman 2009/STOPPIT trial) and are presented elsewhere
2 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25)
3 Assuming independence between twins
4 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
5 Unit of measurement is infant/baby, not the woman

Comparison 1b: Vaginal progesterone versus placebo in twin pregnancy (unselected)

Table 10: Clinical evidence profile for Comparison 1b: vaginal progesterone (daily 90 mg gel) versus placebo for prevention of spontaneous preterm birth in twins – meta-analysis from primary studies of twin pregnancy with any (unselected) CL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (daily 90mg gel)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Maternal mortality												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/247 (0%)	0/247 (0%)	Not calculable	RD 0.0 (-0.01 to 0.01 [1]	⨁⨁⨁⨀ MODERATE	CRITICAL
For the woman: adverse effect (infection)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/247 (0%)	0/247 (0%)	Not calculable	RD 0.0 (-0.01 to 0.01) [1]	⨁⨁⨁⨀ MODERATE	IMPORTANT
For the woman: adverse effect (haemorrhage)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	5/42 (11.9%)	3/42 (7.1%)	RR 1.67 (0.43 to 6.53)	48 more per 1000 (from 41 fewer to 395 more)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
Gestational age at birth (weeks) (better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	247	247	–	MD 0.3 lower (0.87 lower to 0.27 higher)	⨁⨁⨁⨀ MODERATE	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (daily 90mg gel)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks+days) (Better indicated by higher values) *original data presented as median and IQR												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	42	42	-	Difference: 0^{+1} higher [GA weeks^{+} days] (-0^{+4} lower to 1^{+1} higher)[6]	⊕⊕⊖⊖ LOW	CRITICAL
Gestational age at birth/death<34 weeks												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	61/247 (24.7%)	48/247 (19.4%)	RR 1.27 (0.91 to 1.77)	52 more per 1000 (from 17 fewer to 150 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Gestational age at birth/death<34wks - monochorionic twins												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	10/46 (21.7%)	14/45 (31.1%)	RR 0.7 (0.35 to 1.41)	93 fewer per 1000 (from 202 fewer to 128 more)	⊕⊕⊖⊖ LOW	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (daily 90mg gel)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth/death<34 weeks - dichorionic twins												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	51/201 (25.4%)	34/202 (16.8%)	RR 1.51 (1.02 to 2.22)	86 more per 1000 (from 3 more to 205 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Gestational age at birth <37 weeks												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	25/42 (59.5%)	27/42 (64.3%)	RR 0.93 (0.66 to 1.3)	45 fewer per 1000 (from 219 fewer to 193 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (any)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[8]	Very serious[3]	None	2/86 (2.3%)	1/85 (1.2%)	RR 1.98 (0.18 to 21.39)	12 more per 1000 (from 10 fewer to 240 more)	⊕⊕⊖⊖ LOW	CRITICAL
Perinatal mortality (intrauterine death)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	6/247 (2.4%)	4/247 (1.6%)	RR 1.5 (0.43 to 5.25)	8 more per 1000 (from 9 fewer to 69 more)	⊕⊕⊖⊖ LOW	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (daily 90mg gel)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (neonatal death)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	8/247 (3.2%)	6/247 (2.4%)	RR 1.33 (0.47 to 3.79)	8 more per 1000 (from 13 fewer to 68 more)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal morbidity (RDS)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[8]	Serious[9]	None	15/86 (17.4%)	22/85 (25.9%)	RR 0.67 (0.38 to 1.21)	85 fewer per 1000 (from 160 fewer to 54 more)	⨁⨁⨁⊖ MODERATE	IMPORTANT
Perinatal morbidity (IVH)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[8]	Very serious[3]	None	3/86 (3.5%)	1/85 (1.2%)	RR 2.97 (0.31 to 27.94)	23 more per 1000 (from 8 fewer to 317 more)	⨁⨁⊖⊖ LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone (daily 90mg gel)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal morbidity (NEC)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[8]	Very serious[3]	None	1/86 (1.2%)	2/85 (2.4%)	RR 0.49 (0.05 to 5.35)	12 fewer per 1000 (from 22 fewer to 102 more)	⨁⨁⊖⊖ LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MD: mean difference; MID: minimal important difference; NEC: necrotising enterocolitis; RD: risk difference; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation
1 There is no agreed default MID for risk differences. 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
2 Includes non-twin pregnancies (<5% triplets)
3 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses two boundaries for MID (0.8 to 1.25)
4 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID: MID=+/-1.5: calculated from +0.5SD and -0.5SD of control (placebo) arm (SD=+/- 3)
5 Not normally distributed, so reported as median and IQR: no SD to calculate imprecision
6 Not normally distributed, so reported as median and IQR: MD reported as 0^{+1} (weeks+days) and 95%CI as -0^{+4} to 1^{+1} (weeks^{+days})
7 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses upper boundary for MID: (0.8 to 1.25)
8 Unit of measurement is the infant/baby; not woman and so does not need to be downgraded for including triplet gestations
9 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25)

Comparison 2: Intramuscular progesterone versus placebo in twin pregnancy (unselected)

Table 11: Clinical evidence profile for Comparison 2: Intramuscular (17OHPC) progesterone versus placebo for preventing spontaneous preterm birth in twins – data from a systematic review of individual patient data of twin pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular (17OHPC) Progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Maternal mortality – not measured[1]												
0	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Gestational age at birth <28 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	60/1089 (5.5%)	50/944 (5.3%)	RR 0.94 (0.58 to 1.5)	3 fewer per 1000 (from 22 fewer to 26 more)	⨁⨁⊖⊖ LOW	CRITICAL
Gestational age at birth <32 weeks												
6	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	Serious[4]	None	165/1089 (15.2%)	115/944 (12.2%)	RR 1.3 (0.87 to 1.8)	37 more per 1000 (from 16 fewer to 97 more)	⨁⨁⊖⊖ LOW	CRITICAL
Gestational age at birth <37 weeks												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	726/1089 (66.7%)	587/944 (62.2%)	RR 1.1 (0.94 to 1.2)	62 more per 1000 (from 37 fewer to 124 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular (17OHPC) Progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (any) [7]												
6	Randomised trials	No serious risk of bias	Very serious[5]	No serious indirectness	Very serious[2]	None	78/2178 (3.6%)	78/1888 (4.1%)	RR 0.8 (0.33 to 1.9)	8 fewer per 1000 (from 28 fewer to 37 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Perinatal morbidity (RDS) [7]												
6	Randomised trials	No serious risk of bias	Serious[6]	No serious indirectness	Serious[4]	None	330/2178 (15.2%)	233/1888 (12.3%)	RR 1.2 (0.93 to 1.6)	25 more per 1000 (from 9 fewer to 74 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Perinatal morbidity (IVH) [7]												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	23/2178 (1.1%)	12/1888 (0.64%)	RR 1.7 (0.73 to 3.8)	4 more per 1000 (from 2 fewer to 18 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Perinatal morbidity (NEC) [7]												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	16/2178 (0.73%)	11/1888 (0.58%)	RR 1.2 (0.79 to 2.0)	1 more per 1000 (from 1 fewer to 6 more)	⊕⊕⊖⊖ LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MID: minimal important difference; NEC: necrotising enterocolitis; RDS: respiratory distress syndrome; RR: risk ratio
1 Included as outcome in Jarde 2017, but no included studies reported on maternal outcomes for mPROG
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
3 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=59 [0-83]%
4 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses upper boundary for MID (0.8 to 1.25)
5 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=70 [31-87]%
6 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=50 [0-80]%
7 Unit of measurement is an infant/baby, not the woman

Comparison 3: Intramuscular progesterone versus placebo in triplet pregnancy (unselected)

Table 12: Clinical evidence profile for: Comparison 3. Intramuscular (17OHPC) progesterone versus placebo for prevention of spontaneous preterm birth in triplets – data from a systematic review of individual patient data in triplet pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular (17OHPC) progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth <28 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	15/136 (11%)	12/96 (12.5%)	RR 0.88 (0.43 to 1.8)	15 fewer per 1000 (from 71 fewer to 100 more)	⨁⨁⨀⨀ LOW	CRITICAL
Gestational age at birth <32 weeks												
3	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	Very serious[1]	None	48/136 (35.3%)	36/96 (37.5%)	RR 0.92 (0.55 to 1.56)	30 fewer per 1000 (from 169 fewer to 210 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Gestational age at birth <34 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Serious[4]	None	86/136 (63.2%)	64/96 (66.7%)	RR 0.95 (0.78 to 1.2)	33 fewer per 1000 (from 147 fewer to 133 more)	⨁⨁⨁⨀ MODERATE	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular (17OHPC) progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (all cause) [10]												
3	Randomised trials	No serious risk of bias	Serious[5]	No serious indirectness	Very serious[1]	None	25/408 (6.1%)	14/288 (4.9%)	RR 1.3 (0.37 to 4.2)	15 more per 1000 (from 31 fewer to 156 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (neonatal death) [10]												
3	Randomised trials	No serious risk of bias	Serious[6]	No serious indirectness	Serious[6]	None	19/408 (4.7%)	4/288 (1.4%)	–	14 fewer per 1000 (from 14 fewer to 14 fewer)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal mortality (fetal death) [10]												
3	Randomised trials	No serious risk of bias	Serious[6]	No serious indirectness	Serious[6]	None	3/408 (0.74%)	6/288 (2.1%)	–	21 fewer per 1000 (from 21 fewer to 21 fewer)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal morbidity (RDS) [10]												
3	Randomised trials	No serious risk of bias	No serious inconsistency [7]	No serious indirectness	Very serious[1]	None	115/395 (29.1%)	83/278 (29.9%)	RR 0.99 (0.65 to 1.5)	3 fewer per 1000 (from 104 fewer to 149 more)	⨁⨁⊖⊖ LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular (17OHPC) progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal morbidity (IVH 3–4) [10]												
3	Randomised trials	No serious risk of bias	No serious inconsistency[8]	No serious indirectness	Very serious[1]	None	6/391 (1.5%)	7/278 (2.5%)	RR 0.37 (0.089 to 1.5)	16 fewer per 1000 (from 23 fewer to 13 more)	⨁⨁⨀⨀ LOW	IMPORTANT
Perinatal morbidity (NEC) [10]												
3	Randomised trials	No serious risk of bias	No serious inconsistency[9]	No serious indirectness	Very serious[1]	None	10/394 (2.5%)	8/278 (2.9%)	RR 0.94 (0.31 to 2.8)	2 fewer per 1000 (from 20 fewer to 52 more)	⨁⨁⨀⨀ LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; RDS: respiratory distress syndrome; RR: risk ratio
1 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25);
2 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=63%;
3 I^2=4%;
4 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25);
5 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=72%;
6 information not available;
7 I^2=44%;
8 I^2=0%;
9 I^2=23%
10 Unit of measurement is an infant/baby, not the woman

Arabin pessary

Comparison 4a: Pessary (Arabin) versus no pessary (control) in twins (unselected)

Table 13: Clinical evidence profile for: Comparison 4a: Pessary (Arabin) versus no pessary (control) for preventing spontaneous preterm birth in twins – data from a systematic review of RCTs of twin pregnancy with any (unselected) cervical length

Quality assessment							No of women (any cervical length)	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reported as total number, n	Absolute	Quality	Importance
Maternal mortality										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	795	RR 3.05 (0.12 to 74.72)	⨁⨁⨀⨀ LOW	CRITICAL
Gestational age at birth (weeks) (Better indicated by higher values)										
2	Randomised trials	No serious risk of bias	Very serious[2]	No serious indirectness	Serious[3]	None	929	MD 1.17 higher (0.68 lower to 3.03 higher)	⨁⨀⨀⨀ VERY LOW	CRITICAL
PTB <28 weeks										
3	Randomised trials	No serious risk of bias	No serious inconsistency[4]	No serious indirectness	Very serious[5]	None	2106	RR 0.84 (0.49 to 1.44)	⨁⨁⨀⨀ LOW	CRITICAL
PTB <32 weeks										
2	Randomised trials	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	Serious[7]	None	1972	RR 0.91 (0.69 to 1.19)	⨁⨁⨁O MODERATE	CRITICAL
PTB <34 weeks										
2	Randomised trials	No serious risk of bias	Very serious[8]	No serious indirectness	Very serious[5]	None	1311	RR 0.71 (0.29 to 1.71)	⨁⨀⨀⨀ VERY LOW	CRITICAL

Quality assessment							No of women (any cervical length)	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reported as total number, n	Absolute	Quality	Importance
PTB <37 weeks										
2	Randomised trials	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	No serious imprecision	None	929	RR 0.96 (0.86 to 1.07)	⊕⊕⊕⊕ HIGH	CRITICAL
Perinatal mortality (any cause) [12]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	2354	RR 0.91 (0.55 to 1.49)	⊕⊕⊖⊖ LOW	CRITICAL
Perinatal mortality (neonatal death) [12]										
3	Randomised trials	No serious risk of bias	No serious inconsistency[9]	No serious indirectness	Very serious[5]	None	4210	RR 0.89 (0.57 to 1.38)	⊕⊕⊖⊖ LOW	CRITICAL
Perinatal mortality (stillbirth) [12]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	1590	RR 0.70 (0.30 to 1.64)	⊕⊕⊖⊖ LOW	CRITICAL
Perinatal morbidity (RDS) [12]										
2	Randomised trials	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	Serious[10]	None	2559	RR 1.08 (0.84 to 1.39)	⊕⊕⊕⊖ MODERATE	IMPORTANT
Perinatal morbidity (IVH 1–4) [12]										
3	Randomised trials	No serious risk of bias	No serious inconsistency[11]	No serious indirectness	Very serious[5]	None	4149	RR 0.99 (0.49 to 2.00)	⊕⊕⊖⊖ LOW	IMPORTANT

Quality assessment							No of women (any cervical length)	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reported as total number, n	Absolute	Quality	Importance
Perinatal morbidity (NEC) [12]										
3	Randomised trials	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	Very serious[5]	none	4149	RR 1.05 (0.51 to 2.16)	⨁⨁⨀⨀ LOW	IMPORTANT

IVH: intraventricular haemorrhage; MD = mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; PTB: preterm birth; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation

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

2 The quality of the evidence was downgraded by 2 levels due to serious inconsistency (i^2>75%): I^2=88%

3 Unclear due to lack of information regarding SD

4 I^2=30%

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

6 I^2=0%

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

8 The quality of the evidence was downgraded by 2 levels due to serious inconsistency (i^2>75%): I^2=87%

9 I^2=2%

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

11 I^2=21%

12 Unit of measurement is an infant/baby, not the woman

Comparison 4b: Pessary (Arabin) versus no pessary (control) in twins (subgroup CL ≤25 mm)

Table 14: Clinical evidence profile for Comparison 4b: Pessary (Arabin) versus no pessary (control) for preventing spontaneous preterm birth in twins – data from a systematic review of RCTs of twin pregnancy subgroup with cervical length ≤25 mm

Quality assessment							No of women (any cervical length)	Effect	Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reported as total number, N	Absolute		
Gestational age at birth (weeks) (better indicated by higher values)										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	134	MD 2.20 higher (1.03 to 3.37 higher)	⊕⊕⊖⊖ LOW	CRITICAL
PTB <28 weeks										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	134	RR 0.43 (0.14 to 1.33)	⊕⊕⊖⊖ LOW	CRITICAL
PTB <34 weeks										
2	Randomised trials	No serious risk of bias	Very serious[3]	No serious indirectness	Very serious[2]	None	348	RR 0.74 (0.27 to 2.00)	⊕⊖⊖⊖ VERY LOW	CRITICAL
PTB <37 weeks										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	134	RR 0.95 (0.77 to 1.18)	⊕⊕⊕⊖ MODERATE	CRITICAL
Perinatal mortality (any death) [6]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	428	RR 1.70 (0.85 to 3.39)	⊕⊕⊕⊖ MODERATE	CRITICAL

Quality assessment							No of women (any cervical length)	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reported as total number, N	Absolute	Quality	Importance
Perinatal mortality (neonatal death) [6]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	266	RR 0.19 (0.01 to 3.95)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal morbidity (RDS) [6]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	266	RR 0.96 (0.37 to 2.47)	⨁⨁⊖⊖ LOW	1
Perinatal morbidity (IVH 1–4) [6]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	266	RR 0.11 (0.01 to 1.95)	⨁⨁⊖⊖ LOW	IMPORTANT
Perinatal morbidity (NEC) [6]										
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	266	RR 0.19 (0.01 to 3.95)	⨁⨁⊖⊖ LOW	IMPORTANT

IVH: intraventricular haemorrhage; MD = mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; PTB: preterm birth; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation
1 Unclear due to lack of information regarding SD
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
3 The quality of the evidence was downgraded by 2 levels due to serious inconsistency (i^2>75%): I^2=87%
4 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25)
5 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses upper boundary for MID (0.8 to 1.25)
6 Unit of measurement is an infant/baby, not the woman

Comparison 5: Pessary (Bioteque) versus no pessary (control) in twins (CL ≤30 mm)

Table 15: Clinical evidence profile for Comparison 5: Pessary (Bioteque) versus no pessary (control) for preventing spontaneous preterm birth in twins – data from a RCT of twin pregnancy subgroup with cervical length ≤30 mm

Quality assessment							No of women (any cervical length)		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pessary (Bioteque)	No pessary (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2,3]	None	23	23	–	Difference 0.9 higher [3,4]	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <28 weeks												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/23 (17.4%)	4/23 (17.4%)	RR 1.0 (0.28 to 3.52)	0 fewer per 1000 (from 125 fewer to 438 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <34 weeks												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	9/23 (39.1%)	8/23 (34.8%)	RR 1.13 (0.53 to 2.4)	45 more per 1000 (from 163 fewer to 487 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <37 weeks												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	19/23 (82.6%)	19/23 (82.6%)	RR 1.0 (0.76 to 1.3)	0 fewer per 1000 (from 198 fewer to 248 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL

Quality assessment							No of women (any cervical length)		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pessary (Biotequ e)	No pessary (control)	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (neonatal death) [6]												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/46 (8.7%)	3/46 (6.5%)	RR 1.33 (0.32 to 5.63)	22 more per 1000 (from 44 fewer to 302 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Perinatal morbidity (RDS) [6]												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	11/46 (23.9%)	8/46 (17.4%)	RR 1.38 (0.61 to 3.1)	66 more per 1000 (from 68 fewer to 365 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Perinatal morbidity (IVH) [6]												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/46 (4.3%)	1/46 (2.2%)	RR 2.0 (0.19 to 21.3)	22 more per 1000 (from 18 fewer to 441 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Perinatal morbidity (NEC) [6]												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[7]	None	1/46 (2.2%)	0/46 (0%)	POR 7.39 (0.15 to 372.38)	RD 0.02 (-0.04 to 0.08)	⊕⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; CL: cervical length; IQR: interquartile range; IVH: intraventricular haemorrhage; MD = mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; POR: Peto odds ratio; PTB: preterm birth; RD: risk difference; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation

1 Cochrane RoB tool - Unclear in 3 domains (allocation concealment, attrition bias, reporting bias), High in 1 domain (performance bias – unable to blind participants and personnel)

2 No RR calculable

3 No CI available
4 Median and IQR: PESSARY 35.9 (28.9-36.9) weeks, CONTROL 35.0 (33.0-36.7) weeks
5 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
6 Unit of measurement is an infant/baby, not the woman
7 There is no agreed default MID for Peto odds ratio or risk differences. 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

Bedrest

Comparison 6: Inpatient bedrest versus no bedrest/normal activity (control) in twins

Table 16: Clinical evidence profile for Comparison 6: Inpatient bedrest versus no bedrest/normal activity (control) for preventing spontaneous preterm birth in twins – data from RCTs of twin pregnancy with any (unselected) cervical length

Quality assessment							No of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	No bedrest/ normal activity (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
2	Randomised trials	No serious risk of bias[1]	No serious inconsistency[2]	No serious indirectness	No serious imprecision[3]	None	175	176	–	MD 0.3 lower (0.75 lower to 0.15 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
PTB <34 weeks												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	11/70 (15.7%)	12/69 (17.4%)	RR 0.9 (0.43 to 1.91)	17 fewer per 1000 (from 99 fewer to 158 more)	⨁⨁⊖⊖ LOW	CRITICAL
PTB <37 weeks												
2	Randomised trials	No serious risk of bias[1]	Very serious[5]	No serious indirectness	Very serious[4]	none	83/175 (47.4%)	75/176 (42.6%)	RR 1.18 (0.61 to 2.27)	77 more per 1000 (from 166 fewer to 541 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL

Quality assessment							No of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	No bedrest/ normal activity (control)	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (any)												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	8/210 (3.8%)	2/214 (0.93%)	RR 4.08 (0.88 to 18.97)	29 more per 1000 (from 1 fewer to 168 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Perinatal mortality (stillbirths) [8]												
2	Randomised trials	No serious risk of bias[1]	No serious inconsistency[7]	No serious indirectness	Very serious[4]	None	6/350 (1.7%)	4/352 (1.1%)	RR 1.52 (0.43 to 5.32)	6 more per 1000 (from 6 fewer to 49 more)	⊕⊕⊖⊖ LOW	CRITICAL
Perinatal mortality (neonatal deaths) [8]												
2	Randomised trials	No serious risk of bias[1]	No serious inconsistency[7]	No serious indirectness	Very serious[4]	None	4/350 (1.1%)	3/352 (0.85%)	RR 1.35 (0.3 to 5.96)	3 more per 1000 (from 6 fewer to 42 more)	⊕⊕⊖⊖ LOW	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimal important difference; N: number of women (unless specified as babies); PTB: preterm birth; RR: relative risk; SD: standard deviation
1 Performance bias noted - unable to blind allocation to women, but unlikely to affect this outcome
2 I^2=42%
*3 MID=+/- 1.1 (0.5*mean of SDs in control groups=0.5*2.2)*
4 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundary for MID (0.8 to 1.25)
5 The quality of the evidence was downgraded by 2 levels due to serious inconsistency (i^2>75%): I^2=84% using a random effects model due to high heterogeneity (i^2>66%, as per Methods)
6 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses upper boundary for MID (0.8 to 1.25)
7 I^2=0%
8 Unit of measurement is an infant/baby, not the woman

Comparison 7a: Inpatient bedrest versus no bedrest/normal activity (control) in triplets (RCTs)

Table 17: Clinical evidence profile for Comparison 7a: Inpatient bedrest versus no bedrest/normal activity (control) for preventing spontaneous preterm birth in triplets – data from a RCT of triplet pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	No bedrest/ normal activity (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10	9	–	MD 0.7 higher (1.43 lower to 2.83 higher)	⨁⨁⊖⊖ LOW	CRITICAL
PTB <34 weeks												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	3/10 (30%)	4/9 (44.4%)	RR 0.68 (0.2 to 2.23)	142 fewer per 1000 (from 356 fewer to 547 more)	⨁⨁⊖⊖ LOW	CRITICAL
PTB <37 weeks												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	8/10 (80%)	9/9 (100%)	RR 0.81 (0.57 to 1.15)	190 fewer per 1000 (from 430 fewer to 150 more)	⨁⨁⨁⊖ MODERATE	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	No bedrest/ normal activity (control)	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality (stillbirths) [5]												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	1/30 (3.3%)	0/27 (0%)	POR 6.69 (0.13 to 338.79)	RD 0.03 (-0.06 to 0.12)	⨁⨁⨁⊖ MODERATE	CRITICAL
Perinatal mortality (neonatal deaths) [5]												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	0/30 (0%)	3/27 (11.1%)	POR 0.11 (0.01 to 1.13)	RD -0.11 (-0.24 to 0.02)	⨁⨁⨁⊖ MODERATE	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimal important difference; N: number of women (unless specified as babies); POR: Peto odds ratio; PTB: preterm birth; RD: risk difference; RR: risk ratio; SD: standard deviation

1 Performance bias noted - unable to blind women to allocation, unlikely to affect this outcome

*2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 MID thresholds: crosses upper and lower boundary for MID=+/-1.25 (0.5*SD in control group)*

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

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

5 Unit of measurement is an infant/baby, not the woman

6 There is no agreed default MID for Peto odds ratio or risk differences. 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

Comparison 7b: Inpatient bedrest versus no bedrest/normal activity (control) in triplets (cohorts)

Table 18: Clinical evidence profile for Comparison 7b: Inpatient bedrest versus no bedrest/normal activity (control) for preventing spontaneous preterm birth in triplets – data from a cohort study of triplet pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	Normal home activity (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	55	24	–	MD 3.8 higher (1.94 to 5.66 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (any) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	21/165 (12.7%)	31/72 (43.1%)	RR 0.3 (0.18 to 0.48)	301 fewer per 1000 (from 224 fewer to 353 fewer)	⨁⨁⊖⊖ LOW	CRITICAL
Perinatal mortality (intrauterine death) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/165 (4.8%)	17/72 (23.6%)	RR 0.21 (0.09 to 0.45)	187 fewer per 1000 (from 130 fewer to 215 fewer)	⨁⨁⊖⊖ LOW	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bedrest (inpatient)**	**Normal home activity (control)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Perinatal mortality (neonatal death) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/157 (8.3%)	14/55 (25.5%)	RR 0.33 (0.16 to 0.65)	171 fewer per 1000 (from 89 fewer to 214 fewer)	⨁⨁⨀⨀ LOW	CRITICAL
Perinatal morbidity (IVH) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/157 (0%)	1/55 (1.8%)	POR 0.02 (0.00 to 1.85)	RD -0.02 (-0.06 to 0.03)	⨁⨀⨀⨀ VERY LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MD: mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; POR: Peto odds ratio; RD: risk difference; RR: risk ratio; SD: standard deviation
*1 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 MID threshold: crosses upper boundary for MID+/-2.15 (0.5*SD in control group)*
2 There is no agreed default MID for Peto odds ratio or risk differences. 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

3 Unit of measurement is an infant/baby, not the woman

Comparison 8: Inpatient bedrest versus home bedrest (control) in triplets (cohorts)

Table 19: Clinical evidence profile for Comparison 8: Inpatient bedrest versus home bedrest (control) for preventing spontaneous preterm birth in triplets – data from a cohort study of triplet pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	Home bedrest (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (Better indicated by higher values)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	51	48	–	MD 1 higher (0.1 lower to 2.1 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/102 (0.98%)	1/96 (1%)	RR 0.94 (0.06 to 14.84)	1 fewer per 1000 (from 10 fewer to 144 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal morbidity (IVH 1-4) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/102 (0.98%)	1/96 (1%)	RR 0.94 (0.06 to 14.84)	1 fewer per 1000 (from 10 fewer to 144 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Perinatal morbidity (IVH 3-4) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	0/102 (0%)	1/96 (1%)	POR 0.13 (0.00 to 6.42)	RD -0.01 (-0.04 to 0.02)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedrest (inpatient)	Home bedrest (control)	Relative (95% CI)	Absolute	Quality	Importance
Perinatal morbidity (NEC) [3]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/102 (0%)	0/96 (0%)	Not calculable	RD 0.00 (-0.02 to 0.02)	⨁⨁⊖⊖ LOW	IMPORTANT

CI: confidence interval; IVH: intraventricular haemorrhage; MD = mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; POR: Peto odds ratio; PTB: preterm birth; RD: risk difference; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation
*1 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 MID threshold: crosses upper boundary for MID=+/-1.4 (0.5*SD in control group)*
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
3 Unit of measurement is an infant/baby, not the woman
4 There is no agreed default MID for Peto odds ratio or risk differences. 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

Cervical cerclage

Comparison 9a: Cervical cerclage versus no cerclage (control) in twins (unselected)

Table 20: Clinical evidence profile for Comparison 9a: Cervical cerclage versus no cerclage (control) for preventing spontaneous preterm birth in twins – data from an RCT of twin pregnancy with any (unselected) cervical length

Quality assessment							No of women (any length of cervix)		Effect			
Number of studies	Design	Risk of bias	Inconsistency	indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
PTB <37 weeks												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10/22 (45.5%)	11/23 (47.8%)	RR 0.95 (0.51 to 1.78)	24 fewer per 1000 (from 234 fewer to 373 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (neonatal death) [3]												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8/44 (18.2%)	7/46 (15.2%)	RR 1.19 (0.47 to 3.02)	29 more per 1000 (from 81 fewer to 307 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL

CI: confidence interval; MID: minimal important difference; N: number of women (unless specified as babies); PTB: preterm birth; RoB: risk of bias; RR: risk ratio
1 RoB: unclear selection bias (-1), and high performance bias (unlikely to affect outcome)
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
3 Unit of measurement is an infant/baby, not the woman

Comparison 9b: Cervical cerclage versus no cerclage (control) in twins (CL<25 mm)

Table 21: Clinical evidence profile for Comparison 9b: Cervical cerclage versus no cerclage (control) for preventing spontaneous preterm birth in twins – data from a systematic review of individual patient data of twin pregnancy with cervical length <25 mm

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (Better indicated by higher values)												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[2]	None	24	25	–	MD 3.87 lower[3]	⊕⊕⊕⊖ MODERATE	CRITICAL
PTB <28 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Very serious[4]	None	7/24 (29.2%)	2/25 (8%)	RR 2.62 (0.72 to 9.51)[5]	130 more per 1000 (from 22 fewer to 681 more)	⊕⊕⊖⊖ LOW	CRITICAL
PTB <32 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[6]	None	11/24 (45.8%)	4/25 (16%)	RR 2.48 (0.96 to 6.37)[7]	237 more per 1000 (from 6 fewer to 859 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
PTB <34 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency[8]	No serious indirectness	Very serious[4]	None	15/24 (62.5%)	6/25 (24%)	RR 2.19 (0.72 to 6.63)	286 more per 1000 (from 67 fewer to 1000 more)	⊕⊕⊖⊖ LOW	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
PTB <37 weeks												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[6]	None	22/24 (91.7%)	19/25 (76%)	RR 1.18 (0.91 to 1.53)[9]	137 more per 1000 (from 68 fewer to 403 more)	⨁⨁⨁⊖ MODERATE	CRITICAL
Perinatal mortality [13]												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[6]	None	11/48 (22.9%)	3/50 (6%)	RR 2.66 (0.83 to 8.54)[12]	100 more per 1000 (from 10 fewer to 452 more)	⨁⨁⨁⊖ MODERATE	CRITICAL
Perinatal morbidity (RDS) [13]												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	No serious imprecision	None	15/48 (31.3%)	3/50 (6%)	RR 5.07 (1.75 to 14.7)[10]	244 more per 1000 (from 45 more to 822 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
Perinatal morbidity (IVH) [13]												
3	Randomised trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Very serious[4]	None	3/48 (6.3%)	3/50 (6%)	RR 1.13 (0.27 to 4.74)[11]	8 more per 1000 (from 44 fewer to 224 more)	⨁⨁⊖⊖ LOW	IMPORTANT

aOR: adjusted odds ratio; CI = confidence interval; CL: cervical length; IVH: intraventricular haemorrhage; MD: mean difference; MID: minimal important difference; N: number of women (unless specified as babies); PTB: preterm birth; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation
1 Not possible to assess inconsistency as no data reported
2 No SD to calculate MID, no CI to assess imprecision
3 No SDs or 95%CI reported; actual data CERCLAGE 30.33 weeks, CONTROL 34.2 weeks, significance p=0.007
4 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
5 aOR=1.66[0.62-4.01] - adjusted for previous PTB and gestational age at randomisation
6 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses upper boundary for MID (0.8 to 1.25)
7 aOR=1.77[0.88-3.39] - adjusted for previous PTB and gestational age at randomisation
8 I^2=36%
9 aOR=1.13[0.17-8.66] - adjusted for previous PTB and gestational age at randomisation
10 aOR=3.88[1.09-21.03] - adjusted for previous PTB and gestational age at randomisation
11 aOR=1.09[0.21-4.98] - adjusted for previous PTB and gestational age at randomisation
12 aOR=2.04[0.55-8.32] - adjusted for previous PTB and gestational age at randomisation
13 Unit of measurement is an infant/baby, not the woman

Comparison 10a: Cervical cerclage versus no cerclage (control) in triplets (unselected)

Table 22: Clinical evidence profile for Comparison 10a: Cervical cerclage versus no cerclage (control) for preventing spontaneous preterm birth in triplets – data from cohort studies of triplet pregnancy with any (unselected) cervical length

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
5	Observational studies	Very serious[1]	Serious[2]	Serious[3]	No serious imprecision[4]	None	429	3184	–	MD 0.02 lower (0.31 lower to 0.27 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Gestational age at birth (weeks) –Cerclage/suture before gestational age 18 weeks (better indicated by higher values)												
4	Observational studies	Very serious[5]	Serious[6]	Serious[3]	No serious imprecision[7]	None	181	154	–	MD 0.4 lower (1 lower to 0.2 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Gestational age at birth (weeks) –Cerclage/suture "before 32 weeks gestational age" (average 23 weeks) (better indicated by higher values)												
1	Observational studies	Very serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision[8]	None	248	3030	–	MD 0.1 higher (0.24 lower to 0.44 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Gestational age at birth (weeks) –(measured with: median and IQR; better indicated by higher values)												
1	Observational studies	No serious risk of bias[18]	No serious inconsistency	No serious indirectness	Serious[19]	None	91	50	–	Cerclage (TAC and TVC) both less than Control	⨁⊖⊖⊖ VERY LOW	CRITICAL

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute		
										(wide IQR)[20]		
PTB <28 weeks												
4	Observational studies	Very serious[5]	Serious[9]	Serious[3]	Serious[10]	None	68/488 (13.9%)	154/3172 (4.9%)	RR 1.36 (0.95 to 1.96)	17 more per 1000 (from 2 fewer to 47 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <28 weeks – Cerclage/suture before gestational age 18 weeks												
3	Observational studies	No serious risk of bias	Serious[11]	Serious[3]	Serious[10]	None	58/240 (24.2%)	18/142 (12.7%)	RR 1.76 (1.12 to 2.77)	96 more per 1000 (from 15 more to 224 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <28 weeks – Cerclage/suture "before 32 weeks gestational age" (average 23 weeks)												
1	Observational studies	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[12]	None	10/248 (4%)	136/3030 (4.5%)	RR 0.9 (0.48 to 1.69)	4 fewer per 1000 (from 23 fewer to 31 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <32 weeks												
4	Observational studies	Very serious[5]	No serious inconsistency[13]	No serious indirectness	Serious[14]	None	113/414 (27.3%)	876/3159 (27.7%)	RR 0.95 (0.79 to 1.15)	14 fewer per 1000 (from 58 fewer to 42 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <32 weeks – Cerclage/suture before gestational age 18 weeks												
3	Observational studies	No serious	No serious	No serious	Serious[14]	None	45/166 (27.1%)	43/129 (33.3%)	RR 0.83 (0.57 to 1.21)	57 fewer per 1000 (from 143	⨁⊖⊖⊖ VERY LOW	CRITICAL

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute		
		risk of bias	inconsistency[15]	indirectness						fewer to 70 more)		
PTB <32 weeks – Cerclage/suture "before 32 weeks gestational age" (average 23 weeks)												
1	Observational studies	Very serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	68/248 (27.4%)	833/3030 (27.5%)	RR 1 (0.81 to 1.23)	0 fewer per 1000 (from 52 fewer to 63 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <34 weeks												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious[3]	Serious[10]	None	80/94 (85.1%)	31/52 (59.6%)	RR 1.43 (1.12 to 1.81)	256 more per 1000 (from 72 more to 483 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <37 weeks												
2	Observational studies	No serious risk of bias	No serious inconsistency[13]	No serious indirectness	No serious imprecision	None	110/111 (99.1%)	89/89 (100%)	RR 1 (0.96 to 1.03)	0 fewer per 1000 (from 40 fewer to 30 more)	⨁⊖⊖⊖ LOW	CRITICAL
Perinatal mortality (any) [21]												
3	Observational studies	Very serious[1]	No serious inconsistency[16]	No serious indirectness	Very serious[12]	None	10/840 (1.2%)	73/9276 (0.79%)	RR 1.02 (0.54 to 1.92)	0 more per 1000 (from 4 fewer to 7 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (any) – Cerclage/suture before gestational age 18 weeks [21]												
2	Observational studies	Very serious[5]	No serious	No serious	Very serious[12]	None	3/96 (3.1%)	11/186 (5.9%)	RR 0.59 (0.18 to 1.87)	24 fewer per 1000 (from 48	⨁⊖⊖⊖ VERY LOW	CRITICAL

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute		
			inconsistency[17]	indirectness						fewer to 51 more)		
Perinatal mortality (any) – Cerclage/suture "before 32 weeks gestational age" (average 23 weeks) [21]												
1	Observational studies	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[12]	None	7/744 (0.94%)	62/9090 (0.68%)	RR 1.38 (0.63 to 3)	3 more per 1000 (from 3 fewer to 14 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Perinatal mortality (intrauterine death) [21]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[12]	None	5/273 (1.8%)	2/150 (1.3%)	RR 1.37 (0.27 to 6.99)	5 more per 1000 (from 10 fewer to 80 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Perinatal morbidity (RDS) [21]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[14]	None	11/60 (18.3%)	32/117 (27.4%)	RR 0.67 (0.36 to 1.23)	90 fewer per 1000 (from 175 fewer to 63 more)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Perinatal morbidity (IVH) [21]												
2	Observational studies	No serious risk of bias	No serious inconsistency[13]	No serious indirectness	Serious[14]	None	12/333 (3.6%)	28/267 (10.5%)	RR 0.5 (0.26 to 0.95)	52 fewer per 1000 (from 5 fewer to 78 fewer)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Perinatal morbidity (IVH) – IVH any grade [21]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[12]	None	6/60 (10%)	19/117 (16.2%)	RR 0.62 (0.26 to 1.46)	62 fewer per 1000 (from 120	⊕⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute		
										fewer to 75 more)		
Perinatal morbidity (IVH) – IVH Grade 3–4 [21]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[14]	None	6/273 (2.2%)	9/150 (6%)	RR 0.37 (0.13 to 1.01)	38 fewer per 1000 (from 52 fewer to 1 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; IQR: interquartile range; IVH: intraventricular haemorrhage; MD = mean difference; MID: minimal important difference; N: number of women (unless specified as babies); NEC: necrotising enterocolitis; PTB: preterm birth; RDS: respiratory distress syndrome; RR: risk ratio; SD: standard deviation; TAC: transabdominal cerclage; TVC: transvaginal cerclage

1Two studies scored POOR using Newcastle Ottowa (both 0/2 for comparability at baseline)
2 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=62%
3 Includes one study where 10% of population had higher order pregnancies (quadruplets and quintuplets)
*4 MID=+/-1.35 (0.5*medianSD of controls=0.5*2.7)*
5 One study scored POOR using Newcastle Ottowa (0/2 for comparability at baseline)
6 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=65%
*7 MID=+/-1.375 (0.5*medianSD of controls=0.5*2.75)*
*8 MID=+/-1.25 (0.5*SD in control group)*
9 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=60%
10 The quality of the evidence was downgraded by 1 level because the 95% CI crosses default MID threshold: crosses upper boundary for MID (0.8 to 1.25)
11 The quality of the evidence was downgraded by 1 level due to serious inconsistency (i^2>50%): I^2=57%
12 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
13 I^2=0%
14 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary for MID (0.8 to 1.25)
15 I^2=23%
16 I^2=1%
17 I^2=17%
18 Newcastle Ottawa assessed as GOOD quality
19 No SD or CI to calculate MID and assess imprecision
20 Median and IQR: CERCLAGE/TAC 33.1 (2.7) weeks, CERCLAGE/TVC 32.6 (3.6) weeks, CONTROL 33.6 (4.0) weeks
21 Unit of measurement is an infant/baby, not the woman

Comparison 10b: Cervical cerclage versus no cerclage (control) in triplets (CL ≤25 mm)

Table 23: Clinical evidence profile for: Comparison 10b: Cervical cerclage versus no cerclage (control) for preventing spontaneous preterm birth in triplets – data from a cohort study of triplet pregnancy with cervical length ≤25 mm

Quality assessment							No of women (CL </=25 mm)		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage (control)	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	164	85	–	Difference 1.5 higher[6,7]	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <28 weeks												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	3/16 (18.8%)	1/8 (12.5%)	RR 1.5 (0.18 to 12.22)	62 more per 1000 (from 102 fewer to 1000 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PTB <32 weeks												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10/16 (62.5%)	6/8 (75%)	RR 0.83 (0.48 to 1.45)	128 fewer per 1000 (from 390 fewer to 338 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL

CI = confidence interval; CL: cervical length; IQR: interquartile range; MID: minimal important difference; N: number of women (unless specified as babies); PTB: preterm birth; RR: risk ratio; SD: standard deviation
1 Using Newcastle-Ottawa, Quality rated as POOR (0/2 for comparability at baseline)
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25)
3 No SD available to calculate MID (presented as IQR)
4 n=48 infants
5 n=24 infants
6 Median (IQR): CERCLAGE 31.3 (29.3-32.3), CONTROL 29.8 (27.5-32.4) weeks

Oral tocolytics

Comparison 11: Ritodrine (oral tocolytics) versus placebo in twins

Table 24: Clinical evidence profile for: Comparison 11 Ritodrine (oral tocolytics) versus placebo for preventing spontaneous preterm birth in twins – data from an RCT of twin pregnancy with any (unselected) cervical length

Quality assessment							No of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral tocolytics (Ritodrine)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Gestational age at birth (weeks) (better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	25	23	–	MD 1 higher (0.02 lower to 2.02 higher)	⨁⨁⨁⊖ MODERATE	CRITICAL
PTB <37 weeks												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	5/25 (20%)	10/23 (43.5%)	RR 0.46 (0.18 to 1.15)	235 fewer per 1000 (from 357 fewer to 65 more)	⨁⨁⨁⊖ MODERATE	CRITICAL

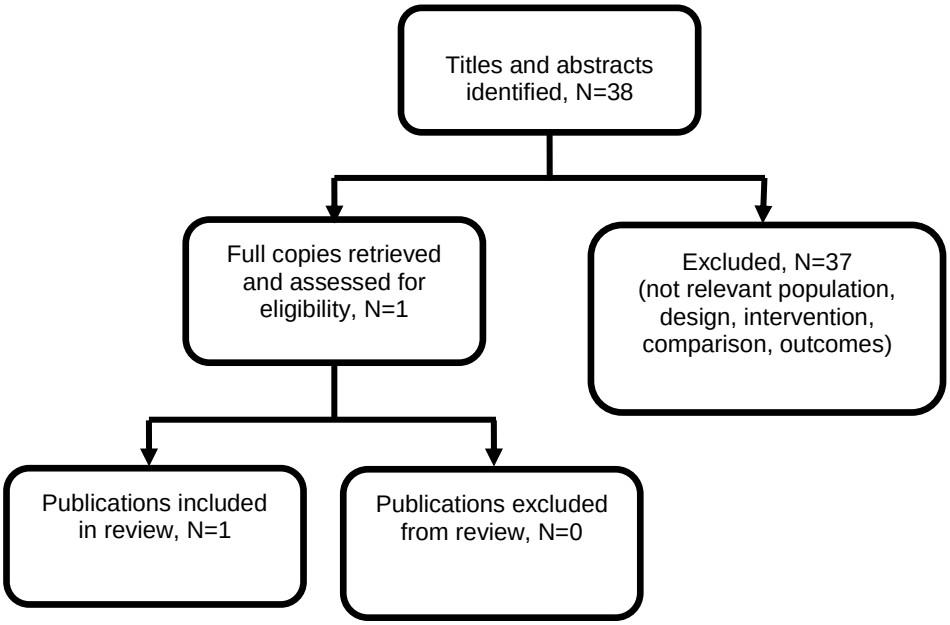
Quality assessment							No of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral tocolytics (Ritodrine)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality [5]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	0/50 (0%)	1/48 (2.1%)	POR 0.13 (0.00 to 6.55)	RD -0.02 (-0.08 to 0.03)	⨁⨁⨁⨀ MODERATE	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimal important difference; N: number of women (unless specified as babies); POR: Peto odds ratio; PTB: preterm birth; RD: risk difference; RR: risk ratio
*1 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 MID threshold: crosses upper boundary of MID=+/-1.05 (0.5*SD in control group)*
2 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold: crosses lower boundary of MID (0.8 to 1.25)
3 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds: crosses upper and lower boundaries for MID (0.8 to 1.25) 4 unit of measurement is an infant/baby, not the woman
4 There is no agreed default MID for Peto odds ratio or risk differences. 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
5 The unit of measurement was the infant/baby

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Figure 4: Flow diagram of economic article selection for interventions that are effective in preventing spontaneous preterm birth in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence tables for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Table 25: Health economic evidence tables for interventions that are effective in preventing spontaneous preterm birth in twin and triplet pregnancy

Study Country Study type	Intervention details	Study population Study design Data sources	Costs: description and values Outcomes: description and values	Results: Cost-effectiveness	Comments
Liem 2014 Netherlands Cost effectiveness analysis Conflict of interest: none Funding: ZonMW (the Netherlands Organisation for Health Research and Development healthcare efficiency programme).	Cervical pessary inserted at a gestational age of 16-20 weeks versus no cervical pessary	Women with a multiple pregnancy Modelling: Economic evaluation alongside RCT Source of clinical effectiveness data: ProTWIN RCT Source of resource use data: unclear Source of unit costs: Dutch costing guideline, top-down calculation, Dutch Health Authority Tariff, PROBAAT trial, Dutch Pharmacotherapeutic Compass	Costs: pessary, tocolysis, corticosteroids, antibiotics, ultrasound examinations, laser treatment, amniodrainage, admission, delivery, packed cells, maternal admission, neonatal admission, extra neonatal care/radiology, travel costs, productivity losses Mean cost per woman: • no pessary: €17,464 • pessary: €17,445 • difference: -€94 Primary measure of outcome: poor perinatal outcomes Mean cases per woman: • no pessary: 0.13 • pessary: 0.14 • difference: -0.01	No statistically significant differences in mean costs or poor perinatal outcomes Cervical pessary dominant strategy in subgroup of women with a cervical length < 38 mm Sensitivity analysis: The findings were not sensitive to changes in unit costs	Perspective: Societal Currency: Euros Cost year: 2011 Time horizon: 16 weeks gestation to 6 weeks postpartum Discounting: not applicable Applicability: partially applicable Quality: potentially serious limitations

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Table 26: Health economic evidence profile for interventions that are effective in preventing spontaneous preterm birth in twin and triplet pregnancy

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost effectiveness	Uncertainty
Liem 2014 Netherlands	Potentially serious limitations[1]	Partially applicable[2]	Cost effectiveness analysis Outcome measure: Poor perinatal outcomes avoided	-€94 per woman	100 per 100,000 women	No statistically significant differences in mean costs or poor perinatal outcomes Cervical pessary dominant strategy in subgroup of women with a cervical length < 38 mm	The analysis adopts a short term horizon when many of the poor perinatal outcomes have a long term impact. Confidence intervals for costs are very wide and the outcomes are based on an RCT that concluded that prophylactic use of a pessary failed to demonstrate a benefit in unselected women with a multiple pregnancy

1. No QALYs, small sample size for subgroup where analysis suggests intervention maybe cost effectiveness, wide confidence intervals
2. Dutch costs may not be applicable to NHS setting, societal rather than health service perspective

Appendix J – Economic analysis

Economic analysis for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Modelling cost utility of cervical length screening and vaginal progesterone treatment to prevent preterm birth in twin pregnancies

Introduction

Twin pregnancies are associated with increased perinatal morbidity and mortality. Spontaneous preterm birth is the major contributor to these adverse outcomes. If women with twin pregnancies at higher risk of preterm birth could be identified and an effective intervention could be used to delay or prevent preterm birth, with resultant reductions in the associated adverse events, this could be cost effective to the NHS due to the high costs of neonatal care for premature infants and would represent good value for money by improving the survival rates and long term health of infants from multiple pregnancies.

In the previous NICE guideline, Multiple pregnancy: antenatal care for twin and triplet pregnancies (CG129) it was recommended that screening for preterm birth by ultrasound cervical length measurement should not be used routinely to predict the risk of spontaneous preterm birth in twin pregnancies as at the time there was insufficient evidence to indicate that there was an effective, evidence-based intervention that would reduce the risk of preterm birth.

However, new evidence, specifically from a meta-analysis of individual patient data (Romero, 2017) focused upon the use of vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in twins with a short cervix, has been identified since the publication of CG129. These data focus on screening for the risk of spontaneous preterm birth and treatment to prevent spontaneous preterm birth in the identified at risk population (see also evidence review [B1] which provides a synthesis of these data).

The prevention of preterm birth in twins and triplets was identified as the most important health economic priority for the guideline as recommendations could potentially have an important resource impact to the NHS if they lead to a change from current practice. No health economic literature published since the previous guideline was identified and therefore an original analysis was undertaken for this guideline update. The model developed for the guideline addressed both screening to predict the risk of spontaneous preterm birth and treatment to prevent it in those women identified at risk by screening. This is because the cost effectiveness of screening and treatment are not interdependent, with the effectiveness of screening being determined by the availability of efficacious treatment and the cost-effectiveness of treatment being in part determined by the costs of identifying a sub-group of the population who would benefit most from that treatment.

Methods

Setting and population

The model setting was for the NHS and the population was pregnant women with a twin pregnancy (there was insufficient evidence for triplet pregnancies to be included in the analysis). The time horizon was largely focused on the pregnancy and neonatal period, but a 2-year horizon was adopted for post-discharge NHS costs and a lifetime horizon was adopted with respect to mortality and lifelong morbidity of the babies arising from adverse health outcomes, such as cerebral palsy

Model structure

A cohort Markov decision analytic model was developed in Microsoft Excel® to evaluate the cost effectiveness of cervical length screening and vaginal progesterone treatment to prevent or delay spontaneous preterm birth in twin pregnancies, reflecting the new clinical evidence identified for this guideline on effective screening and treatment to prevent preterm birth.

A total of 6 screening strategies, including no screening, were compared in the analysis:

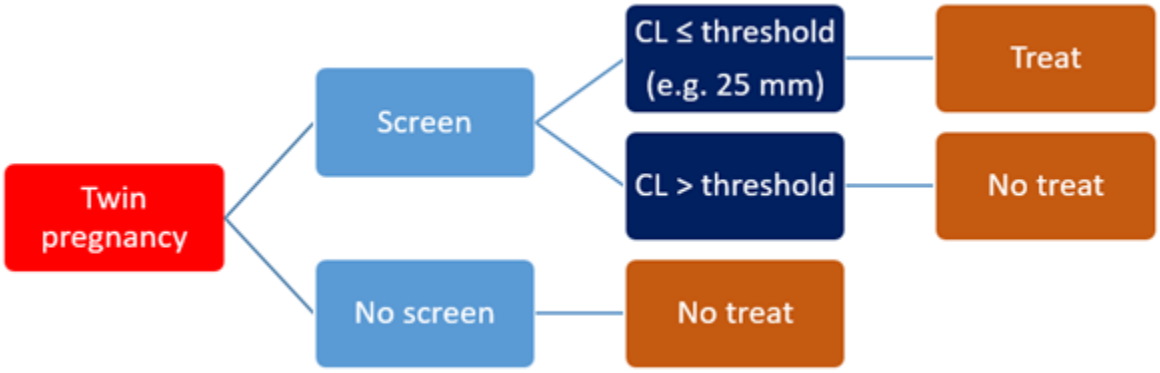
1. no screening
2. cervical length ≤ 5mm
3. cervical length ≤ 10mm
4. cervical length ≤ 15mm
5. cervical length ≤ 20mm
6. cervical length ≤ 25 mm

These screening thresholds were chosen as there was a recently published study (Kindinger, 2016) which gives data on the probability of spontaneous preterm birth at different gestational ages for women with these cervical lengths and because a new individual patient data meta-analysis (Romero, 2017 – see the clinical evidence section above and appendix D for details of this study) has demonstrated a treatment benefit of vaginal progesterone in women with a cervical length of 25 mm or below.

Screening and the starting point of progesterone therapy (if indicated) was assumed to take place by gestational age of 21 weeks as the committee agreed that if cervical length screening was assessed during the mid-trimester fetal anomaly scan it would avoid an extra visit to the hospital.

For those pregnancies identified by the screening strategy as at higher risk of preterm birth, the model evaluated the benefits of vaginal progesterone treatment continued until birth, in terms of delay or prevention of preterm birth. A schematic illustrating how screening was used as the basis for treatment is depicted in Figure 5.

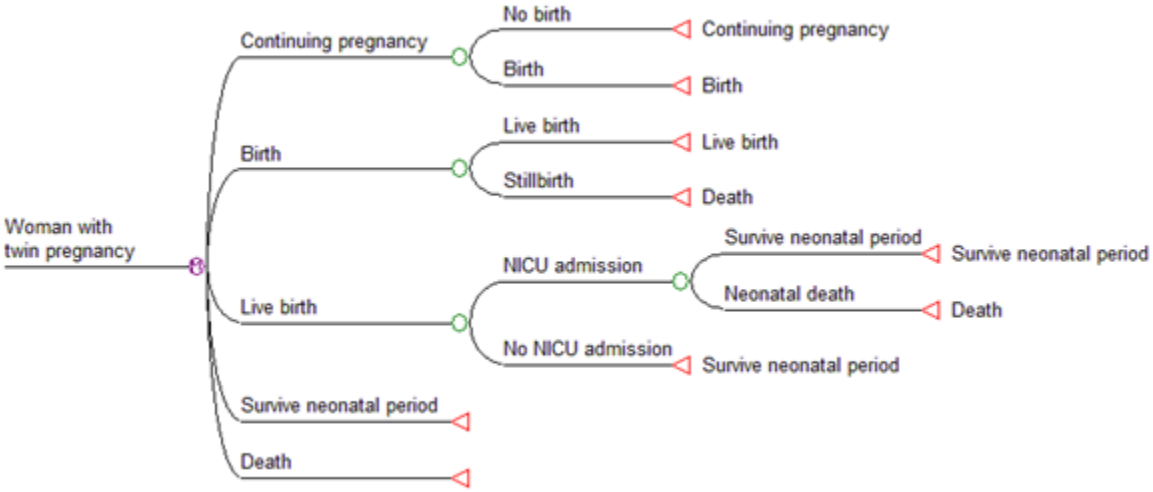
Figure 5: Schematic chart to illustrate decision analytic approach of screening by cervical length to identify women at higher risk of preterm birth for treatment



From a gestational age of 24 weeks to 37 weeks a Markov approach was used to model the impact of vaginal progesterone on the timing of birth and neonatal outcomes linked to prematurity and this is shown in Figure 6. The model assumes that all twin pregnancies will have resulted in birth by a gestational age of 37 weeks.

Pregnant women with twins enter the model in a health state of 'continuing pregnancy' but for each week of gestation, the Markov cycle duration, they can transition to the state of 'birth'. This Markov process serves as the 'birth engine' in the model with the transition probabilities dependant on gestational age, the distribution of cervical length across the model population, the probability of preterm birth at each gestational age by cervical length, the screening strategy and the effectiveness of treatment to prevent preterm birth in the women identified for treatment by screening. Figure 6 also highlights the health state transitions from 'birth' which are used to quantify the probability of various adverse neonatal outcomes, with these probabilities being tied with gestational age at birth.

Figure 6: Schematic to illustrate Markov approach across pregnancy and the neonatal period



For babies surviving the neonatal period a basic decision analytic approach was used to assess the impact of longer term morbidity on health related quality of life and "downstream" costs. Figure 7, based on a published UK study (Khan, 2015) on costs associated with moderate and late preterm birth, shows the decision tree used to estimate the costs incurred by the NHS in the 2 years post-discharge for babies surviving the neonatal period. Figure 8 illustrates the decision analytic structure used to analyse the longer term impact of morbidity arising from adverse neonatal outcomes.

Figure 7: Schematic to illustrate decision analytic approach used to estimate costs incurred by the NHS in the 2 years from initial discharge from hospital

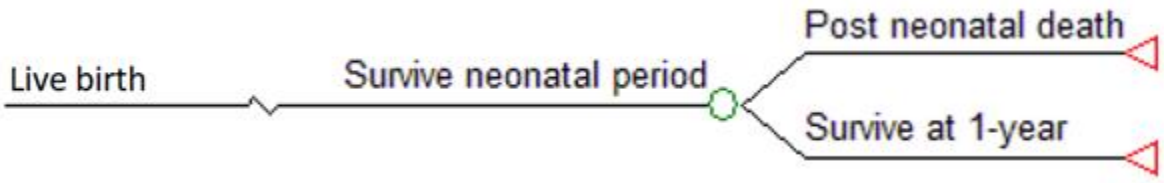
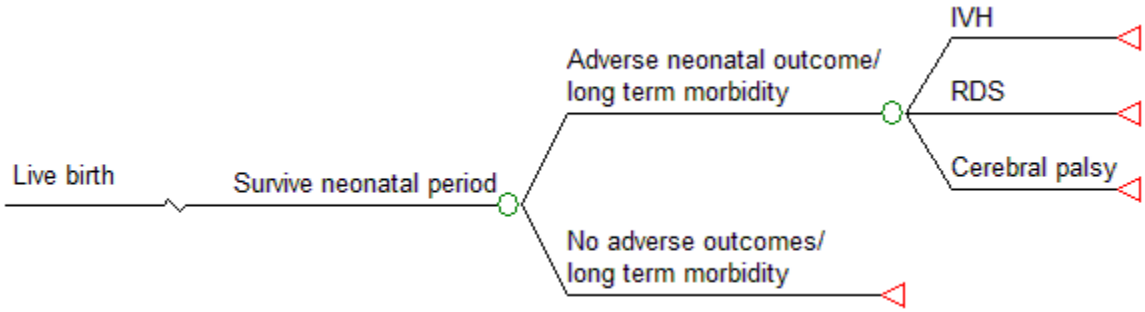


Figure 8: Schematic to illustrate decision analytic approach to long term morbidity arising from adverse neonatal outcomes



IVH = intraventricular haemorrhage; RDS = respiratory distress syndrome

Distribution of cervical length in twin pregnancies

The model required that the distribution of cervical length be estimated across the population, women with a twin pregnancy, at a gestational age of 21 weeks, the time of screening. This determined the proportion of women who would receive treatment as a result of a particular screening strategy. It was possible to populate the model with any one of 3 distributions of cervical length, all estimated either from personal communication or the published literature. These distributions are summarised in Table 27 and Figure 9 below. Liem (personal communication, 2018[b]) was used for the distribution of cervical length in the base case analysis as measurement of cervical length was most closely aligned with the gestational age that screening would occur. In addition, it was also least favourable to strategies screening for preterm birth as less women would be identified for treatment and is therefore the most conservative of the three.

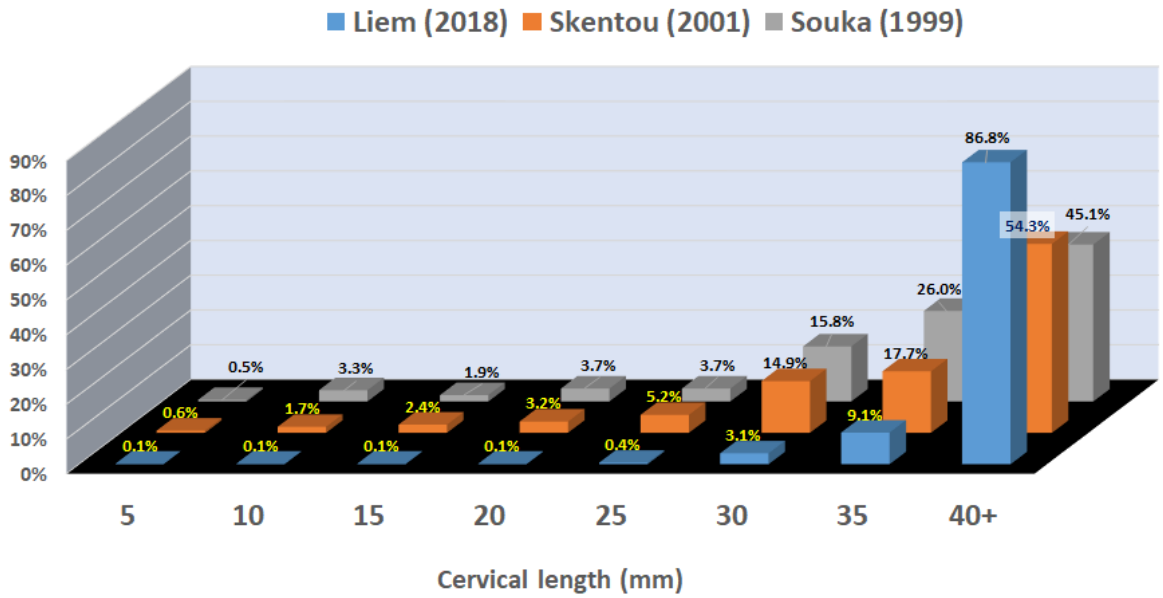
Table 27: Distribution of cervical length in twin pregnancies at approximate gestational age of screening[a]

Cervical length (mm)	Liem (2018)[b]	Skentou (2001)[c]	Souka (1999)[d]
5	0.14%	0.65%	0.47%
10	0.14%	1.72%	3.26%
15	0.14%	2.37%	1.86%
20	0.14%	3.23%	3.72%
25	0.43%	5.17%	3.72%
30	3.13%	14.87%	15.81%
35	9.09%	17.67%	26.05%
40+	86.79%	54.31%	45.12%

(a) All percentages had to be estimated from charts
(b) Based on a gestational age of 18-22 weeks
(c) Based on a gestational age of 23 weeks
(d) Based on a gestational age of 23 weeks

[b] The communication was by e-mail correspondence between the guideline topic advisor and Dr Sophie Liem, an obstetrician, who has published on cervical length distribution (https://www.ajog.org/article/S0002-9378(17)32042-2/pdf)

Figure 9: Chart to show model distribution of cervical length in twin pregnancies at the time of screening



For probabilistic sensitivity analysis cervical length distributions were sampled using a Dirichlet distribution. A count was made for each distribution using the observed frequencies reported in Table 28 and sampled using a cumulative gamma function. The sampled cervical length proportion was calculated as its sample count ÷ sum of the sample count for all cervical length categories.

Table 28: Frequency of cervical length used to sample the distribution of cervical length in probabilistic analysis

Cervical length	Liem (2018)	Skentou (2001)	Souka (1999)
5mm	1	3	1
10mm	1	8	7
15mm	1	11	4
20mm	1	15	8
25 mm	3	24	8
30mm	22	69	34
35mm	64	82	56
≥40mm	611	252	97
Count	**704**	**464**	**215**

Clinical outcomes

Women with twin pregnancies are at higher risk of preterm birth than women with singleton pregnancies and most of the excess morbidity and mortality of a twin pregnancy arise from this increased rates of premature birth. Delay or prevention of spontaneous preterm birth improves outcomes for babies by mitigating the adverse impact of prematurity. Therefore, the clinical outcomes assessed in the model, listed below, are important outcomes for babies related to preterm birth.

- Stillbirth
- Neonatal death
- Post neonatal death
- Neonatal intensive care unit admission
- Cerebral palsy
- Intraventricular haemorrhage
- Respiratory distress syndrome

These outcomes all have a potentially large impact on health related quality of life and/or NHS costs.

Baseline

The model defines a relationship between all the assessed clinical outcomes and gestational age at birth. The baseline risk of these outcomes is thus determined from the twin birth rate by gestational age in the absence of treatment. The twin birth rate by gestational age and cervical length is estimated using the 'birth engine' developed for this model which is described in detail below. Treatment effects the baseline risk of these outcomes by changing the distribution of births by gestational age.

The "birth engine"

The model 'birth engine' represents the Markov process used to estimate the rate of twin births by gestational age as women in the model cohort transition from a health state of 'continuing pregnancy' to a state of 'birth' over gestational ages 24-37 weeks.

The screening strategies mean that the decision to treat is based on cervical length and therefore it was important to model the twin birth rate by gestational age according to cervical length at the time of screening. A recently published paper (Kindinger, 2016) allowed these estimates to be made with this data summarised in Table 29.

Table 29: Proportion of spontaneous birth by gestational age and cervical length[a]

	Gestational age			
Cervical length	<28 weeks	28 – 32 weeks	32-36 weeks	37 weeks
5 mm	0.475	0.382	0.119	0.023
10 mm	0.461	0.385	0.119	0.035
15 mm	0.386	0.392	0.160	0.062
20 mm	0.308	0.381	0.206	0.105
25 mm	0.230	0.348	0.258	0.166

Cervical length	Gestational age			
	<28 weeks	28 – 32 weeks	32-36 weeks	37 weeks
30 mm	0.164	0.301	0.285	0.251
35 mm	0.108	0.241	0.302	0.350
40 mm	0.066	0.180	0.299	0.454

(a) Table data based on predicted probabilities reported in a published study (Kindinger, 2016) at a gestational age of 22 weeks

Table 30 illustrates how the data in Table 29 translates into transitions from the health state of 'continuing pregnancy' to 'twin birth' from a gestational age of 24-37 weeks by cervical length.

Table 30: Health state transition from 'continuing pregnancy'

Health state	Gestational age				
	Start	24-28 weeks	28-32 weeks	32-36 weeks	37 weeks
Cervical length = 5mm					
Continuing pregnancy	1.000	0.525	0.143	0.023	0.000
Twin birth	0.000	0.475	0.858	0.977	1.000
Cervical length = 10 mm					
Continuing pregnancy	1.000	0.539	0.154	0.035	0.000
Twin birth	0.000	0.461	0.846	0.965	1.000
Cervical length = 15 mm					
Continuing pregnancy	1.000	0.614	0.222	0.062	0.000
Twin birth	0.000	0.386	0.778	0.938	1.000
Cervical length = 20 mm					
Continuing pregnancy	1.000	0.692	0.311	0.105	0.000
Twin birth	0.000	0.308	0.689	0.895	1.000
Cervical length = 25 mm					
Continuing pregnancy	1.000	0.771	0.423	0.166	0.000
Twin birth	0.000	0.230	0.577	0.835	1.000
Cervical length = 30 mm					
Continuing pregnancy	1.000	0.836	0.536	0.251	0.000
Twin birth	0.000	0.164	0.465	0.749	1.000
Cervical length = 35 mm					
Continuing pregnancy	1.000	0.892	0.652	0.350	0.000
Twin birth	0.000	0.108	0.349	0.650	1.000
Cervical length = 40 mm					
Continuing pregnancy	1.000	0.934	0.754	0.454	0.000
Twin birth	0.000	0.066	0.247	0.546	1.000

However, Kindinger (2016) does not give a prediction of the spontaneous birth probabilities by gestational age for women with a cervical length greater than 40mm. Therefore, we additionally used data reported in a Japanese study (Kato 2004), summarised in Table 31, to estimate the twin birth rate by gestational age across the whole cohort. For probabilistic

analysis the proportion of twin births at any given age was sampled using a Dirichlet distribution using the frequencies reported in Table 31. The model assumptions about the birth rates by gestational age for women with a cervical length greater than 25 mm are trivial in some respects as these women do not get treated under any of the screening strategies and therefore do not contribute to any differences in incremental costs or quality adjusted life years (QALYs) between the different strategies.

Table 31: Twin births by gestational age

Gestational age (weeks)	Twin births	Proportion	Cumulative frequency
24	140	0.0022	0.0022
25	232	0.0036	0.0058
26	221	0.0034	0.0092
27	321	0.0050	0.0142
28	404	0.0063	0.0205
29	415	0.0064	0.0269
30	596	0.0093	0.0362
31	752	0.0117	0.0479
32	1,222	0.0190	0.0669
33	1,750	0.0272	0.0941
34	2,722	0.0423	0.1364
35	4,428	0.0688	0.2052
36	8,389	0.1304	0.3355
37[a]	42,673	0.6645	1.0000

(a) This includes all births in the Japanese data that occurred at 37 weeks or later. These births were all grouped together as our model made the simplifying assumption that twin pregnancies would not continue beyond 37 weeks.

The model assumed that the relative distribution of twin births by each week of gestational age within the gestational age bands reported in Table 29 could be approximated using the data in Table 31. So, for example, in Table 31 a total of 1,318 births occur between a gestational age of 24 and 28 weeks. Within that period 140 births occur at a gestational age of 24 weeks, 10.6% of all births between 24 and 28 weeks. Therefore the model assumes that 10.6% of all births that occur between 24 and 28 weeks, reported in the second column of Table 29, occur at a gestational age of 24 weeks. For example, the derivation of twin birth rate for each week of gestational age for women with a cervical length of 25 mm at the time of screening is illustrated in Table 32.

Table 32: Model estimate of twin birth rate by gestational age for women with a cervical length of 25 mm at the time of screening

Gestational age weeks	Twin birth rate
24	0.230 x 0.106 = 0.024
25	0.230 x 0.176 = 0.040
26	0.230 x 0.168 = 0.039
27	0.230 x 0.244 = 0.056
28	0.230 x 0.307 = 0.071

Gestational age weeks	Twin birth rate
29	0.348 x 0.139 = 0.048
30	0.348 x 0.200 = 0.070
31	0.348 x 0.252 = 0.088
32	0.348 x 0.409 = 0.142
33	0.258 x 0.101 = 0.026
34	0.258 x 0.157 = 0.041
35	0.258 x 0.256 = 0.066
36	0.258 x 0.485 = 0.125
37	0.166 x 1.000 = 0.166

Using data on the distribution of cervical length in women with a twin pregnancy, derived from the data shown in Table 29 and Figure 9, it was possible to calculate the proportion of births accounted for by women with a cervical length of 5mm, 10mm, 15mm, 20mm and 25 mm at each week of gestational age.

Stillbirth by gestational age

Table 33 summarises the 2016 data for stillbirths in England and Wales by gestational age at birth (ONS, 2017). This data is for all pregnancies but it was assumed in the model that stillbirth rate was only a function of gestational age and that a twin birth was not at any increased risk of stillbirth at any given gestational age when compared with a singleton birth. Of course, even under this assumption, the risk of stillbirth is greater with a twin pregnancy because of the greater risk of prematurity.

Table 33: Live and stillbirths by gestational age at birth

Gestational age	Stillbirths	All births	Stillbirth rate
24 weeks	242	679	0.356
25 weeks	218	684	0.319
26 weeks	200	840	0.238
27 weeks	162	966	0.168
28 weeks	164	1,160	0.141
29 weeks	141	1,298	0.109
30 weeks	99	1,589	0.062
31 weeks	138	2,122	0.065
32 weeks	149	2,834	0.053
33 weeks	128	3,955	0.032
34 weeks	144	7,064	0.020
35 weeks	153	10,478	0.015
36 weeks	203	21,778	0.009
37 weeks	190	53,532	0.004

(a) ONS (2017) – Birth characteristics (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthcharacteristicsinenglandandwales)

Neonatal and post neonatal deaths by gestational age

The neonatal and postnatal death rate by gestational age at birth was derived from official statistics for England and Wales in 2014 (ONS, 2017) which are summarised in Table 34 below. This data is based on all pregnancies and the model assumes that twin birth does not affect neonatal and post neonatal death independently of gestational age.

Table 34: Neonatal deaths and postnatal deaths by gestational age at birth

Gestational age	Births	Neonatal deaths	Post neonatal deaths	Neonatal death rate	Post neonatal death rate
24 weeks	650	129	30	0.199	0.046
25 weeks	730	84	31	0.115	0.043
26 weeks	817	67	30	0.082	0.037
27 weeks	872	52	27	0.060	0.031
28 weeks	1,106	42	16	0.038	0.015
29 weeks	1,218	29	9	0.024	0.007
30 weeks	1,592	39	12	0.025	0.008
31 weeks	2,095	40	22	0.019	0.011
32 weeks	2,850	45	20	0.016	0.007
33 weeks	3,947	33	18	0.008	0.005
34 weeks	6,963	52	19	0.008	0.003
35 weeks	10,159	52	27	0.005	0.003
36 weeks	20,699	54	31	0.003	0.002
37 weeks	46,701	72	65	0.002	0.001

(a) ONS (2017) - Pregnancy and ethnic factors influencing births and infant mortality (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/datasets/pregnancyandethnicfactorsinfluencingbirthsandinfantmortalityengland)

Neonatal intensive care unit admission by gestational age

Data from the Neonatal Data Analysis Unit was used to estimate the proportion of babies who would be admitted to neonatal care by gestational age at birth (https://www1.imperial.ac.uk/resources/98E6A2BD-03B3-4D5D-89B8-A7DEC031537D/ndau2014reportv1.2.pdf). This 2014 data, reproduced in Table 35, is taken from 182 neonatal units in England, Scotland and Wales in 2014. The cumulative frequency of neonatal care admissions by gestational age between 24 and 36 weeks was estimated by fitting a curve to the cumulative frequency data in Table 35 as shown in Figure 10. The resulting fitted cumulative frequency distribution of neonatal care admission by gestational age is shown in Table 36.

Table 35: Number of babies admitted to neonatal care by gestational age at birth

Gestational age at birth	Babies admitted	Cumulative Frequency
≤ 25 weeks	1,144	1.27%
26 – 32 weeks	9,637	11.95%
33 – 36 weeks	24,470	39.40%
≥ 37 weeks	54,674	100%

Figure 10: Estimated cumulative frequency of neonatal care admission by gestational age at birth

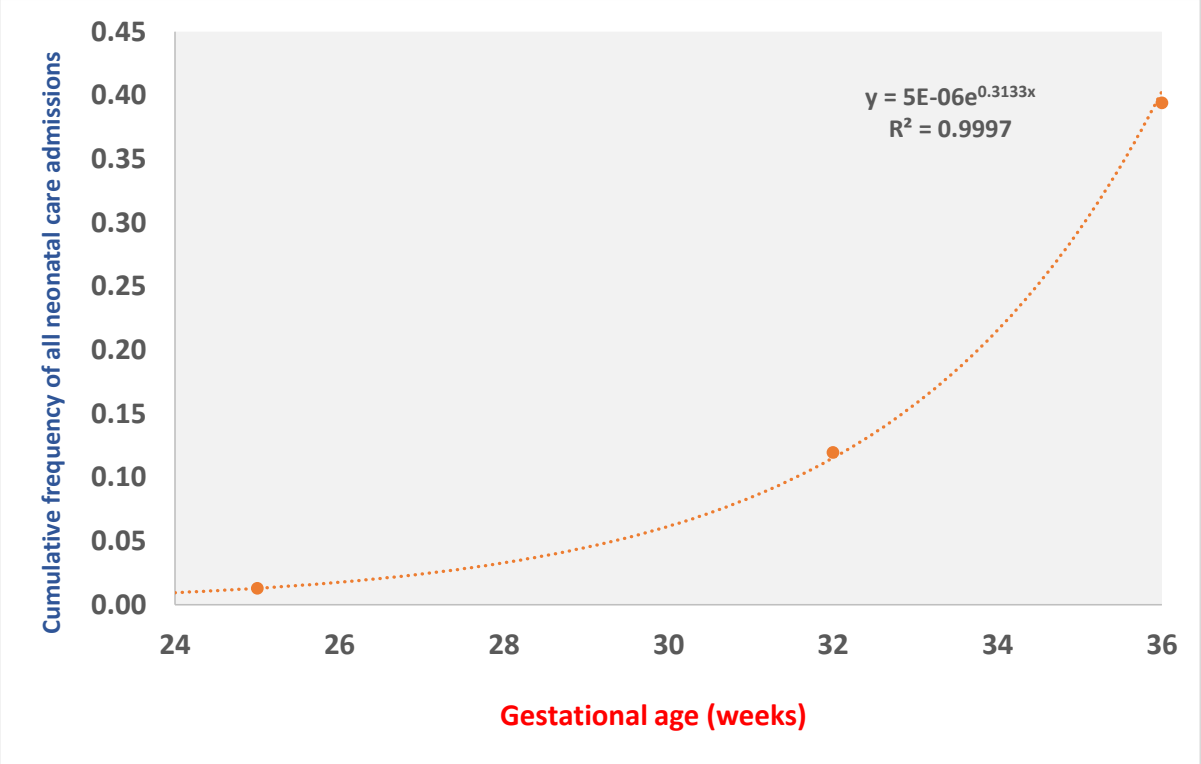


Table 36: Observed and fitted cumulative frequency distribution of neonatal care admission by gestational age at birth

Gestational age	Observed cumulative frequency	Fitted cumulative frequency
24 weeks	-	0.009
25 weeks	0.0127	0.013
26 weeks	-	0.017
27 weeks	-	0.024
28 weeks	-	0.032
29 weeks	-	0.044
30 weeks	-	0.060
31 weeks	-	0.083
32 weeks	0.1195	0.113
33 weeks	-	0.155
34 weeks	-	0.211
35 weeks	-	0.289
36 weeks	0.3940	0.396

It was assumed that all live births at a gestational age of 25 weeks and under would be admitted to neonatal care but the fitted cumulative frequency distribution was then used to estimate a neonatal care admission rate by gestational age between 24 and 37 weeks using data on live births as illustrated in Table 37.

Table 37: Neonatal care admission rates

Gestational age	Live births, 2016	Fitted cumulative frequency	Estimated admissions to neonatal care[a]	Neonatal care admission rate
24 weeks	437	0.009	437	1.000
25 weeks	466	0.013	466	1.000
26 weeks	640	0.017	534	0.835
27 weeks	804	0.024	529	0.658
28 weeks	996	0.032	723	0.726
29 weeks	1,157	0.044	990	0.855
30 weeks	1,490	0.060	1,354	0.909
31 weeks	1,984	0.083	1,852	0.933
32 weeks	2,685	0.113	2,533	0.944
33 weeks	3,827	0.155	3,465	0.906
34 weeks	6,920	0.211	4,741	0.685
35 weeks	10,325	0.289	6,485	0.628
36 weeks	21,575	0.396	8,871	0.411
37 weeks	639,321	1.00	50,380	0.079

(a) The number of estimated admissions to neonatal care for each gestational age is estimated using the fitted cumulative frequency distribution of neonatal care admissions by gestational age with data on the total number of neonatal care admissions. Table 35 gives the total neonatal care admissions across England, Scotland and Wales but as the live births in this table are for England and Wales a multiplier was used to estimate the total number of neonatal care admissions for England and Wales only. In Scotland a total of 54,488 births were reported for 2016 (National Records of Scotland, 2018). In England and Wales there were 695,247 live births in 2016 (ONS, 2017) implying a total of 749,735 birth across England, Scotland and Wales. Therefore, it was estimated that England and Wales would account for 93% of all neonatal care admissions and that this would amount to a total of 83,360 neonatal care admissions in England and Wales based on the data in Table 35.

Cerebral palsy by gestational age

A published meta-analysis (Himpens, 2008) was used to estimate the risk of cerebral palsy by gestational age at birth in babies that survive the neonatal period. A curve was fitted to the observed data using Microsoft Excel®, as displayed in Figure 11. The equation for that curve was used to estimate the risk of cerebral palsy for each week of gestational age, see Table 38.

Figure 11: Graph to show observed and estimated risk of cerebral palsy by gestational age at birth

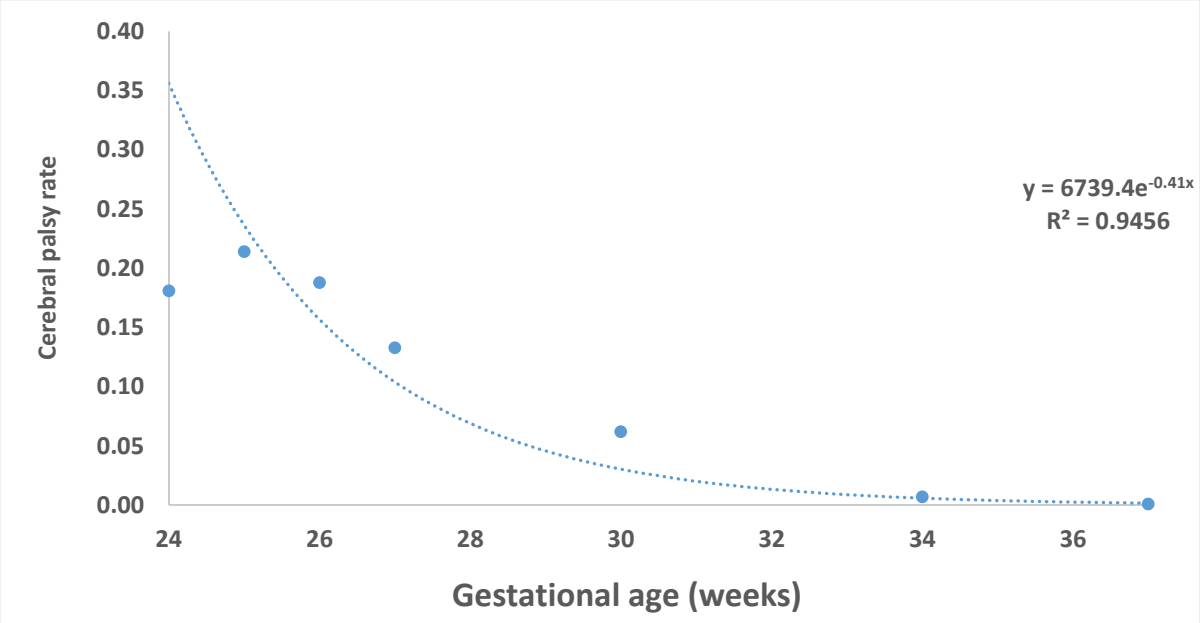


Table 38: Risk of cerebral palsy by gestational age at birth

Gestational age	Observed cerebral palsy prevalence	Fitted cerebral palsy risk
24 weeks	0.181	0.359
25 weeks	0.214	0.238
26 weeks	0.188	0.158
27 weeks	0.133	0.105
28 weeks	-	0.070
29 weeks	-	0.046
30 weeks	0.062	0.031
31 weeks	-	0.020
32 weeks	-	0.014
33 weeks	-	0.009
34 weeks	0.007	0.006
35 weeks	-	0.004
36 weeks	-	0.003
37 weeks	0.001	0.002

Intraventricular haemorrhage by gestational age

An article on preterm labour (Ross, 2018 - https://emedicine.medscape.com/article/260998-overview) was used to estimate the risk of IVH by gestational age at birth. A proportion of neonatal death would be accounted for by mortality due to IVH and to avoid double counting, long term costs and QALY loss associated with IVH was restricted to babies who did not die from the condition. It was assumed that the mortality from IVH was not related to gestational age and the risk was estimated from the NICE guideline on preterm labour and birth (NG25). The IVH risk by gestational age at birth and the IVH mortality rate are shown in Table 39.

Table 39: Risk of IVH and associated mortality

Gestational age	IVH rate	IVH mortality rate
24 weeks	0.249	0.300
25 weeks	0.300	0.300
26 weeks	0.300	0.300
27 weeks	0.160	0.300
28 weeks	0.040	0.300
29 weeks	0.035	0.300
30 weeks	0.020	0.300
31 weeks	0.010	0.300
32 weeks	0.000	0.300
33 weeks	0.000	0.300
34 weeks	0.000	0.300
35 weeks	0.000	0.300
36 weeks	0.000	0.300
37. weeks	0.000	0.300

Respiratory distress syndrome by gestational age

The RDS rate by gestational age at birth born before 35 weeks was estimated from the literature (Ross, 2018 - https://emedicine.medscape.com/article/260998-overview). For babies born later the RDS rate was taken from the NICE guideline on preterm labour and birth (NG25). The mortality rate from RDS was taken from published US data and, as with IVH, it was assumed that this did not vary with gestational age. To avoid double counting, the model restricted an estimation of long term costs and QALY losses attributable to RDS to those babies who survived the neonatal period. The RDS risk by gestational age at birth and the RDS mortality rate are given in Table 40.

Table 40: Risk of RDS and associated mortality

Gestational age	RDS rate	RDS mortality rate
24 weeks	0.700	0.054
25 weeks	0.899	0.054
26 weeks	0.929	0.054
27 weeks	0.839	0.054
28 weeks	0.649	0.054

Gestational age	RDS rate	RDS mortality rate
29 weeks	0.622	0.054
30 weeks	0.550	0.054
31 weeks	0.370	0.054
32 weeks	0.280	0.054
33 weeks	0.340	0.054
34 weeks	0.140	0.054
35 weeks	0.120	0.054
36 weeks	0.007	0.054
37. weeks	0.035	0.054

Treatment effectiveness

The relative treatment effectiveness of vaginal progesterone (up to 400mg daily) to prevent preterm birth, compared to no treatment, were derived from a published individual patient data meta-analysis (Romero 2017). These relative treatment effects along with their 95% confidence intervals are listed in Table 41. These relative risks are applied to the baseline risks of birth for each gestational age from 24 to 36 weeks, for pregnancies identified as at higher risk of preterm birth by screening, in order to determine the weekly health state transition from on-going pregnancy to birth.

Table 41: Relative treatment effect of vaginal progesterone compared to no treatment to prevent preterm birth

Outcome	Relative risk (95% confidence intervals)	Source
Preterm birth < 28 weeks	0.51 (0.24 – 1.08)	Romero 2017
Preterm birth < 32 weeks	0.51 (0.34 – 0.77)	Romero 2017
Preterm birth < 36 weeks	0.92 (0.80 – 1.05)	Romero 2017

For probabilistic sensitivity analysis the relative treatment effects were sampled using a log-normal distribution, with the distribution parameters presented in Table 42, and the standard deviation estimated from the confidence intervals reported in Table 41.

Table 42: Parameters of log-normal distribution for sampling relative treatment effect

Outcome	Mean	Standard deviation
Preterm birth < 28 weeks	Ln (0.51)	(Ln (1.08) – Ln (0.51)) ÷ 1.96
Preterm birth < 32 weeks	Ln (0.51)	(Ln (0.77) – Ln (0.51)) ÷ 1.96
Preterm birth < 36 weeks	Ln (0.92)	(Ln (1.05) – Ln (0.92)) ÷ 1.96

Quality adjusted life-years (QALYs)

In order to estimate the impact of screening and treatment on health related quality of life, a QALY decrement was applied to the adverse health outcomes assessed within the model. These decrements are listed in Table 43. Future QALY losses were discounted at a rate of 3.5%, unless stated, in accordance with the NICE reference case.

Table 43: QALY decrement for adverse health outcomes

Outcome	QALY decrement	Source
Stillbirth	25.36	Kind (1999), National Life Tables, England and Wales 2014-16 (ONS, 2017)[a]
Neonatal death	25.36	Kind (1999), National Life Tables, England and Wales 2014-16 (ONS, 2017)[a]
Postnatal death	25.36	Kind (1999), National Life Tables, England and Wales 2014-16 (ONS, 2017)[a]
Cerebral palsy	11.16	Cahill (2011) National Life Tables, England and Wales 2014-16 (ONS, 2017), NG25[b]
Intraventricular haemorrhage	4.50	NICE guideline NG25
Respiratory distress syndrome	3.85	NICE guideline NG25

(a) A death was assumed to result in a loss of 81 years of life based on current life expectancy estimates (ONS, 2017 - https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014to2016). Health state utilities, weighted by age, were taken from the literature (Kind 1999) and It was assumed the health state utilities across 81 years of life would be as follows: age <25 = 0.94; age 25-34 = 0.93; age 35-44 = 0.91; age 45-54 = 0.85; age 55-64 = 0.81; age 65-74 = 0.78; age ≥75 = 0.71. Future years were discounted at a rate of 3.5%

(b) It was assumed that each year of life with cerebral palsy would be lived with a health state utility of 0.55 and that life expectancy would be 60 years. The results in 14.2 discounted QALYs. The QALY loss from cerebral palsy was estimated by subtracting 14.2 QALYs from the discounted QALYs gained from living 81 years

Costs and resource use

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). Costs were based on a 2016/17 price year reflecting the most recently available NHS Reference Costs at the time of writing. Any future costs were discounted at a rate of 3.5%, unless stated, in line with the NICE reference case.

Table 44 gives the unit costs related to the intervention. Screening for preterm birth was undertaken by measurement of cervical length using transvaginal ultrasound. Treatment, consisting of a 400mg daily dose of progesterone administered by a vaginal pessary, would be initiated in women screened positive and was assumed to continue until birth.

Table 44: Screening and treatment costs

Variable	Cost	Standard deviation	Distribution	Source
Screening	£144 [a]	£6.73 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)
Daily treatment cost	£0.86 [c]	-	Deterministic	NHS Electronic Drug Tariff (November 2018) [d]

(a) Outpatient procedure; Service code 501, Currency code MA36Z; Transvaginal ultrasound

(b) The method of estimating a standard error from data included in NHS Reference Costs is described in detail in https://www.nice.org.uk/guidance/ng3

(c) The daily treatment cost is based on a progesterone 400mg pessary which costs £12.96 for a pack of 15

(d) http://www.drugtariff.nhsbsa.nhs.uk/#/00655804-DA/DA00655461/Part VIIIA products P; accessed 23/11/2018

Women with on-going pregnancies would continue to receive the monitoring as per the schedule recommended in this guideline, as shown for monochorionic and dichorionic twin pregnancies in Table 45 and Table 46. It is assumed that woman would receive an obstetric review for each scan. Data from the published literature was used to estimate the proportion of twins that would be either monochorionic or dichorionic as described in Table 47. The unit costs used to derive the costs from these monitoring appointments are given in Table 48.

Table 45: Monochorionic appointment schedule

	Gestational age (weeks)													
Appointment	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**
Specialist midwife follow-up	✓		✓		✓		✓		✓		✓			
Consultant specialist obstetrician follow-up	✓								✓					
Scan for monitoring for FFTS/sIUGR/TAPS	✓		✓		✓		✓		✓		✓			

Table 46: Dichorionic appointment schedule

	Gestational age (weeks)													
Appointment	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**
Specialist midwife follow-up	✓				✓				✓		✓		✓	
Consultant obstetrician follow-up	✓								✓					
Scan for IUGR	✓				✓				✓				✓	

Table 47: Proportion of twin type

Type	Proportion	Source
Monozygotic	0.33	http://www.multiplebirths.org.uk/media.asp
Monochorionic|monozygotic [a]	0.75	Shulman 2006
Dichorionic|monozygotic|	0.25	Shulman 2006
Dyzygotic	0.67	http://www.multiplebirths.org.uk/media.asp
Monochorionic|dyzygotic	0.00	Shulman 2006
Dichorionic|dyzygotic|	1.00	Shulman 2006

(a) | denotes a conditional probability, the probability that a pregnancy is monochorionic given that it is monozygotic

Table 48: Antenatal appointment costs

Variable	Cost	Standard deviation	Distribution	Source
Specialist midwife follow-up	£76 [a]	£9.19 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)
Consultant obstetrician follow-up	£120 [c]	£10.98 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)

Variable	Cost	Standard deviation	Distribution	Source
Obstetrician review	£106 [d]	£4.93 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)
Scan	£86 [e]	£7.14 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)

(a) Consultant led; Service code 560, Midwifery services; Currency code WF01A; Non-admitted face-to-face attendance, follow-up
(b) The method of estimating a standard error from data included in NHS Reference Costs is described in detail in https://www.nice.org.uk/guidance/ng3
(c) Consultant led; Service code 501; Obstetrics; Currency code WF01A; Non-admitted face-to-face attendance, follow-up
(d) Non consultant led; Service code 501; Obstetrics; Currency code WF01A; Non-admitted face-to-face attendance, follow-up
(e) Outpatient procedure; Service code 560, Midwifery services; Currency code NZ21Z; Ante-Natal Standard Routine Ultrasound Scan

The model incorporated the healthcare costs associated with stillbirth such as postpartum care for parents and parental anxiety and depression. In the base case analysis it has been assumed that the costs of a neonatal or postnatal death would be subsumed within the costs of a neonatal intensive care admission. However, the model has been devised so that additional costs related to death itself can be considered as part of a sensitivity analysis. The base case costs associated with mortality are shown in Table 49.

Table 49: Costs associated with mortality

Variable	Cost	Distribution	Source
Stillbirths	£4,361 [a]	Deterministic	Campbell 2018
Neonatal death/postnatal death	£0 [b]	Deterministic	Assumption

(a) Updated to 2016-17 prices using the HCHS pay and inflation index, with a multiplier of 1.04 derived from the HCHS index for 2013-14 and 2016-17
(b) Assumption

Table 50 shows the unit costs associated with neonatal intensive care unit (NICU) admissions. The costs of a neonatal care admission are estimated using these costs and an estimation of length of stay by gestational and weighted by the level of care, also by gestational age. We used data from the Neonatal Data Analysis Unit (NDAU 2012 Service Provision v1.0; https://www1.imperial.ac.uk/resources/195C8F2D-0CBD-4B80-8C7A-C957242DF614/ndau2012serviceprovisionreportv1.pdf) to estimate the length of stay by gestational age at birth. The estimates of NICU length of stay by gestational age are given in Table 51. In order to weight a NICU admission by the level of care we used estimates from the previous NICE guideline on multiple pregnancy (CG129) which are summarised in Table 52. The methods for estimating the costs of a NICU admission are described in more detail in the Twin Birth Costing Report (https://www.hfea.gov.uk/media/2650/nga-twin-pregnancy-costing-final.pdf).

Table 50: Neonatal intensive care costs

Variable	Costs per bed day	Standard deviation	Distribution	Source
Neonatal Critical Care, Normal Care (Level 1)	£423 [a]	£19 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)

Variable	Costs per bed day	Standard deviation	Distribution	Source
Neonatal Critical Care, Intensive Care (Level 2)	£1,295 [c]	£35 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)
Neonatal Critical Care, High Dependency	£897 [d]	£18 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)
Neonatal Critical Care, Special Care	£542 [e]	£17 [b]	Normal	NHS Reference Costs 2016-17 (NHS Improvement)

(a) Critical care; Currency code XA05Z; Neonatal Critical Care, Normal Care
(b) The method of estimating a standard error from data included in NHS Reference Costs is described in detail in https://www.nice.org.uk/guidance/ng3
(c) Critical care; Currency code XA01Z; Neonatal Critical Care, Intensive Care
(d) Critical care; Currency code XA02Z; Neonatal Critical Care, High Dependency
(e) Weighted average of Critical care; Currency code XA03Z; Neonatal Critical Care, Special Care, without External Carer and Critical care; Currency code XA04Z; Neonatal Critical Care, Special Care, with External Carer

Table 51: NICU admission length of stay by gestational age (days)

Gestational age (weeks)													
24	25	26	27	28	29	30	31	32	33	34	35	36	37
103	103	103	103	75	55	40	21	15	11	8	6	4	4

Table 52: Proportion of NICU admission by level of care and gestational age

Gestational age	SCBU	NICU level 1	NICU level 2	HDU
24-31 weeks	0.56	0.22	0.00	0.22
32-35 weeks	0.67	0.00	0.33	0.00
36-37 weeks	1.00	0.00	0.00	0.00

SCBU = Special Care Baby Unit; HDU = High Dependency Unit

Table 53 gives the costs that are assumed for model outcomes with long term morbidity while Table 54 gives the NHS costs associated with moderate and late preterm birth in the 2 years following initial discharge from hospital based on data from a UK study (Khan, 2015).

Table 53: Costs associated with long term morbidity [a]

Variable	Cost	Source
Cerebral palsy	£85,349	Kruse 2009
Intraventricular haemorrhage	£25,605	Marti 2016
Respiratory distress syndrome	£4,005	NG25

(a) Updated to 2016/17 prices from the 2015//16 value reported in Twin Birth Costing Report (https://www.hfea.gov.uk/media/2650/nga-twin-pregnancy-costing-final.pdf) using the HCHS Pay and Inflation Index with a multiplier of 1.018 derived from the HCHS Index for 2015/16 and 2016/17

Table 54: NHS costs in first 2 years after initial discharge from hospital by gestational age

Gestational Age	0-6 months	6-12 months	12-24 months
24 weeks	£1,476	£883	£463

Gestational Age	0-6 months	6-12 months	12-24 months
25 weeks	£1,476	£883	£463
26 weeks	£1,476	£883	£463
27 weeks	£1,476	£883	£463
28 weeks	£1,476	£883	£463
29 weeks	£1,476	£883	£463
30 weeks	£1,476	£883	£463
31 weeks	£1,476	£883	£463
32 weeks	£1,476	£883	£463
33 weeks	£1,476	£883	£463
34 weeks	£1,476	£883	£463
35 weeks	£1,476	£883	£463
36 weeks	£1,476	£883	£463
37 weeks	£845	£745	£316

Results

The results from the model are presented below. The incremental cost effectiveness ratio (ICER) is a summary measure of cost effectiveness where a ratio is calculated by dividing the additional costs of an intervention compared to some comparator by the additional benefits of the intervention, measured by QALYs in this analysis. The ICER is then compared with some cost effectiveness threshold and if the ICER lies below this threshold the intervention is considered cost effective. If the intervention is both cheaper and more effective than the comparator then the ICER is not required, as the intervention is unambiguously cost effective and is said to dominate the comparator. Another summary measure of cost effectiveness used in the presentation of results below is the net monetary benefit (NMB) which is calculated as the product of the QALYs from the intervention and the cost effectiveness threshold (which gives a monetary valuation of benefit) less the costs of the intervention. The strategy with the highest NMB is the most cost effective strategy. The NMB statistic will always give the same conclusion with respect to cost effectiveness as the ICER but can be easier to interpret when there are multiple comparisons. It is also more straightforward to quantify the uncertainty around an NMB point estimate than it is for an ICER. All net monetary benefit values were calculated using a cost effectiveness threshold of £20,000 per QALY.

Base case analysis

Probabilistic sensitivity analysis

A total of 10,000 Monte Carlo simulations were run using the Liem (2018) data on the distribution of cervical length in women with a twin pregnancy, as described in Table 27 and Figure 9, with deterministic model inputs set to their base case values. The results for Liem (2018) are summarised in Table 55, Figure 12 and Figure 13.

Table 55: Summary of probabilistic sensitivity analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental cost	Incremental QALY	ICER	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	-	-	1.5%
Cervical length ≤ 5 mm	£222	0.0097	Dominated	-£28 (-£33 to -£23)	0.0%
Cervical length ≤ 10 mm	£179	0.0195	Dominated	£210 (£203 to £218)	0.0%
Cervical length ≤ 15 mm	£142	0.0281	Dominated	£418 (£410 to £427)	0.0%
Cervical length ≤ 20 mm	£111	0.0353	Dominated	£594 (£584 to £604)	0.0%
Cervical length ≤ 25 mm	£35	0.0525	£667	£1,013 (£1,001 to £1,025)	98.5%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 12: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

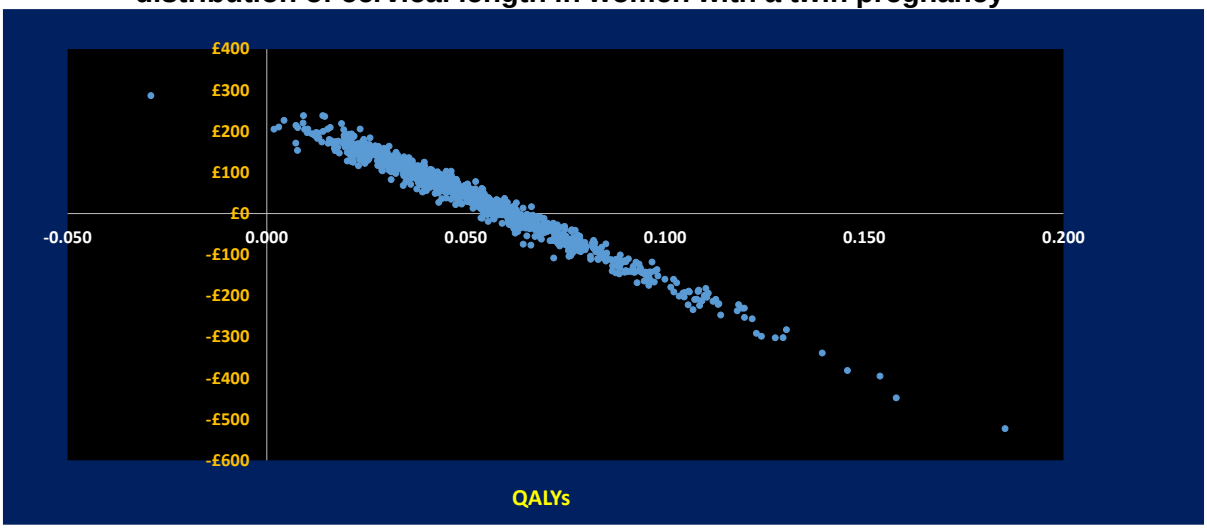
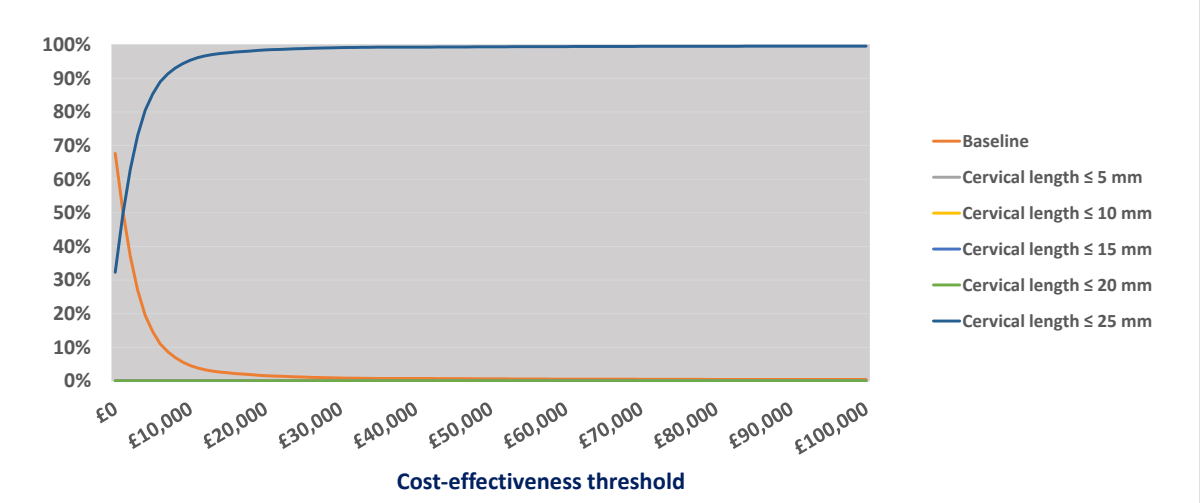


Figure plots first 1,000 Monte Carlo simulations

Figure 13: Cost effectiveness acceptability curve using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy



Deterministic sensitivity analysis

The base case deterministic results using the Liem (2018) data on the distribution of cervical length in women with a twin pregnancy are shown in Table 56 and Figure 14. The incremental net monetary benefit is calculated relative to the baseline strategy of no screening and no treatment. The strategies are ordered in ascending order of cost and the final column indicates the cost impact to the NHS relative to baseline, based on 10,951 twin maternities per annum, the number in England and Wales in 2016. The other columns are calculated per pregnancy.

Table 56: Summary of deterministic base case analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental Cost [a]	Incremental QALY [a]	ICER	iNMB [a]	Cost impact to NHS
Cervical length ≤ 25 mm	-£45	0.044	Dominant	£919	-£490,073
No screening/ No treatment (Baseline)	-	-	-	-	-
Cervical length ≤ 20 mm	£16	0.030	Dominated	£586	£181,328
Cervical length ≤ 15 mm	£42	0.024	Dominated	£440	£463,719

Screening strategy	Incremental Cost [a]	Incremental QALY [a]	ICER	iNMB [a]	Cost impact to NHS
Cervical length ≤ 10 mm	£73	0.017	Dominated	£264	£799,795
Cervical length ≤ 5 mm	£108	0.009	Dominated	£62	£1,183,908

(a) Calculated relative to the no screening/no treatment baseline

Figure 14: Cost effectiveness plane showing the incremental costs and QALYs of screening strategies when compared to no screening using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

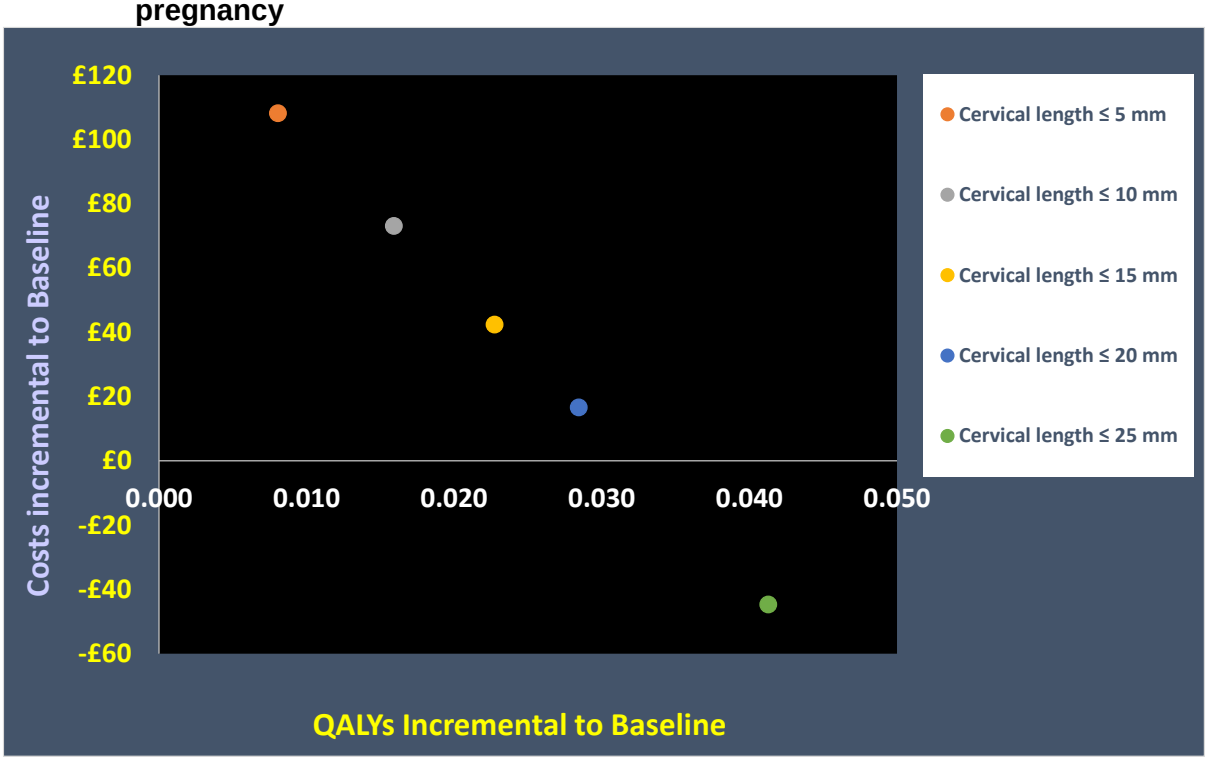


Table 57 shows the modelled impact of the various strategies on the clinical outcomes included in the model for a population of 10,951 women with twin pregnancies for the Liem (2018) data.

Table 57: Clinical outcomes for different screening strategies in the deterministic base case analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

Screening Strategy	Stillbirths	Neonatal deaths	Postnatal deaths	CP cases	IVH cases	RDS cases	NICU admissions
Cervical length ≤ 25 mm	293.0	91.2	50.7	115.7	49.3	1,741	5,538
No screening/ No treatment (Baseline)	302.1	93.7	51.6	121.0	54.0	1,764	5,537
Cervical length ≤ 20 mm	295.9	92.0	51.0	117.3	50.7	1,749	5,538
Cervical length ≤ 15 mm	297.1	92.3	51.1	118.1	51.4	1,752	5,538
Cervical length ≤ 10 mm	298.6	92.7	51.3	118.9	52.1	1,756	5,538
Cervical length ≤ 5 mm	300.3	93.2	51.5	120.0	53.0	1,760	5,537

CP = cerebral palsy; IVH = intraventricular haemorrhage; RDS = respiratory distress syndrome; NICU = neonatal intensive care unit

Table 58 shows the breakdown of costs by category for the different screening strategies.

Table 58: Breakdown of costs per woman for different screening strategies in the deterministic base case analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy

	Dx	Rx	Antenatal appts	Stillbirths	CP	IVH	RDS	NICU	Post neonatal	Total
No screening/ No treatment (Baseline)	£0	£0	£1,382.01	£120.29	£943	£126	£645	£4,417	£4,251.51	**£11,885**
Cervical length ≤ 5 mm	£144	£0.26	£1,382.25	£119.59	£935	£124	£644	£4,392	£4,253.36	**£11,993**
Cervical length ≤ 10 mm	£144	£0.53	£1,382.49	£118.91	£927	£122	£642	£4,368	£4,253.19	**£11,958**
Cervical length ≤ 15 mm	£144	£0.80	£1,382.70	£118.32	£920	£120	£641	£4,347	£4,253.88	**£11,927**
Cervical length ≤ 20 mm	£144	£1.07	£1,382.88	£117.83	£914	£119	£640	£4,329	£4,254.43	**£11,901**
Cervical length ≤ 25 mm	£144	£1.90	£1,383.32	£116.69	£901	£115	£637	£4,285	£4,255.64	**£11,840**

Dx = screening; Rx = treatment; Appts = appointments; CP = cerebral palsy; IVH = intraventricular haemorrhage; RDS = respiratory distress syndrome; NICU = neonatal intensive care unit

Additional sensitivity analysis

i) Using Skentou (2001) data on the distribution of cervical length in twin pregnancy

The results of the probabilistic sensitivity analysis (PSA) with 10,000 Monte Carlo using the Skentou (2001) data are shown in Table 59, Figure 15 and Figure 16.

Table 59: Summary of probabilistic sensitivity analysis using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental cost	Incremental QALY	ICER	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	Dominated	-	0.2%
Cervical length ≤ 5 mm	£70	0.0451	Dominated	£831 (£817 to £845)	0.0%
Cervical length ≤ 10 mm	-£436	0.1622	Dominated	£3,679 (£3,648 to £3,710)	0.0%
Cervical length ≤ 15 mm	-£1,048	0.3030	Dominated	£7,108 (£7,059 to £7,157)	0.0%
Cervical length ≤ 20 mm	-£1,760	0.4656	Dominated	£11,070 (£11,003 to £11,137)	0.0%
Cervical length ≤ 25 mm	-£2,676	0.6732	Dominant	£16,139 (£16,050 to £16,228)	99.8%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 15: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy

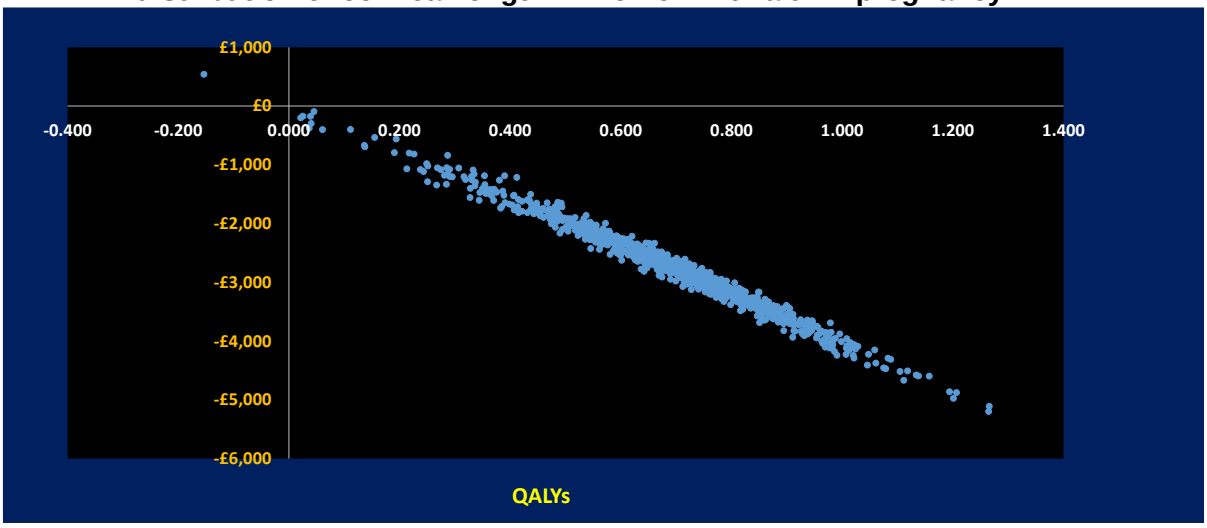


Figure plots first 1,000 Monte Carlo simulations

Figure 16: Cost effectiveness acceptability curve using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy

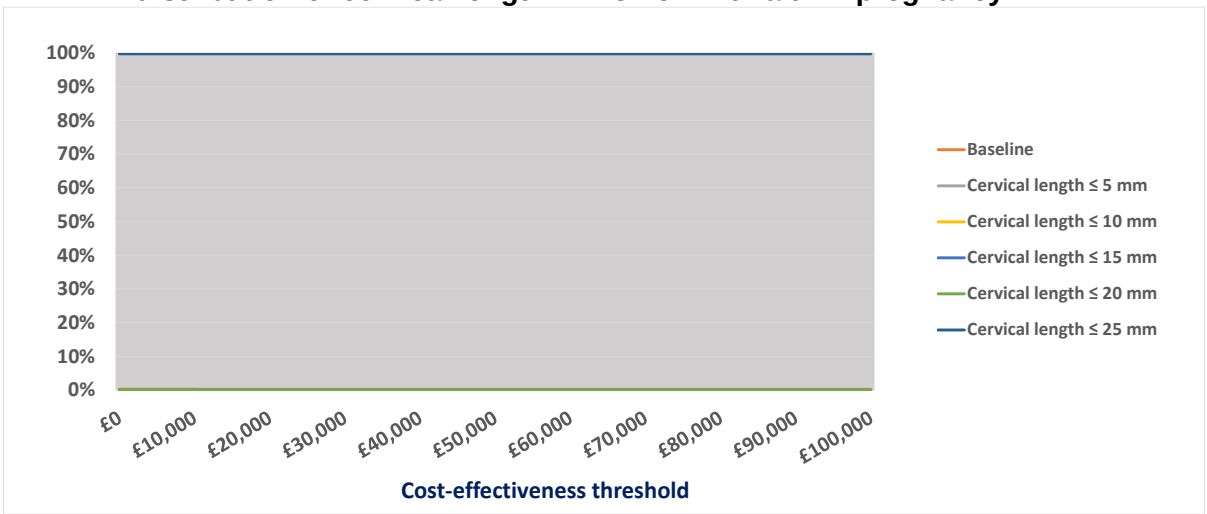


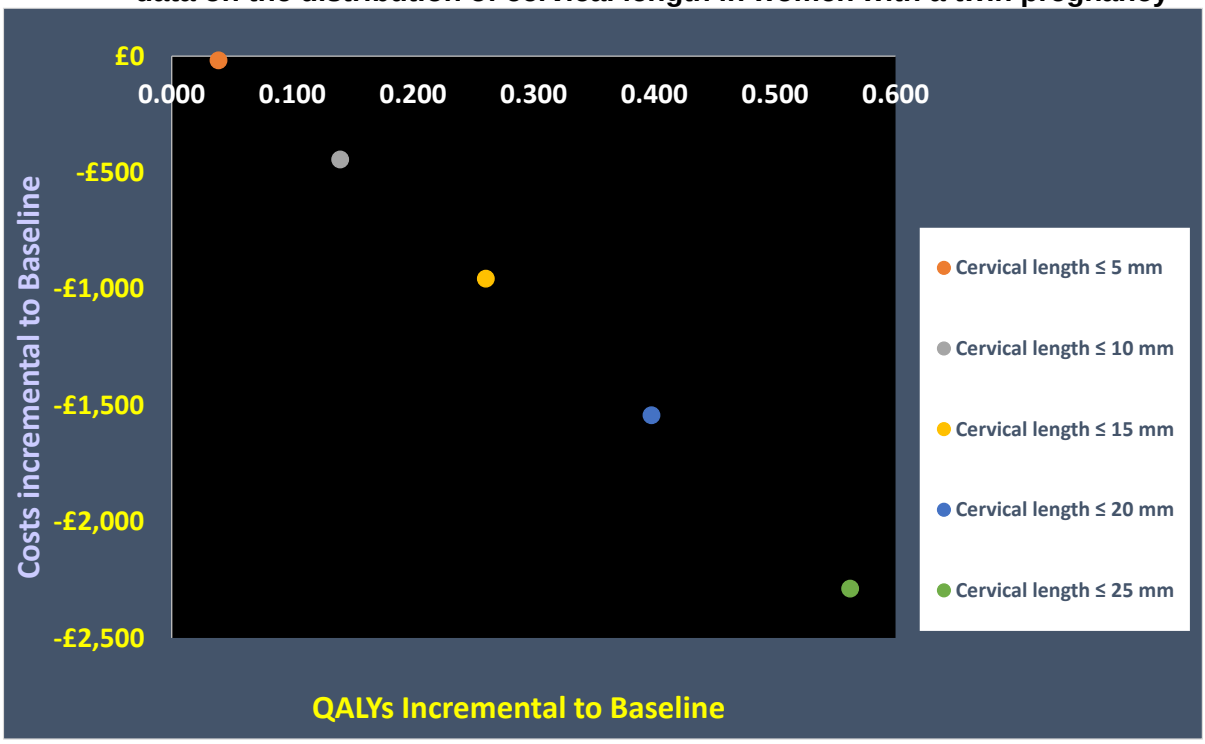
Table 60 and Figure 17 depict the deterministic results using the Skentou (2001) distribution of cervical length in women with a twin pregnancy. The strategies are ordered in ascending order of cost.

Table 60: Summary of deterministic base case analysis using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental Cost [a]	Incremental QALY [a]	ICER	iNMB [a]	Cost impact to NHS
Cervical length ≤ 25 mm	-£2,288	0.563	Dominant	£13,538	-£25,059,615
Cervical length ≤ 20 mm	-£1,544	0.398	Dominated	£9,499	-£16,910,199
Cervical length ≤ 15 mm	-£957	0.260	Dominated	£6,167	-£10,483,376
Cervical length ≤ 10 mm	-£445	0.140	Dominated	£3,241	-£4,874,383
Cervical length ≤ 5 mm	-£19	0.039	Dominated	£795	-£212,047
No screening/ No treatment (Baseline)	-	-	Dominated	-	-

(a) Calculated relative to the no screening/no treatment baseline

Figure 17: Cost effectiveness plane showing the incremental costs and QALYs of screening strategies when compared to no screening using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy



In this sensitivity analysis, the strategy of screening for preterm birth using a cervical length threshold of 25 mm followed by treatment in those women identified as at higher risk of preterm birth was even more cost effective than in the base case analysis, with larger incremental NMB, a higher probability of being cost-effective and with substantial savings to the NHS.

ii) Using Souka (1999) data on the distribution of cervical length in twin pregnancy

The results of the PSA using the Souka (1999) data are shown in Table 61, Figure 18 and Figure 19.

Table 61: Summary of probabilistic sensitivity analysis using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental cost	Incremental QALY	ICER	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	Dominated	-	0.3%
Cervical length ≤ 5 mm	£128	0.0315	Dominated	£501 (£485 to £517)	0.0%

Screening strategy	Incremental cost	Incremental QALY	ICER	Mean iNMB (95% CI)	Probability CE
Cervical length ≤ 10 mm	-£828	0.2529	Dominated	£5,885 (£5,831 to £5,939)	0.0%
Cervical length ≤ 15 mm	-£1,314	0.3648	Dominated	£8,608 (£8,540 to £8,676)	0.0%
Cervical length ≤ 20 mm	-£2,138	0.5530	Dominated	£13,197 (£13,107 to £13,287)	0.0%
Cervical length ≤ 25 mm	-£2,798	0.7026	Dominant	£16,848 (£16,742 to £16,955)	99.7%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 18: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy

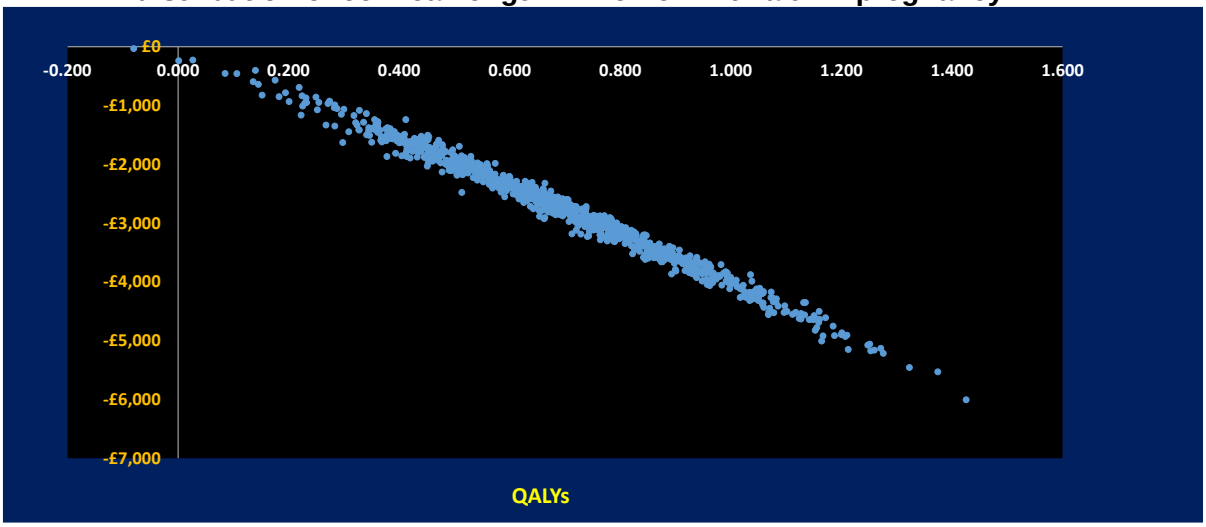


Figure plots first 1,000 Monte Carlo simulations

Figure 19: Cost effectiveness acceptability curve using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy

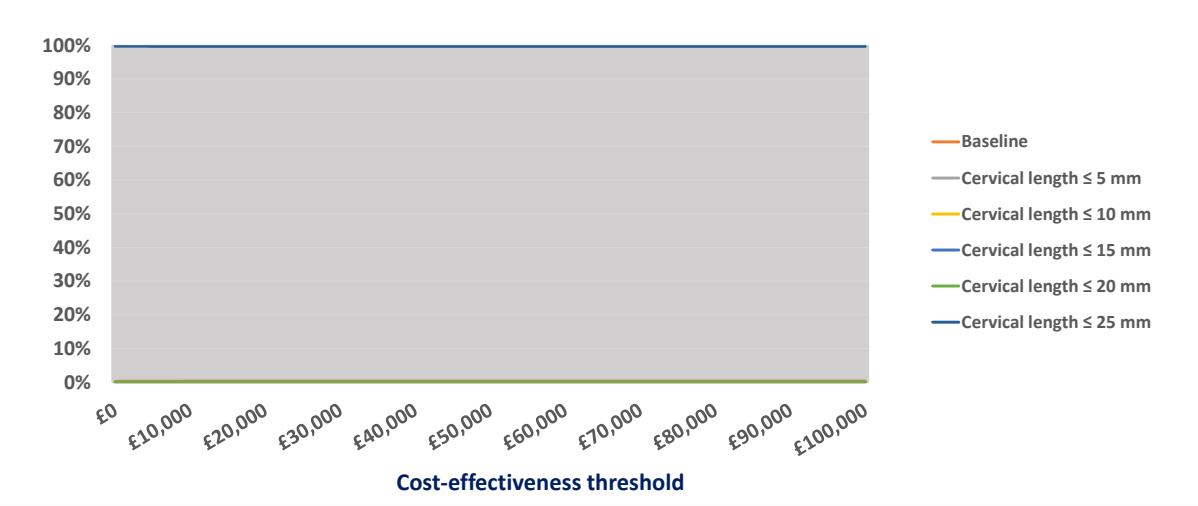


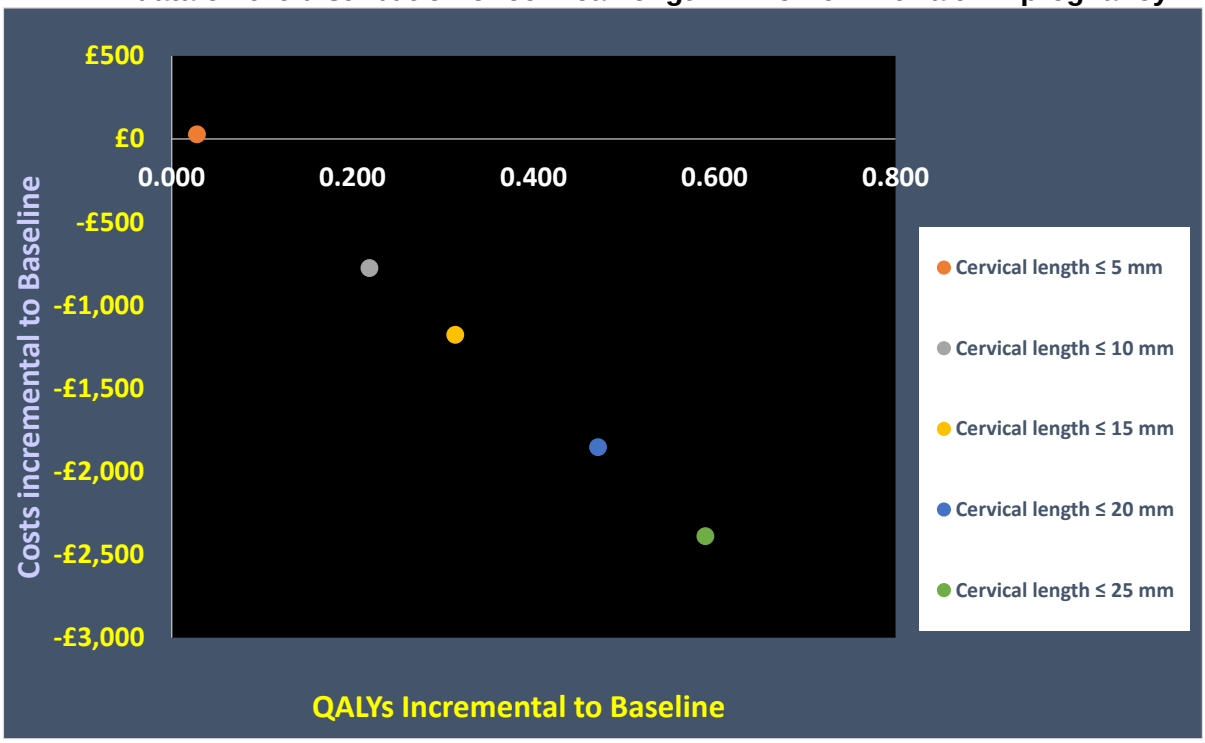
Table 62 and Figure 20 illustrate the deterministic results using the Souka (1999) distribution of cervical length in women with a twin pregnancy. The strategies are ordered in ascending order of cost.

Table 62: Summary of deterministic base case analysis using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy

Screening strategy	Incremental Cost [a]	Incremental QALY [a]	ICER	iNMB [a]	Cost impact to NHS
Cervical length ≤ 25 mm	-£2,390	0.590	Dominant	£14,187	-£26,175,908
Cervical length ≤ 20 mm	-£1,855	0.471	Dominated	£11,282	-£20,313,383
Cervical length ≤ 15 mm	-£1,180	0.313	Dominated	£7,447	-£12,916,060
Cervical length ≤ 10 mm	-£778	0.219	Dominated	£5,151	-£8,514,246
No screening/ No treatment (Baseline)	-	-	Dominated	-	-
Cervical length ≤ 5 mm	£26	0.028	Dominated	£532	£289,980

(a) Calculated relative to the no screening/no treatment baseline

Figure 20: Cost effectiveness plane showing the incremental costs and QALYs of screening strategies when compared to no screening using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy



The distribution of cervical length used in this sensitivity analysis produced the most favourable assessment of the cost effectiveness of screening for preterm birth using a cervical length threshold of 25 mm followed by treatment in those women identified as at higher risk of preterm birth.

iii) Reducing treatment effectiveness

The base case analyses strongly suggested that screening for preterm birth and treatment based on a cervical length at screening of 25 mm is cost effective. To subject this conclusion to rigorous testing a “worst” case sensitivity analysis was undertaken with respect to treatment effectiveness. This involved setting all the relative treatment effects to the upper bound of the reported confidence intervals. For probabilistic sensitivity analysis new confidence intervals were specified. These were based on the original confidence intervals but incremented by the same amount as the point estimate. The revised relative treatment effect parameters are shown in Table 63.The presentation of comparisons was limited to a baseline of no screening and screening using a cervical length of 25 mm as other cervical length strategies continued to be dominated by screening using a cervical length of 25 mm.

Table 63: Revised relative treatment effect of vaginal progesterone compared to no treatment to prevent preterm birth for sensitivity analysis

Outcome	Relative risk (95% confidence intervals)
Preterm birth < 28 weeks	1.08 (0.81 – 1.65)
Preterm birth < 32 weeks	0.77 (0.60 – 1.03)
Preterm birth < 36 weeks	1.05 (0.93 – 1.18)

a) Using Liem (2018) data on distribution of cervical length in women with a twin pregnancy

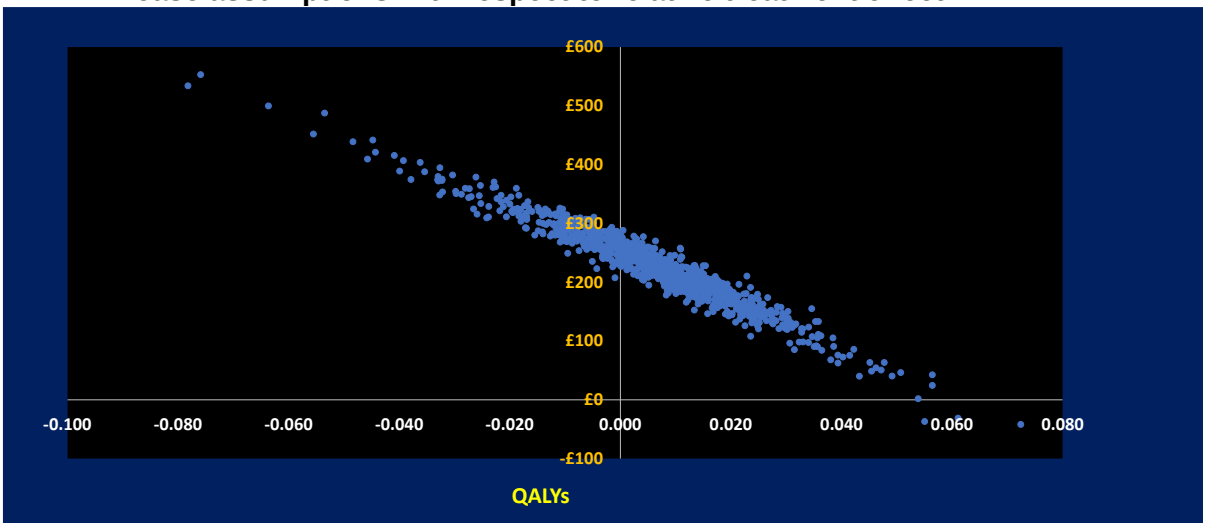
Table 64, Figure 21 and Figure 22 summarise 10,000 Monte Carlo simulations using "worst" case assumptions with respect to treatment effectiveness using the Liem (2018) data on the distribution of cervical length on women with a twin pregnancy. Table 65 shows the deterministic result for these worst case assumptions on relative treatment effect.

Table 64: Summary of probabilistic sensitivity analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions about treatment effectiveness

Screening strategy	Incremental cost	Incremental QALY	ICER Per QALY	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	-	-	63.0%
Cervical length ≤ 25 mm	£228	0.0059	£38,352	-£110 (-£118 to -£103)	37.0%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 21: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect



Source: Figure plots first 1,000 Monte Carlo simulations

Figure 22: Cost effectiveness acceptability curve using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect

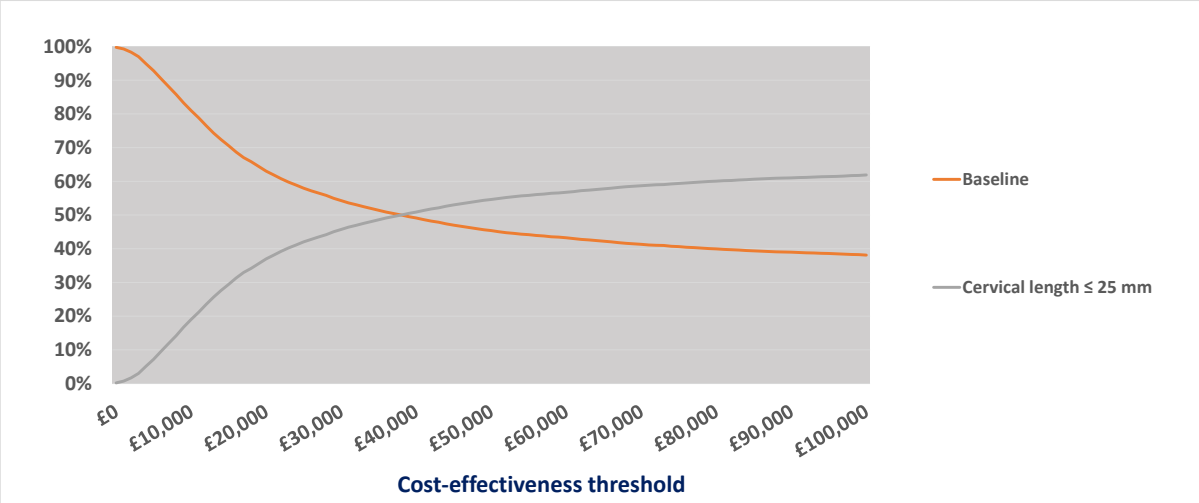


Table 65: Summary of deterministic sensitivity analysis using Liem (2018) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumption with respect to relative treatment effect

Screening strategy	Incremental Cost	Incremental QALY	ICER	iNMB	Cost impact to NHS
No screening / no treatment (Baseline)	-	-	-	-	-
Cervical length ≤ 25 mm	£112	0.006	£20,959	-£5	£1,226,512

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit

This "worst" case sensitivity analysis using the Liem (2018) data on the distribution of cervical length suggested that screening for preterm birth using a cervical length threshold of 25 mm followed by treatment of women identified as being at higher risk of preterm birth was borderline cost effective. The deterministic result yielded an ICER of just over £20,000 per QALY for a strategy of screening for preterm birth using a cervical length threshold of 25 mm followed by treatment of women identified as being at higher risk of preterm birth, whilst the PSA indicated that there was a 37% probability this was cost effective at a cost effectiveness threshold of £20,000 per QALY, rising to 46% at a more generous cost effectiveness threshold of £30,000 per QALY.

b) Using Skentou (2001) data on distribution of cervical length in women with a twin pregnancy

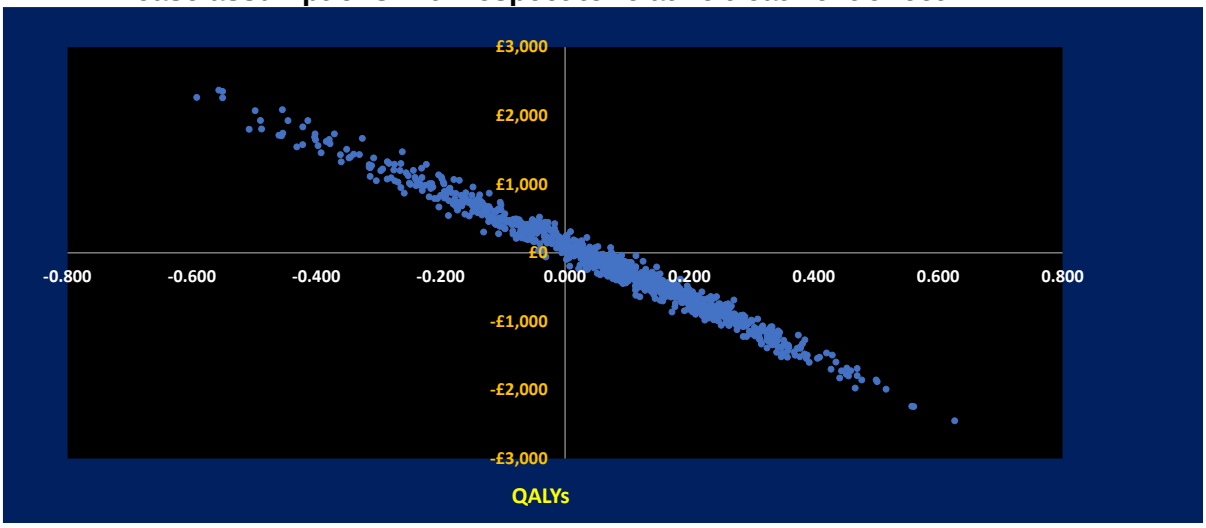
The PSA results using "worst" case assumptions on relative treatment effect and the Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy are shown in Table 66, Figure 23 and Figure 24. The deterministic result for this sensitivity analysis is given in Table 67.

Table 66: Summary of probabilistic sensitivity analysis using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions about treatment effectiveness

Screening strategy	Incremental cost	Incremental QALY	ICER Per QALY	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	Dominated	-	32.3%
Cervical length ≤ 25 mm	-£202	0.0766	Dominant	£1,733 (£1,643 to £1,823)	67.7%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 23: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect



Source: Figure plots first 1,000 Monte Carlo simulations

Figure 24: Cost effectiveness acceptability curve using Skentou (2001) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect

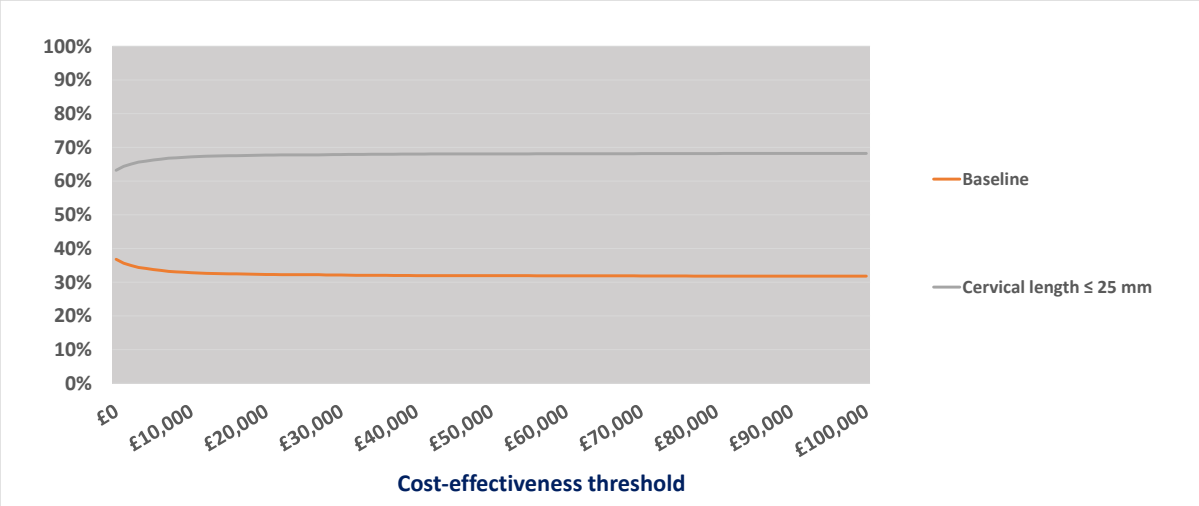


Table 67: Summary of deterministic sensitivity analysis using Skentou (1999) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumption with respect to relative treatment effect

Screening strategy	Incremental Cost	Incremental QALY	ICER	iNMB	Cost impact to NHS
Cervical length ≤ 25 mm	-£263	0.070	Dominant	£1,651	-£2,880,113
No screening/ No treatment (Baseline)	-	-	Dominated	-	-

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit

With "worst" case assumptions about treatment effectiveness, screening for preterm birth using a cervical length of 25 mm and treatment of women identified as being at higher risk of preterm birth was still found to be cost-effective when using the Skentou (2001) distribution of cervical length, dominating the alternative of no screening.

c) Using Souka (1999) data on distribution of cervical length in women with a twin pregnancy

Table 68, Figure 25 and Figure 26 illustrate the PSA results for 10,000 Monte Carlo simulations for the sensitivity analysis of "worst" case assumptions with respect to relative treatment effect and using the Souka (1999) data on the distribution of cervical length in women with a twin pregnancy. Table 69 summarises the deterministic result for this sensitivity analysis.

Table 68: Summary of probabilistic sensitivity analysis using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions about treatment effectiveness

Screening strategy	Incremental cost	Incremental QALY	ICER Per QALY	Mean iNMB (95% CI)	Probability CE
No screening / no treatment (Baseline)	-	-	Dominated	-	32.4%
Cervical length ≤ 25 mm	-£209	0.0773	Dominant	£1,754 (£1,660 to £1,848)	67.6%

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit; CI = confidence interval; CE = cost effective

Figure 25: Cost effectiveness plane showing the outcome of Monte Carlo simulations for a strategy of screening based on a cervical length of ≤ 25 mm when compared to no screening using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect

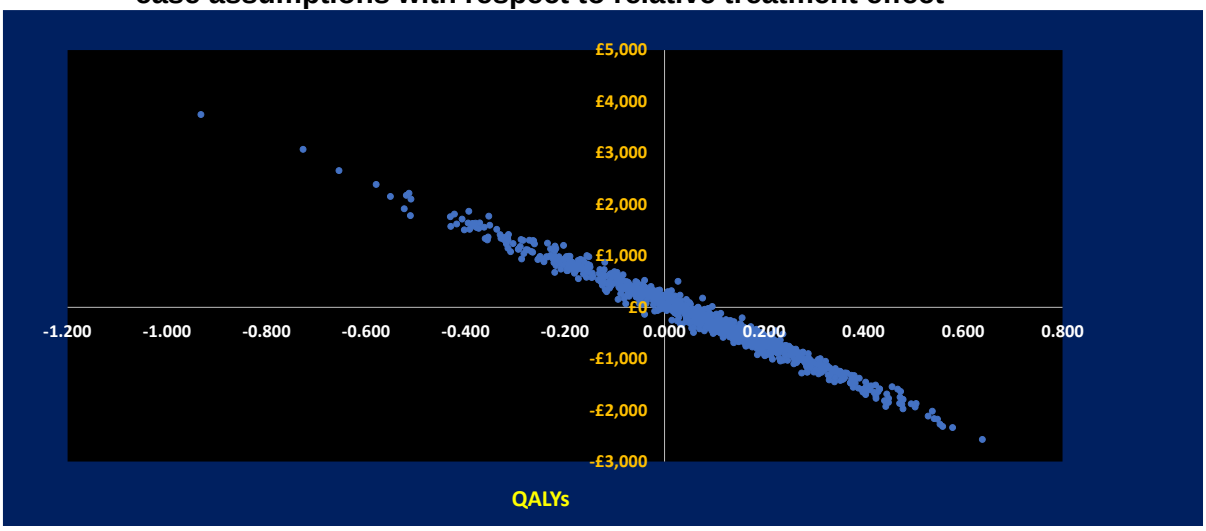


Figure plots first 1,000 Monte Carlo simulations

Figure 26: Cost effectiveness acceptability curve using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumptions with respect to relative treatment effect

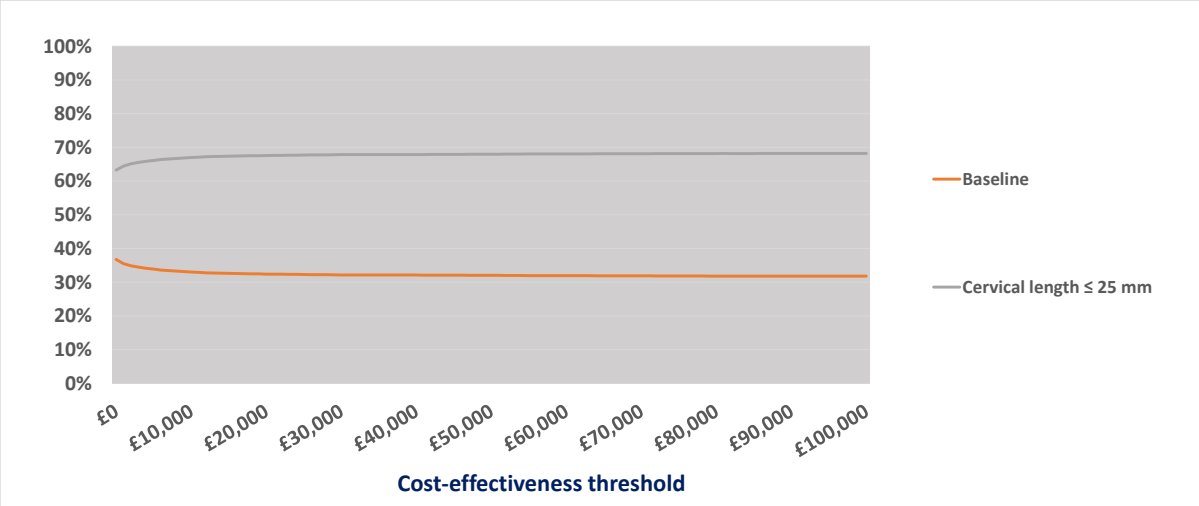


Table 69: Summary of deterministic sensitivity analysis using Souka (1999) data on the distribution of cervical length in women with a twin pregnancy and "worst" case assumption with respect to relative treatment effect

Screening strategy	Incremental Cost	Incremental QALY	ICER	iNMB	Cost impact to NHS
Cervical length ≤ 25 mm	-£278	0.072	Dominant	£1,712	-£3,044,378
No screening/ No treatment (Baseline)	-	-	Dominated	-	-

QALY = Quality Adjusted Life Year; ICER = incremental cost effectiveness ratio; iNMB = incremental net monetary benefit

Using the Souka (1999) distribution of cervical length and "worst" case assumptions about treatment effectiveness, screening and treatment was still found to be cost-effective relative to a strategy of no screening.

iv) One-way threshold sensitivity analysis

In this sensitivity analysis a single input value was varied from its base case value up to the point or threshold where screening at a cervical length of 25 mm or less would no longer be cost effective at a cost effectiveness threshold of £20,000 per QALY when compared to a baseline strategy of no screening. These threshold analyses were restricted to the Liem (2018) data on distribution of cervical length in women with a twin pregnancy as of the 3 distributions considered this is the least favourable to the cost effectiveness of screening and treatment to prevent or delay preterm birth. The equivalent thresholds for the Skentou (2001) and Souka (1999) data would be more extreme and therefore less plausible based on current evidence.

These threshold analyses are summarised in Table 70, showing the default base case value and the threshold value at which point an ICER of £20,000 per QALY would be exceeded.

Table 70: Base case and threshold values for cost effectiveness for model input parameters varied one at a time

Variable	Base case value	Threshold value
Relative risk preterm birth < 28 weeks	0.51	1.56
Relative risk preterm birth < 32 weeks	0.51	1.33
Relative risk preterm birth < 36 weeks	0.92	1.84
Cost of screening	£144	£1,063
Treatment cost per day	£0.86	£1,122
Specialist midwife follow up appointment cost	£76	£190,000
Consultant obstetrician follow up appointment cost	£120	£86,000
Obstetrician Review	£106	£209,000
Scan cost	£86	£209,000

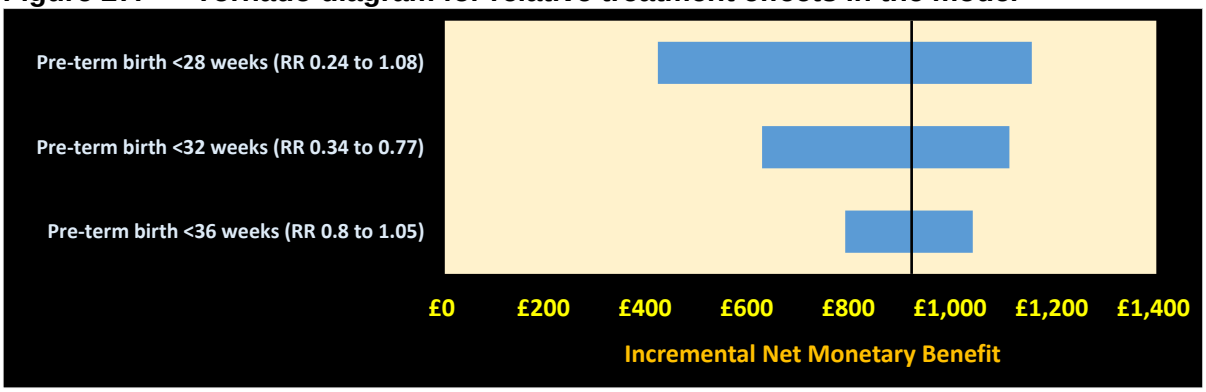
Variable	Base case value	Threshold value
Mortality cost of stillbirth	£4,361	None[a]
Cerebral palsy cost	£85,349	None[a]
IVH cost	£25,605	None[a]
RDS cost	£4,005	None[a]
Neonatal care cost per bed day[b]	£423 to £1,295	None[a]
Stillbirth QALY loss	23.86	None[a]
Neonatal death QALY loss	23.86	None[a]
Postnatal death QALY loss	23.86	None[a]
Cerebral palsy QALY loss	9.66	None[a]
Intraventricular haemorrhage QALY loss	4.50	None[a]
Respiratory distress syndrome QALY loss	3.85	None[a]

(a) Lowering these parameter values reduces the cost effectiveness of screening but screening remained cost effective even when these values were set to zero
(b) In the model neonatal care costs per bed-day vary according to the level of care. In this threshold analysis all parameter values were adjusted simultaneously

v) Tornado analysis

The one-way threshold sensitivity analysis above indicated that the model was more sensitive to changes in relative risk parameters within plausible ranges than other model inputs. This was explored in a Tornado analysis for the Liem (2018) data on distribution of cervical length in women with a twin pregnancy, where the relative risks were varied one at a time using the upper and lower bounds of their 95% confidence intervals (see Table 41) keeping all other model inputs constant at their base case values. The results are presented in the Tornado diagram, shown in Figure 27.

Figure 27: Tornado diagram for relative treatment effects in the model



RR = relative risk

Discussion

The results from the base case analysis demonstrate that screening for preterm birth using ultrasound determined cervical length measurement (at 21 weeks) and treatment with

vaginal progesterone is cost effective. This was the case irrespective of the threshold used for cervical length to identify a pregnancy at higher risk of preterm birth as the incremental NMB was greater for all screening strategies than for the baseline strategy of no treatment, (Table 56). However, the model suggested that cost effectiveness improved with increasing cervical length up to a threshold of 25 mm, with probabilistic analysis showing an increasing mean incremental NMB and a 98.5% probability of this being the most cost effective strategy at a cost effectiveness threshold of £20,000 per QALY (Table 55). The probabilistic analysis, showed that a cervical length screening threshold of 25 mm had an incremental cost effectiveness ratio (ICER) of £667, substantially below a cost effectiveness threshold of £20,000 per QALY. A screening cervical length threshold of 25 mm dominated other screening cervical length thresholds, being cheaper and more effective.

Both the deterministic and probabilistic base case analysis indicated that increasing the screening threshold of cervical length to 25 mm was cost saving relative to other cervical length screening thresholds and the deterministic analysis even suggested that a cervical length screening threshold of 25 mm could be cost saving relative to no screening. Whilst, the PSA did not show that a screening cervical length threshold of 25 mm would be cost saving relative to no screening, the overall resource impact was limited.

In the sensitivity analyses using alternative estimates of cervical length distribution (Souka 1999; Skentou 2001) the cost effectiveness of screening for preterm birth using a cervical length threshold of 25 mm and treatment in those identified at higher risk of preterm birth was even greater than in the base case analysis. This is evinced by the highest incremental NMB and a greater than 99% probability of being cost effective, see Table 59 and Table 61. These analyses also suggested that screening for preterm birth and treatment of those identified as being at higher risk could potentially generate large savings to the NHS, in the order of £25 million (Table 60 and Table 62). The reason these distributions were more cost effective than the Liem (2018) distribution, used in the base case, analysis was that they both identified a considerably higher, albeit still small, proportion of women with twin pregnancy with a shorter cervix and therefore at increased risk of prematurity with a corresponding increased capacity to benefit from treatment.

A sensitivity analysis was undertaken using a “worst” case scenario for screening for preterm birth and treatment of those identified as being at higher risk of preterm birth to subject the cost effectiveness conclusion of other analyses to rigorous scrutiny. This involved setting all measures of treatment effect to the value of their upper 95% confidence limit. Even when using the least favourable distribution of cervical length, of the 3 available (Liem, 2018), the model suggested that screening using a cervical length threshold of 25 mm was borderline cost effective at a cost effectiveness threshold of £20,000 per QALY. The deterministic assessment of this “worst” case scenario produced an ICER of £20,959 relative no screening, as shown in Table 65.The PSA results were less favourable to screening when compared to a strategy of no screening with a negative incremental NMB and screening having a 37% probability of being cost effective at a cost effectiveness threshold of £20,000 per QALY (Table 64). However, this probability rose to 46% if a higher cost effectiveness threshold of £30,000 per QALY was used, see Figure 22. Of course, it is highly unlikely that the true treatment effect size for all 3 variables varied would be given by the value of the upper 95% confidence limit from their sampled distribution.

The Tornado diagram presented in Figure 27 illustrates the extent to which the incremental net monetary benefit varies with different assumptions about treatment effectiveness at different gestational ages. It shows that, when varied one at a time, conclusion about the cost

effectiveness of screening for preterm birth and treatment of those identified as being at higher risk of preterm birth remains robust with respect to uncertainty in the treatment effect size.

A series of one way sensitivity analyses were also undertaken to determine the parameter value for specific variables at which screening for preterm birth and treatment of those identified as being at higher risk would just cease to be cost effective using a cost effectiveness threshold of £20,000 per QALY. This analysis, reported in Table 70, generally shows that these threshold values would have to be way in excess of a plausible value in order to negate the finding that screening for preterm birth and treatment of those identified as being at a higher risk is cost effective. This, further to the PSA and other sensitivity analysis, gives further confidence in the robustness of the model's conclusions whilst recognising that the PSA provides a better overall assessment of cost-effectiveness in the context of parameter uncertainty.

Table 57 and Table 58 give important insights into what drives the cost effectiveness conclusions of the model as it shows the impact that screening for preterm and treatment of those identified as being at higher risk has on important clinical outcomes having a large bearing on health related quality of life and "downstream" costs. The absolute reductions in these outcomes is relatively small although that needs to be considered in the context of the model that suggests, based on the available data on the distribution of cervical length, that only 0.85% to 13% of women would be identified for treatment based on a cervical screening length threshold of 25 mm. The numbers in Table 57 are based on just 100 women receiving vaginal progesterone for a twin pregnancy at higher risk of preterm birth. The reduction in the number of adverse outcomes from such a small treated population is derived from the best available clinical evidence (Romero 2016) which indicates that treatment can substantially reduce the risk of preterm birth.

Increasing the screening cervical length threshold does not increase the costs of screening, as all women with a twin pregnancy would be screened in any of the screening strategies. More women are identified for treatment as a result of increasing the cervical threshold and therefore a higher cervical length screening threshold will always generate a greater QALY gain even though the risks of prematurity decrease somewhat with increasing cervical length. Identifying more women obviously results in a higher treatment cost but in all the analyses this was more than offset by savings from reduced prematurity, as can be seen in Table 56, Table 60 and Table 62. Thus, a cervical length screening threshold of 25 mm always dominated screening thresholds of a shorter length, given the best available evidence on treatment effectiveness.

Whether, a cervical length screening threshold of 25 mm will be cheaper and hence dominant when compared to no screening depends on whether the savings from reduced prematurity more than offset the costs of screening and treatment as well as the additional monitoring costs incurred as a result delaying or preventing preterm birth. Most of the analyses undertaken demonstrated such dominance but not all.

We recognise that this model has a number of limitations. Perhaps most importantly is the uncertainty with respect to the actual distribution of cervical length in women who will be screened as a result of this guideline's recommendation. The distributions of cervical length used in this model were derived from the published literature and personal communication but in all cases percentages had to be estimated from a histogram bar chart. Two of the distributions were based on cervical length measured at 23 weeks (Souka 1999; Skentou 2001) which is later than screening is recommended in the guideline and as the cervix

shortens with gestational age it seems as though these distributions might under-estimate the number of women who would be identified as at higher risk of preterm birth by this guideline's recommendations. However, counter intuitively the Liem (2001) data reports women as being at lower risk of preterm birth as determined by cervical length despite cervical length been measured earlier in pregnancy and at a time more consistent with the gestational age of screening recommended in this guideline. This seeming anomaly highlights the uncertainty which exists with regard to the true underlying distribution of cervical length at the time of screening in women with a twin pregnancy. On balance we consider that the cervical length distribution used in the base case analysis (Liem, 2018) is more likely to represent the true distribution of cervical length as the reductions in adverse events using the other distributions (Skentou 2001, Souka 1999) in the very preterm would suggest that nearly all the risk is concentrated in the groups identified by screening. Nevertheless, it is important to recognise that this model demonstrated the cost-effectiveness of screening for preterm birth even when only 0.85% of twin pregnancies were identified as being at higher risk of preterm birth.

Pivotal to the analysis, are the modelled relationship between gestational age at birth and adverse outcomes. The model makes a simplifying assumption that the risks of adverse clinical outcomes relates solely to prematurity and that there are no independent risks from the twin pregnancy. Whilst recognising that there may be other fetal risks associated with twin pregnancy, such as fetal weight and co-existing pathologies, the purpose of the intervention is to prevent spontaneous preterm birth and the committee considered that it was reasonable to assume that preterm birth is the major concern at the point of care and that spontaneous preterm birth is the major risk to perinatal mortality and morbidity if it occurs. Therefore, much of the data used to inform the relationship between gestational age and adverse outcomes is derived from preterm singleton pregnancies in the absence of equivalent data for twin pregnancies. Whilst, there was very good data for stillbirths and neonatal deaths by gestational age somewhat crude estimates were necessary for some outcomes such as NICU admissions and cerebral palsy. The curve fitted to observed data on the risk of cerebral palsy, in order to derive an estimate cerebral palsy risk for each week of gestational age, generally gave a good approximation of the observed risk but the modelled risk was substantially over-estimated at a gestational age of 24 weeks and under-estimated at a gestational age of 30 weeks. Although these estimates of the risk of adverse outcomes were sourced from the literature, some additional simplifying assumptions were also required. For example, although the model includes a number of important baby outcomes known to be related to prematurity, it does not, because of complexity and the lack of available data, model all outcomes, such as all the neurodevelopmental problems that may result. Even with the outcomes that are included, the real world relationship with gestational age is more complicated than could be modelled. For example, the severity of cerebral palsy will also be related to gestational age at birth but in the model cerebral palsy is treated as a single entity. Nevertheless, these simplifying assumptions made with respect to gestational age and outcomes are unlikely to invalidate the findings of the model. Importantly, the fact that there is a relationship between the adverse outcomes in the model and gestational age at birth is not disputed and threshold sensitivity analysis suggested that the model conclusions were not sensitive to changes in the relevant parameter values, at least not in the context of an evidence based estimate of treatment effectiveness. Indeed the fact that not all outcomes linked to preterm birth are included in the analysis may mean that the cost effectiveness is potentially underestimated. It is also true that there are societal benefits beyond the health care sector from reducing preterm birth that are not factored into this analysis.

So, whilst the model has a number of limitations and simplifying assumptions we think it unlikely that they result in a misleading interpretation of the cost effectiveness of screening for preterm birth and treatment in those identified as being at higher risk of prematurity. Cost-effectiveness in the model is driven by evidence based estimates on treatment efficacy and the undisputed fact that preterm birth is associated with adverse outcomes leading to reductions in health related quality of life and "downstream" costs to the NHS.

Conclusion

The model suggested from the available distributions of cervical length in women with a twin pregnancy that a relatively small proportion of women pregnant with twins would be identified as at a higher risk of preterm birth by screening. Despite this, the analysis demonstrated that, with the best available clinical evidence, screening for preterm birth using a cervical length threshold of 25 mm followed by daily treatment with vaginal progesterone in those women identified as at higher risk of preterm birth was highly cost effective. Sensitivity analysis which subjected this finding to rigorous challenge suggested that the cost effectiveness conclusion was robust with respect to parameter uncertainty within the model. Therefore, the results of this economic evaluation provides good cost effectiveness evidence to support the recommendations made by the committee.

In addition to providing evidence on cost effectiveness the analyses also suggested that a screening strategy using a cervical length threshold of 25 mm would either be cost saving or only have a fairly limited cost impact to the NHS.

References – Appendix J

Campbell 2018
Campbell, H. E., Kurinczuk, J. J., Heazell, A., Leal, J. & Rivero-Arias, O., Healthcare and wider societal implications of stillbirth: a population-based cost-of-illness study. BJOG, 125, 108-117, 2018

Himpens 2008

Himpens, E., Van den Broeck, C., Oostra, A., Calders, P., Vanhaesebrouck, P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Child Neurol. 50(5):334-40, 2008.

Kato 2004

Kato, N. Reference birthweight range for multiple birth neonates in Japan. BMC Pregnancy Childbirth; 3;4(1):2. 2004

Khan 2015

Khan, K.A., Petrou, S., Dritsaki, M., Johnson, S.J., Manktelow, B., Draper, E.S., Smith, L.K., Seaton, S.E., Marlow, N., Dorling, J., Field, D.J., Boyle, E.M. Economic costs associated with moderate and late preterm birth: a prospective population-based study. BJOG; 122:1495–1505; 2015

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Kind, P., Hardman, G. & Macran, S., Centre for Health Economics Discussion Paper 172: UK population norms for EQ-5D, Centre for Health Economics, University of York, UK, 1999

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Kindinger, L.M., Poon, L.C., Cacciatore, S., MacIntyre, D.A., Fox, N.S., Schuit, E., Mol, B.W., Liem, S., Lim, A.C., Serra, V., Perales, A., Hermans, F., Darzi, A., Bennett, P., Nicolaides, K.H., Teoh, T.G. The effect of gestational age and cervical length measurements in the prediction of spontaneous preterm birth in twin pregnancies: an individual patient level meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 123(6):877-84, 2016.

Kruse 2009
Kruse, M., Michelsen, S. I., Flachs, E. M., Bronnum-Hansen, H., Madsen, M., & Uldall, P. Lifetime costs of cerebral palsy. Dev Med Child Neurol, 51(8), 622-628, 2009

Romero 2017

Romero, R., Conde-Agudelo, A., El-Refaie, W., Rode, L., Brizot, M. L., Cetingoz, E., Serra, V., Da Fonseca, E., Abdelhafez, M. S., Tabor, A., Perales, A., Hassan, S. S., Nicolaides, K. H., Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. Ultrasound in Obstetrics & Gynecology, 49, 303-314, 2017

Shulman 2006

Shulman, Lee S.; Vugt, John M. G. van (2006). Prenatal medicine. Washington, DC: Taylor & Francis. pp. Page 447. ISBN 0-8247-2844-0.CS1 maint:

Skentou 2001

Skentou C, Souka AP, To MS, Liao AW, Nicolaides KH. Prediction of preterm delivery in twins by cervical assessment at 23 weeks. Ultrasound Obstet Gynecol, 17(1):7-10, 2001

Souka 1999

Souka, A.P, Sevastopoulou, I., Nicolaides K.H. Cervical length at 23 weeks in twins in predicting spontaneous preterm delivery.

Appendix K – Excluded studies

Excluded studies for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?

Clinical studies

Study	Reason for Exclusion
Cerclage in multiple gestations with short cervix, ACOG Clinical Review, 11, 2, 2006	Abstract only
You be the judge. Should steroids, tocolytics have been given to stop premature birth of twins? , Ob-Gyn Malpractice Prevention, 6, 61, 1999	Narrative review
Progesterone does not appear to prevent twin preterm birth, Contemporary Ob/Gyn, 54, 16, 2009	Abstract only
Progesterone treatment does not reduce early preterm birth in twin pregnancy, Nurse Prescribing, 7, 330-331, 2009	Abstract only
Abdel-Aleem, H., Shaaban, O. M., Abdel-Aleem, M. A., Cervical pessary for preventing preterm birth, The Cochrane database of systematic reviews, 5, CD007873, 2013	Includes multiples and singletons
Aboulghar,M., Islam,Y., Twin and Preterm Labor: Prediction and Treatment, Current Obstetrics and Gynecology Reports, 2, 232-239, 2013	Narrative overview
Aboulghar,M.M., Aboulghar,M.A., Amin,Y.M., Al-Inany,H.G., Mansour,R.T., Serour,G.I., The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies, Reproductive Biomedicine Online, 25, 133-138, 2012	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Agra, I. K. R., Carvalho, M. H. B., Hernandez, W. R., Francisco, R. P. V., Zugaib, M., Brizot, M. L., The effect of prenatal vaginal progesterone on cervical length in nonselected twin pregnancies, Journal of Maternal-Fetal & Neonatal Medicine, 1-5, 2017	Secondary analysis of Brizot 2015 - no additional relevant outcomes
Ahn, K. H., Bae, N. Y., Hong, S. C., Lee, J. S., Lee, E. H., f, H. J., Cho, G. J., Oh, M. J., Kim, H. J., The safety of progestogen in the prevention of preterm birth: meta-analysis of neonatal mortality, Journal of Perinatal Medicine, 45, 11-20, 2017	Relevant studies included elsewhere
Ahuja, M., Bed rest in pregnancy and its related complications: Is it needed?, Journal of SAFOG, 4, 147-150, 2012	Abstract only
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	Observational, no intervention
Alsad,A.E., Murphy,J.F., The value of cervical cerclage in preventing pregnancy loss, Bahrain Medical Bulletin, 34, -, 2012	Non RCT for twins

Study	Reason for Exclusion
Al-Sunaidi,M., Al-Shahrani,M.S., Fetomaternal and neonatal outcome of triplet pregnancy. Promising results, Saudi Medical Journal, 32, 685-688, 2011	Not asymptomatic
Althuisius,S.M., Dekker,G.A., Hummel,P., Bekedam,D.J., van Geijn,H.P., Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone, American Journal of Obstetrics and Gynecology, 185, 1106-1112, 2001	Singletons only
Anonymous,, Progestogens and prevention of preterm birth in women at risk, Prescrire international, 25, 185-188, 2016	Narrative overview
Awwad, J, Usta, Im, Ghazeeri, G, Yacoub, N, Succar, J, Hayek, S, Saasouh, W, Nassar, Ah, A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 122, 71-79, 2015	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Azria, E., The use of progestatives for the prevention of spontaneous preterm birth, Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1280-1298, 2016	Article in French
Berghella,V., Baxter,J.K., Hendrix,N.W., Cervical assessment by ultrasound for preventing preterm delivery, Cochrane database of systematic reviews (Online), 1, CD007235-, 2013	Screening review -transvaginal ultrasound of cervical length (TVU CL) screening
Berghella,V., Odibo,A.O., Tolosa,J.E., Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial, American Journal of Obstetrics and Gynecology, 191, 1311-1317, 2004	Mainly singletons - cannot separate data
Biggio, J. R., Anderson, S., Spontaneous Preterm Birth in Multiples, Clinical Obstetrics & Gynecology, 58, 654-67, 2015	Screening narrative review
Briery,C.M., Veillon,E.W., Klauser,C.K., Martin,R.W., Chauhan,S.P., Magann,E.F., Morrison,J.C., Progesterone does not prevent preterm births in women with twins, Southern Medical Journal, 102, 900-904, 2009	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Brizot, Ml, Hernandez, W, Liao, Aw, Bittar, Re, Francisco, Rp, Krebs, Vl, Zugaib, M, Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study, American Journal of Obstetrics and Gynecology, 213, 82.e1-9, 2015	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Brun, S., Cervical pessary and spontaneous preterm birth, Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1324-1336, 2016	Article in French

Study	Reason for Exclusion
Campbell, S., Prevention of spontaneous preterm birth: universal cervical length assessment and vaginal progesterone in women with a short cervix: time for action!, American Journal of Obstetrics and Gynecology, 218, 151-158, 2018	Narrative overview
Caritis, S. N., Rouse, D. J., Peaceman, A. M., Sciscione, A., Momirova, V., Spong, C. Y., Iams, J. D., Wapner, R. J., Varner, M., Carpenter, M., Lo, J., Thorp, J., Mercer, B. M., Sorokin, Y., Harper, M., Ramin, S., Anderson, G., Eunice Kennedy Shriver National Institute of Child, Health, Human Development, Maternal-Fetal Medicine Units Network, Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial, Obstet Gynecol, 113, 285-92, 2009	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Caritis, Sn, Simhan, Hn, Zhao, Y, Rouse, Dj, Peaceman, Am, Sciscione, A, Spong, Cy, Varner, Mw, Malone, Fd, Iams, Jd, Mercer, Bm, Thorp, Jm, Sorokin, Y, Carpenter, M, Lo, J, Ramin, Sm, Harper, M, Relationship between 17-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation, American Journal of Obstetrics and Gynecology, 207, 396.e1-8, 2012	Secondary analysis of Rouse 2007 (additional blood analysis) - no additional relevant outcomes
Carreras,E., Arevalo,S., Bello-Munoz,J.C., Goya,M., Rodo,C., Sanchez-Duran,M.A., Peiro,J.L., Cabero,L., Arabin cervical pessary to prevent preterm birth in severe twin-to-twin transfusion syndrome treated by laser surgery, Prenatal Diagnosis, 32, 1181-1185, 2012	Non RCT of twins
Centre for Reviews and Dissemination, Nifedipine versus ritodrine for suppression of preterm labor: a meta-analysis (Structured abstract), Database of Abstracts of Reviews of Effects, 4, 2009	Abstract only
Cetingoz,E., Cam,C., Sakalli,M., Karateke,A., Celik,C., Sancak,A., Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial, Archives of Gynecology and Obstetrics, 283, 423-429, 2011	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Cetrulo,C.L., Freeman,R.K., Ritodrine HCL for the prevention of premature labor in twin pregnancies, Acta Geneticae Medicae et Gemellologiae, 25, 321-324, 1976	Preliminary results only/ overview of protocol to date
Choi, S. J., Use of progesterone supplement therapy for prevention of preterm birth: review of literatures, Obstetrics & Gynecology Science, 60, 405-420, 2017	Focus on singles, only relevant studies already included
Collins, A., Shennan, A., A clinical opinion on how to manage the risk of preterm birth in twins based on literature review, Journal of Maternal-Fetal & Neonatal Medicine, 29, 1125-30, 2016	Narrative overview

Study	Reason for Exclusion
Combs, C. A., Garite, T., Maurel, K., Das, A., Porto, M., Obstetrix Collaborative Research, Network, Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial, Am J Obstet Gynecol, 203, 248 e1-9, 2010	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Combs, Ca, Garite, T, Maurel, K, Das, A, Porto, M, 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial, American Journal of Obstetrics and Gynecology, 204, 221.e1-8, 2011	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Combs,C.A., Vaginal progesterone for asymptomatic cervical shortening and the case for universal screening of cervical length, American Journal of Obstetrics and Gynecology, 206, 101-103, 2012	Narrative overview
Combs,C.A., Garite,T., Maurel,K., Das,A., Porto,M., 17-Hydroxyprogesterone caproate for twin pregnancy: A double-blind, randomized clinical trial, Obstetrical and Gynecological Survey, 66, 393-394, 2011	Editorial comments only
Crowther, C. A., Ashwood, P., McPhee, A. J., Flenady, V., Tran, T., Dodd, J. M., Robinson, J. S., Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial, PLoS Medicine, 14 (9) (no pagination), 2017	Cannot separate singletons and twins. Only 12/787 were twins
Crowther, CA, Hospitalisation and bed rest for multiple pregnancy, Cochrane Database of Systematic Reviews, 4, 2009	Duplicate
Crowther, CA, Selected Cochrane systematic reviews. Bed rest in hospital for multiple pregnancy, Birth: Issues in Perinatal Care, 26, 201-202, 1999	Abstract only
Crowther, Caroline A, Han, Shanshan, Hospitalisation and bed rest for multiple pregnancy, Cochrane Database of Systematic Reviews, 2010	Included more recent review - da Silva Lopes (2017) update instead
Crowther,C.A, Han,S., Hospitalisation and bed rest for multiple pregnancy, Cochrane Database of Systematic Reviews, -, 2010	Duplicate
Crowther,C.A., Middleton,P.F., Wilkinson,D., Ashwood,P., Haslam,R., Magnesium sulphate at 30 to 34 weeks' gestational age: Neuroprotection trial (MAGENTA) - study protocol, BMC Pregnancy and Childbirth, 13 , 2013. Article Number, -, 2013	No relevant outcomes
da, Silva Lopes Katharina, Takemoto, Yo, Ota, Erika, Tanigaki, Shinji, Mori, Rintaro, Bed rest with and without hospitalisation in multiple pregnancy for improving perinatal outcomes, Cochrane Database of Systematic Reviews, 2017	Review of multiples - cannot separate twin from triplet data. Meta analyses of combined data

Study	Reason for Exclusion
de Heus, R., Mol, B. W., Erwich, J. J., van Geijn, H. P., Gyselaers, W. J., Hanssens, M., Harmark, L., van Holsbeke, C. D., Duvekot, J. J., Schobben, F. F., Wolf, H., Visser, G. H., Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study, BMJ, 338, b744, 2009	Cannot separate data for singletons and multiples. Non RCT
De La Calle, M., Arevalo, S., Martinez, N., Rodo, C., Antolin, E., Carreras, E., Bartha, J. L., The use of cervical pessary in a spanish population of triplet pregnancies, Twin Research and Human Genetics, 20, 636-637, 2017	Abstract only
De La Calle, M., Illescas, T., Goya, M. M., Fernandez, S., Arevalo, S., Martin Boado, E., Rodo, C., Carreras, E., Bartha, J. L., The use of cervical pessary in a spanish population of triplet pregnancies, Journal of Maternal-Fetal and Neonatal Medicine, 29, 69, 2016	Abstract only
Dodd, J. M, Jones, L, Flenady, V, Cincotta, R, Crowther, C. A., Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, Cochrane Database of Systematic Reviews, 7, CD004947, 2013	Duplicate
Dodd, J. M., Crowther, C. A., Hospitalisation for bed rest for women with a triplet pregnancy: an abandoned randomised controlled trial and meta-analysis, BMC Pregnancy Childbirth, 5, 8, 2005	Case series
Dodd, J. M., Grivell, R. M., Obrien, C. M., Dowswell, T., Deussen, A. R., Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy, Cochrane Database of Systematic Reviews, 2017 (10) (no pagination), 2017	Combined as "multiples": cannot separate data
Dodd, Jodie M, Jones, Leanne, Flenady, Vicki, Cincotta, Robert, Crowther, Caroline A, Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, Cochrane Database of Systematic Reviews, 2013	All relevant studies covered elsewhere
Dodd,J.M., Flenady,V.J., Cincotta,R., Crowther,C.A., Progesterone for the prevention of preterm birth: a systematic review, Obstetrics and Gynecology, 112, 127-134, 2008	Only 2 relevant studies, already included
Downing, M., Sulo, S., Parilla, B. V., Perinatal and Neonatal Outcomes of Triplet Gestations Based on Chorionicity, American journal of perinatology reports, 7, e59-e63, 2017	No interventions, observational/ audit of all interventions for preterm birth: DC&MC-v-TC triplets
Doyle,L.W., Antenatal progesterone to prevent preterm birth, The Lancet, 373, 2000-2002, 2009	Commentary/narrative article
Dudenhausen, J. W., Tocolysis in the management of multiple pregnancy, BJOG: An International Journal of Obstetrics and Gynaecology, 110, 107, 2003	Short narrative overview

Study	Reason for Exclusion
Dunn, B., Bed rest in twin pregnancy, J Obstet Gynaecol Br Emp, 68, 685-7, 1961	Non RCT for twins
Durnwald, C. P, Momirova, V, Rouse, D. J, Caritis, S. N, Peaceman, A. M, Sciscione, A, Varner, M. W, Malone, F. D, Mercer, B. M, Thorp, J. M, Jr, Sorokin, Y, Carpenter, M. W, Lo, J, Ramin, S. M, Harper, M, Spong, C. Y, Eunice Kennedy Shriver National Institute of Child, Health, Human Development Maternal-Fetal Medicine Units, Network, Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17-alpha hydroxyprogesterone caproate, Journal of Maternal-Fetal & Neonatal Medicine, 23, 1360-4, 2010	Secondary analysis of Rouse 2007, already included. No further usable data to original study publication
El-refaie, W, Abdelhafez, Ms, Badawy, A, Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety, Archives of Gynecology and Obstetrics, 293, 61-67, 2016	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Endl, J., Baumgarten, K., [Results of prophylactic oral long term tocolysis and cerclage for the prolongation of twin pregnancy (a multi-center study)], Z Geburtshilfe Perinatol, 186, 319-25, 1982	Full text identified as German
Eskandar,M., Shafiq,H., Almushait,M.A., Sobande,A., Bahar,A.M., Cervical cerclage for prevention of preterm birth in women with twin pregnancy, International Journal of Gynaecology and Obstetrics, 99, 110-112, 2007	Not randomised
Falcao, V., Melo, C., Matias, A., Montenegro, N., Cervical pessary for the prevention of preterm birth: is it of any use?, Journal of Perinatal Medicine, 45, 21-27, 2017	Narrative overview
Folterman, C., Cervical Pessary and Vaginal Progesterone in Twin Pregnancies With a Short Cervix, Obstetrics & Gynecology, 128, 407-8, 2016	Correspondence/letter
Fonseca, E. B., Celik, E., Parra, M., Singh, M., Nicolaides, K. H., Fetal Medicine Foundation Second Trimester Screening, Group, Progesterone and the risk of preterm birth among women with a short cervix, N Engl J Med, 357, 462-9, 2007	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Friedman, A. M., Ananth, C. V., Siddiq, Z., D'Alton, M. E., Wright, J. D., Trends and Predictors of Cerclage Use in the United States from 2005 to 2012, Obstetrics and Gynecology, 126, 243-249, 2015	Data cannot be separated for triplets. Available data can be calculated for twins and triplet only. Unmatched cohorts
Goya, M, Calle, M, Pratcorona, L, Merced, C, Rodó, C, Muñoz, B, Juan, M, Serrano, A, Llurba, E, Higueras, T, Carreras, E, Cabero, L, Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins), American	Covered in systematic review - Jarde 2017

Study	Reason for Exclusion
Journal of Obstetrics and Gynecology, 214, 145-152, 2016	
Goya, M., Cabero, L., Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial, American Journal of Obstetrics & Gynecology, 214, 301-2, 2016	Letter/reply to Nicolaides study
Gummerus, M., Halonen, O., [The value of bed rest and beta-sympathomimetic treatment in multiple pregnancies], Duodecim, 101, 1966-71, 1985	Full text identified as Finnish
Gummerus,M., Halonen,O., Prophylactic long-term oral tocolysis of multiple pregnancies, British Journal of Obstetrics and Gynaecology, 94, 249-251, 1987	Includes women with uterine contractions (not asymptomatic)
Haas,D.M., Caldwell,D.M., Kirkpatrick,P., McIntosh,J.J., Welton,N.J., Tocolytic therapy for preterm delivery: systematic review and network meta-analysis, BMJ, 345, e6226-, 2012	No separate data for multiples
Hartikainen-Sorri, AL; Jouppila, P, Is routine hospitalization needed in antenatal care of twin pregnancy?, Journal of Perinatal Medicine, 12, 31-34, 1984	No relevant outcomes (short communication)
Hartikainen-Sorri,A.L., Kauppila,A., Tuimala,R., Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy, Obstetrics and Gynecology, 56, 692-695, 1980	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Hernandez, W. R., Francisco, R. P. V., Bittar, R. E., Gomez, U. T., Zugaib, M., Brizot, M. L., Effect of vaginal progesterone in tocolytic therapy during preterm labor in twin pregnancies: Secondary analysis of a placebo-controlled randomized trial, Journal of Obstetrics and Gynaecology Research, 43, 1536-1542, 2017	Secondary analysis - no additional outcomes - women were participating in the primary study
Jeffrey, R. L., Bowes, W. A., Jr., Delaney, J. J., Role of bed rest in twin gestation, Obstet Gynecol, 43, 822-6, 1974	Non RCT for twins
Jia, Xy, Liu, Xr, Luo, X, Xiao, Xq, Qi, Hb, Cervical cerclage for preventing preterm birth in twin pregnancies: a systematic review and meta-analysis (Provisional abstract), Saudi Medical JournalSaudi Med J, 34, 632-638, 2013	Only one relevant included study(Dor 1982) already included elsewhere
Jonas, E. G., The value of prenatal bed-rest in multiple pregnany, J Obstet Gynaecol Br Emp, 70, 461-4, 1963	No relevant outcomes
Jorgensen, A. L., Alfirevic, Z., Tudur Smith, C., Williamson, P. R., cerclage, I. P. D. Meta-analysis Group, Cervical stitch (cerclage) for preventing pregnancy loss: individual patient data meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 114, 1460-76, 2007	Multiples excluded from main outcome analysis

Study	Reason for Exclusion
Kappel, B., Hansen, K. B., Moller, J., Faaborg-Andersen, J., Bed rest in twin pregnancy, Acta Genet Med Gemellol (Roma), 34, 67-71, 1985	Non RCT for twins
KarisAllen, L., Schulz, J., Flood, C., Ross, S., Naud, K., Retrospective Cohort Study of Cervical Pessary Use in Women with Short Cervix at Risk of Preterm Delivery, Journal of Obstetrics and Gynaecology Canada, 39, 1137-1142, 2017	Non RCT (for twins). Cohort for triplets: only n=3/115 cases. Cannot be separated from other data
Kawaguchi,H., Ishii,K., Yamamoto,R., Hayashi,S., Mitsuda,N., Perinatal death of triplet pregnancies by chorionicity, American Journal of Obstetrics and Gynecology, 209, 36e1-36e7, 2013	Unmatched cohort - no comparison group. (Different chorionicities compared)
Klein, K., Rode, L., Nicolaides, K. H., Krampl-Bettelheim, E., Tabor, A., Predict Group, Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 38, 281-287, 2011	Secondary analysis of PREDICT - no additional relevant outcomes
Komaromy, B., Lampe, L., The value of bed rest in twin pregnancies, Int J Gynaecol Obstet, 15, 262-6, 1977	Non RCT for twins
Kyvernitakis, I., Arabin, B., Re: Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial, Ultrasound in Obstetrics & Gynecology, 50, 408-409, 2017	Correspondence - no abstract available
Laursen, B., Twin pregnancy. The value of prophylactic rest in bed and the risk involved, Acta Obstet Gynecol Scand, 52, 367-71, 1973	Non RCT for twins
Liem, S., Schuit, E., Hegeman, M., Bais, J., de Boer, K., Bloemenkamp, K., Brons, J., Duvekot, H., Bijvank, B. N., Franssen, M., Gaugler, I., de Graaf, I., Oudijk, M., Papatsonis, D., Pernet, P., Porath, M., Scheepers, L., Sikkema, M., Sporken, J., Visser, H., van Wijngaarden, W., Woiski, M., van Pampus, M., Mol, B. W., Bekedam, D., Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial, Lancet, 382, 1341-9, 2013	Covered in systematic review - Jarde 2017
Liem, S., Schuit, E., Hegeman, M., Bais, J., De Boer, K., Bloemenkamp, K., Brons, J., Duvekot, H., Bijvank, B. N., Franssen, M., Gaugler, I., De Graaf, I., Oudijk, M., Papatsonis, D., Pernet, P., Porath, M., Scheepers, L., Sikkema, M., Sporken, J., Visser, H., Van Wijngaarden, W., Woiski, M., Van Pampus, M., Willem Mol, B., Bekedam, D., Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): A multicentre, open-label	Editorial overview/ abstract of proTWIN study (included elsewhere)

Study	Reason for Exclusion
randomised controlled trial, Obstetrical and Gynecological Survey, 69, 73-75, 2014	
Liem, Sm, Schuit, E, Pampus, Mg, Melick, M, Monfrance, M, Langenveld, J, Mol, Bw, Bekedam, D, Cervical pessaries to prevent preterm birth in women with a multiple pregnancy: a per-protocol analysis of a randomized clinical trial, Acta Obstetricia et Gynecologica Scandinavica, 95, 444-451, 2016	Included elsewhere - proTWIN (Liem 2013) study - secondary analysis (no additional outcomes)
Likis, F. E., Edwards, D. R. V., Andrews, J. C., Woodworth, A. L., Jerome, R. N., Fonnesbeck, C. J., McKoy, J. N., Hartmann, K. E., Progestogens for preterm birth prevention: A systematic review and meta-analysis, Obstetrics and Gynecology, 120, 897-907, 2012	All relevant studies covered elsewhere
Lim, A. C, Schuit, E, Bloemenkamp, K, Bernardus, R. E, Duvekot, J. J, Erwich, J. J, van Eyck, J, Groenwold, R. H, Hasaart, T. H, Hummel, P, Kars, M. M, Kwee, A, van Oirschot, C. M, van Pampus, M. G, Papatsonis, D, Porath, M. M, Spaanderman, M. E, Willekes, C, Wilpshaar, J, Mol, B. W, Bruinse, H. W., 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial, Obstetrics & Gynecology, 118, 513-20, 2011	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Lim, A. C., Bloemenkamp, K. W., Boer, K., Duvekot, J. J., Erwich, J. J., Hasaart, T. H., Hummel, P., Mol, B. W., Offermans, J. P., van Oirschot, C. M., Santema, J. G., Scheepers, H. C., Schols, W. A., Vandenbussche, F. P., Wouters, M. G., Bruinse, H. W., Amphia study group, Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial, BMC Pregnancy & Childbirth, 7, 7, 2007	Protocol only
Lim, A. C., Schuit, E., Papatsonis, D., van Eyck, J., Porath, M. M., van Oirschot, C. M., Hummel, P., Hasaart, T. H., Kleiverda, G., de Graaf, I. M., van Ginkel, A. A., Mol, B. W., Bruinse, H. W., Effect of 17-alpha hydroxyprogesterone caproate on cervical length in twin pregnancies, Ultrasound in Obstetrics & Gynecology, 40, 426-30, 2012	AMPHIA study included elsewhere - secondary analysis - examines cervical length only
Lim, Ac, Schuit, E, Papatsonis, D, Eyck, J, Porath, Mm, Oirschot, Cm, Hummel, P, Hasaart, Th, Kleiverda, G, Graaf, Im, Ginkel, Aa, Mol, Bw, Bruinse, Hw, Effect of 17-alpha hydroxyprogesterone caproate on cervical length in twin pregnancies, Ultrasound in Obstetrics & Gynecology, 40, 426-430, 2012	No relevant outcomes - secondary analysis of cervical length
Lim,A.C., Mol,B.W.J., Schuit,E., Bruinse,H.W., 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: A randomized controlled trial, Obstetrics and Gynecology, 119, 385-386, 2012	Abstract only

Study	Reason for Exclusion
Liu, X. R., Luo, X., Xiao, X. Q., Qi, H. B., Cervical cerclage for preventing preterm birth in twin pregnancies. A systematic review and meta-analysis, Saudi Medical Journal, 34, 632-8, 2013	SR with MA of cerclage for preterm birth - not specifically asymptomatic
MacNaughton, M; Chalmers, I; Dubowitz, V; Dunn, P; Grant, A;, McPherson, K., Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomised trial of cervical cerclage, Br J Obstet Gynaecol, 100, 516-23, 1993	Singletons and twins, cannot separate data
MacPhedran, S. E., Sexual Activity Recommendations in High-Risk Pregnancies: What is the Evidence?, Sexual Medicine Reviews, 6, 343-357, 2018	Systematic review with no usable data
Maisonneuve, E., Lifestyle recommendations for prevention of spontaneous preterm birth in asymptomatic pregnant women, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 45, 1231-1246, 2016	French Guideline (article in French)- expert recommendation, not study or SR
Marasinghe, J. P., Cervical Pessary and Vaginal Progesterone in Twin Pregnancies With a Short Cervix, Obstetrics & Gynecology, 128, 408, 2016	Correspondence/letter
Marcellin, L., Prevention of preterm birth by uterine cervical cerclage, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 45, 1299-1323, 2016	Article in French (expert/professional guideline/consensus statement)
Marret, S., Ancel, P. Y., Neuroprotection for preterm infants with antenatal magnesium sulphate, Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1418-1433, 2016	Article in French. Consensus statement/overview
Matsui, M., Takahashi, Y., Iwagaki, S., Chiaki, R., Asai, K., Kawabata, I., Preliminary preventive protocol from first trimester of pregnancy to reduce preterm birth rate for dichorionic-diamniotic twins, Taiwanese Journal of Obstetrics & Gynecology, 56, 23-26, 2017	Non RCT (case-control study)
Miyazaki, C., Moreno, R. G., Ota, E., Swa, T., Oladapo, O. T., Mori, R., Tocolysis for inhibiting preterm birth in extremely preterm birth, multiple gestations and in growth-restricted fetuses: a systematic review and meta-analysis, Reproductive Health, 13 (1) (no pagination), 2016	SR with MA - no RCTs included for twins, or nonRCTs for triplets
Monfrance, M. J. M., Schuit, E., Groenwold, R. H., Oudijk, M. A., De Graaf, I. M., Bax, C. J., Bekedam, D. J., Mol, B. W., Langenveld, J., Pessary placement in the prevention of preterm birth in multiple pregnancies: A propensity score analysis, European Journal of Obstetrics Gynecology and Reproductive Biology, 197, 72-77, 2016	Cohort - cannot separate triplet data from other data
Mulder,E.J., Versteegh,E.M., Bloemenkamp,K.W., Lim,A.C., Mol,B.W., Bekedam,D.J., Kwee,A.,	Secondary analysis of AMPHIA trial - no additional relevant outcomes

Study	Reason for Exclusion
Bruinse,H.W., Christiaens,G.C., Does 17-alpha-hydroxyprogesterone caproate affect fetal biometry and birth weight in twin pregnancy?, Ultrasound in Obstetrics and Gynecology, 42, 329-334, 2013	
Nassar,A.H., Sakhel,K., Maarouf,H., Naassan,G.R., Usta,I.M., Adverse maternal and neonatal outcome of prolonged course of magnesium sulfate tocolysis, Acta Obstetricia et Gynecologica Scandinavica, 85, 1099-1103, 2006	Twins and triplets, cannot separate data - non RCT
Newman,R.B., Krombach,R.S., Myers,M.C., McGee,D.L., Effect of cerclage on obstetrical outcome in twin gestations with a shortened cervical length, American Journal of Obstetrics and Gynecology, 186, 634-640, 2002	Non RCT for twins
Nicolaides, K. H., Syngelaki, A., Poon, L. C., de Paco Matallana, C., Plasencia, W., Molina, F. S., Picciarelli, G., Tul, N., Celik, E., Lau, T. K., Conturso, R., Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial, American Journal of Obstetrics and Gynecology, 214, 3.e1-9, 2016	Covered in systematic review - Jarde 2017
Norman, Je, Yuan, M, Anderson, L, Howie, F, Harold, G, Young, A, Jordan, F, McInnes, I, Harnett, Mm, Effect of prolonged in vivo administration of progesterone in pregnancy on myometrial gene expression, peripheral blood leukocyte activation, and circulating steroid hormone levels, Reproductive sciences (thousand oaks, calif.), 18, 435-446, 2011	Secondary analysis of STOPPIT trial - no additional relevant outcomes
O'Brien, J. M., Lewis, D. F., Prevention of preterm birth with vaginal progesterone or 17-alpha-hydroxyprogesterone caproate: a critical examination of efficacy and safety, American Journal of Obstetrics & Gynecology, 214, 45-56, 2016	Narrative overview/ expert review
O'Brien, J. M., Santolaya, J. L., Palomares, K., Blitzer, D., Santolaya-Forgas, J., Association of histological chorioamnionitis and magnesium sulfate treatment in singleton and dichorionic twin pregnancies with preterm premature rupture of membranes: preliminary observations, Journal of Perinatal Medicine, 05, 05, 2017	Observational, no intervention
O'Brien,J.M., 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: A randomized controlled trial, Obstetrics and Gynecology, 119, 384-385, 2012	Correspondence/letter
Odibo,A.O., Elkousy,M., Ural,S.H., Macones,G.A., Prevention of preterm birth by cervical cerclage compared with expectant management: a systematic review, Obstetrical and Gynecological Survey, 58, 130-136, 2003	SR - only one relevant study - included elsewhere

Study	Reason for Exclusion
Oliveira, La, Brizot, Ml, Liao, Aw, Bittar, Re, Francisco, Rp, Zugaib, M, Prenatal administration of vaginal progesterone and frequency of uterine contractions in asymptomatic twin pregnancies, Acta Obstetricia et Gynecologica Scandinavica, 95, 436-443, 2016	Secondary analysis of included study (Brizot) - no relevant outcome - uterine contraction
Park,J.M., Tuuli,M.G., Wong,M., Carbone,J.F., Ismail,M., Macones,G.A., Odibo,A.O., Cervical cerclage: one stitch or two?, American Journal of Perinatology, 29, 477-481, 2012	Only 12% multiple gestation (remainder singletons) cannot separate data
Pittrof, R., The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy, Br J Obstet Gynaecol, 98, 416-7, 1991	Correspondence/letter
Pulkkinen, M. O., Gronroos, M., Bed rest did not prevent prematurity in twins because the etiology lies in the stretch and poor progesteronegenesis, Acta Obstet Gynecol Scand, 58, 569-70, 1979	Correspondence/letter
Rafael, T. J., Berghella, V., Alfirevic, Z., Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy, Cochrane Database of Systematic Reviews, 9, CD009166, 2014	Only one relevant study (Dor 1982) already included elsewhere
Rebarber,A., Bender,S., Silverstein,M., Saltzman,D.H., Klauser,C.K., Fox,N.S., Outcomes of emergency or physical examination-indicated cerclage in twin pregnancies compared to singleton pregnancies, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 173, 43-47, 2014	Non RCT, comparing twins to singles. Unmatched cohort
Redulla, R., Bed rest with and without hospitalization in multiple pregnancy for improving perinatal outcomes, International Journal of Nursing PracticeInt J Nurs Pract, e12667, 2018	Appears to be an Executive Summary of a systematic review, presents no usable data, and no link to full review
Rode, L, Klein, K, Larsen, H, Holmskov, A, Andreasen, Kr, Uldbjerg, N, Ramb, J, Bødker, B, Skibsted, L, Sperling, L, Hinterberger, S, Krebs, L, Zingenberg, H, Weiss, Ec, Strobl, I, Laursen, L, Christensen, Jt, Skogstrand, K, Hougaard, Dm, Krampl-Bettelheim, E, Rosthøj, S, Vogel, I, Tabor, A, Cytokines and the risk of preterm delivery in twin pregnancies, Obstetrics and Gynecology, 120, 60-68, 2012	Secondary analysis of PREDICT trial - no additional relevant outcomes
Rode, L., Klein, K., Nicolaides, K. H., Krampl-Bettelheim, E., Tabor, A., Predict Group, Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 38, 272-280, 2011	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD

Study	Reason for Exclusion
Rode,L., Tabor,A., Prevention of preterm delivery in twin pregnancy, Best Practice and Research in Clinical Obstetrics and Gynaecology, 28, 273-283, 2014	Overview of reviews and studies with Practice points (narrative)
Roman, A., Rochelson, B., Fox, N. S., Hoffman, M., Berghella, V., Patel, V., Calluzzo, I., Saccone, G., Fleischer, A., Efficacy of ultrasound-indicated cerclage in twin pregnancies, American Journal of Obstetrics & Gynecology, 212, 788.e1-6, 2015	Non RCT (retrospective cohort) in twins
Roman,A.S., Saltzman,D.H., Fox,N., Klauser,C.K., Istwan,N., Rhea,D., Rebarber,A., Prophylactic cerclage in the management of twin pregnancies, American Journal of Perinatology, 30, 751-754, 2013	Non RCT - retrospective cohort study (in twins)
Roman,A.S., Fishman,S., Fox,N., Klauser,C., Saltzman,D., Rebarber,A., Maternal and neonatal outcomes after delayed-interval delivery of multifetal pregnancies, American Journal of Perinatology, 28, 91-95, 2011	Retrospective cohort - delayed interval birth (on twin born, then other twin birth delayed by days/weeks)
Romero, R., Nicolaides, K., Conde-Agudelo, A., Tabor, A., O'Brien, J. M., Cetingoz, E., Da Fonseca, E., Creasy, G. W., Klein, K., Rode, L., Soma-Pillay, P., Fusey, S., Cam, C., Alfirevic, Z., Hassan, S. S., Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: A systematic review and metaanalysis of individual patient data, American Journal of Obstetrics and Gynecology, 206, 124.e1-124.e19, 2012	Update of this SR (Romero 2017) included instead
Rouse, D. J., Caritis, S. N., Peaceman, A. M., Sciscione, A., Thom, E. A., Spong, C. Y., Varner, M., Malone, F., Iams, J. D., Mercer, B. M., Thorp, J., Sorokin, Y., Carpenter, M., Lo, J., Ramin, S., Harper, M., Anderson, G., National Institute of Child, Health, Human Development Maternal-Fetal Medicine Units, Network, A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins, N Engl J Med, 357, 454-61, 2007	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Rust, O. A., Atlas, R. O., Reed, J., van Gaalen, J., Balducci, J., Revisiting the short cervix detected by transvaginal ultrasound in the second trimester: why cerclage therapy may not help, Am J Obstet Gynecol, 185, 1098-105, 2001	Singles and multiples. Approx. one-third twins, no detail, cannot separate singleton and twin data
Saccone, G., Ciardulli, A., Xodo, S., Dugoff, L., Ludmir, J., D'Antonio, F., Boito, S., Olearo, E., Votino, C., Maruotti, G. M., Rizzo, G., Martinelli, P., Berghella, V., Cervical pessary for preventing preterm birth in twin pregnancies with short cervical length: a systematic review and meta-analysis, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 30, 2918-2925, 2017	Only relevant studies already in included list

Study	Reason for Exclusion
Schmouder,V.M., Prescott,G.M., Franco,A., Fan-Havard,P., The rebirth of progesterone in the prevention of preterm labor, Annals of Pharmacotherapy, 47, 527-536, 2013	SR but no MA (included papers reported elsewhere)
Scott-Findlay, S., Days of waiting. Bedrest with a twin pregnancy, AWHONN Lifelines, 8, 480, 477-9, 2004	Non RCT
Senat, Mv, Porcher, R, Winer, N, Vayssière, C, Deruelle, P, Capelle, M, Bretelle, F, Perrotin, F, Laurent, Y, Connan, L, Langer, B, Mantel, A, Azimi, S, Rozenberg, P, Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial, American Journal of Obstetrics and Gynecology, 208, 194.e1-8, 2013	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Serra,V., Perales,A., Meseguer,J., Parrilla,J.J., Lara,C., Bellver,J., Grifol,R., Alcover,I., Sala,M., Martinez-Escoriza,J.C., Pellicer,A., Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 50-57, 2013	No additional relevant data to that extracted and analysed in SR with MA or MA with IPD
Smith, J., DeFranco, E. A., Tocolytics used as adjunctive therapy at the time of cerclage placement: a systematic review, Journal of PerinatologyJ Perinatol, 35, 561-5, 2015	SR - no relevant included studies
Society for Maternal-Fetal Medicine Publications, Committee, The role of cervical pessary placement to prevent preterm birth in clinical practice, American Journal of Obstetrics & Gynecology, 216, B8-B10, 2017	Overview/narrative review
Sotiriadis,A., Papatheodorou,S., Makrydimas,G., Perinatal outcome in women treated with progesterone for the prevention of preterm birth: a meta-analysis, Ultrasound in Obstetrics and Gynecology, 40, 257-266, 2012	More recent SR available with IPD for triplets - Combs 2015 (includes same two triplet studies, and more recent RCT)
Stock, S. J., Ismail, K. M., Which intervention reduces the risk of preterm birth in women with risk factors?, BMJ, 355, i5206, 2016	Narrative overview
Sullivan, S. A., Newman, R., Prediction and prevention of preterm delivery in multiple gestations, Clin Obstet GynecolClinical obstetrics and gynecology, 47, 203-15, 2004	Narrative overview
Sureau, C; Breart, G, The prevention of premature birth, Annales Nestle, 47, 89-96, 1989	Narrative overview
Swaby, S, Pilot randomized controlled trial of vaginal progesterone to prevent preterm birth in multiple pregnancy, JOGC: Journal of Obstetrics and Gynaecology Canada, 29, S47, 2007	Abstract only

Study	Reason for Exclusion
TambyRaja, R. L., Atputharajah, V., Salmon, Y., Prevention of prematurity in twins, Aust N Z J Obstet Gynaecol, 18, 179-81, 1978	Non RCT in twins
Thangatorai, R., Lim, F. C., Nalliah, S., Cervical pessary in the prevention of preterm births in multiple pregnancies with a short cervix: PRISMA compliant systematic review and meta-analysis, Journal of Maternal-Fetal & Neonatal Medicine, 31, 1638-1645, 2018	Only relevant studies already in included list
Tita, A. T., Rouse, D. J., Progesterone for preterm birth prevention: an evolving intervention, Am J Obstet Gynecol, 200, 219-24, 2009	All relevant studies already included
van Zijl, M. D., Koullali, B., Naaktgeboren, C. A., Schuit, E., Bekedam, D. J., Moll, E., Oudijk, M. A., van Baal, W. M., de Boer, M. A., Visser, H., van Drongelen, J., van de Made, F. W., Vollebregt, K. C., Muller, M. A., Bekker, M. N., Brons, J. T. J., Sueters, M., Langenveld, J., Franssen, M. T., Schuitemaker, N. W., van Beek, E., Scheepers, H. C. J., de Boer, K., Tepe, E. M., Huisjes, A. J. M., Hooker, A. B., Verheijen, E. C. J., Papatsonis, D. N., Mol, B. W. J., Kazemier, B. M., Pajkrt, E., Pessary or Progesterone to Prevent Preterm delivery in women with short cervical length: The Quadruple P randomised controlled trial, BMC Pregnancy and Childbirth, 17, 284, 2017	Protocol only
Wilson,M.S., Ingersoll,M., Meschter,E., Bodea-Braescu,A.V., Edwards,R.K., Evaluating the side effects of treatment for preterm labor in a center that uses "high-dose" magnesium sulfate, American Journal of Perinatology, 31, 711-716, 2014	Triplet data cannot be extracted from other "high risk", side effects versus no side effects as cohorts
Xiao,C., Gangal,M., Abenhaim,H.A., Effect of magnesium sulfate and nifedipine on the risk of developing pulmonary edema in preterm births, Journal of Perinatal Medicine, 42, 585-589, 2014	No relevant population
Xu, Y. J., Ran, L. M., Luo, X. H., Zhai, S. S., Zhou, Z. Y., Zhang, Y. Y., Liu, Y. H., Peng, J., Ren, L. D., Hong, T., Liu, R., Clinical efficacy of atosiban treatment in late abortion and preterm labour of twin pregnancy, International Journal of Clinical and Experimental Medicine, 9, 3946-3952, 2016	No asymptomatic - diagnosed with the threat of preterm labour (with uterine contractions)
Yamasmit, W, Chaithongwongwatthana, S, Tolosa, J. E, Limpongsanurak, S, Pereira, L, Lumbiganon, P., Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD004733, 2015	Duplicate
Yamasmit, W; Chaithongwongwatthana, S; Tolosa, JE , Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy, Cochrane Database of Systematic Reviews, 4, 2009	More recent update available

Study	Reason for Exclusion
Yamasmit, Waralak, Chaithongwongwatthana, Surasith, Tolosa, Jorge E, Limpongsanurak, Sompop, Pereira, Leonardo, Lumbiganon, Pisake, Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy, Cochrane Database of Systematic Reviews, 2015	Only relevant study included elsewhere (O'Connor 1979)
Yamasmit,W, Chaithongwongwatthana,S, Tolosa,J.E, Limpongsanurak,S, Pereira,L, Lumbiganon,P., Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy, Cochrane database of systematic reviews (Online), 9, CD004733-, 2012	More recent update available
Zheng, L., Dong, J., Dai, Y., Zhang, Y., Shi, L., Wei, M., Jin, X., Li, C., Zhang, S., Cervical pessaries for the prevention of preterm birth: a systematic review and meta-analysis, Journal of Maternal-Fetal & Neonatal Medicine, 1-10, 2017	Only relevant studies already in included list

Economic studies

No health economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What interventions are effective in preventing spontaneous preterm birth in twin and triplet pregnancy?