Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
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Results section 8.2

Comparison cerclage vs no cerclage

From the HTA-report:
Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies

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Abbreviations/Acronyms

17-OHPC 17-alpha-hydroxyprogesterone caproate
ART assisted reproductive technology
ASA acetylsalicylic acid
ASQ ages and stages questionnaire
BPD bronchopulmonary dysplasia
CDI child developmental inventory
CI confidence interval
CL cervical length
cm centimetre
d days
g gram
GDM gestational diabetes mellitus
HDP hypertensive disorders in pregnancy
HTA health technology assessment
ICP intrahepatic cholestasis in pregnancy
ICTRP International Clinical Trials Registry Platform
im intramuscular injection
IVF in vitro fertilization
IVH intraventricular haemorrhage
IQR interquartile range
LY life year
MD mean difference
mg milligram
mm millimetre
NEC necrotizing enterocolitis
NICU neonatal intensive care unit
PPROM preterm prelabour rupture of membranes
PROSPERO the international prospective register of systematic reviews
PTB preterm birth
RCT randomised controlled trial
RD risk difference
RDS respiratory distress syndrome
ROP retinopathy of prematurity
RR relative risk/risk ratio
SBU assessment of social service
SD standard deviation
SEK Swedish krona
SoF summary of findings
sPTB spontaneous preterm birth
SR systematic review
TVS transvaginal sonography
UK United Kingdom
US United States
VGR Region Västra Götaland
WHO World Health Organization

Results in singleton pregnancies

Included studies

Ten RCTs were included reporting on singleton pregnancies (Appendix 2). Four trials were classified as having low risk of bias, and six as having high risk of bias (Table 1). Three trials included both singleton and twin pregnancies, two of these presented results separately for singletons and twins (Macnaughton et al., 1993; Berghella et al., 2004) while one study did not (Rust et al., 2000). In the trial by Macnaughton et al. (1993), there were 2% twins, in Berghella et al. (2004), there were 7% twins, and in Rust et al. (2000), there were 11% twins. One trial (Ezechi et al., 2004) did not state if only singleton pregnancies were included; however, Ezechi et al. (2004) reported individual patient data for singletons for a Cochrane meta-analysis (Alfirevic et al., 2017).
In addition, one systematic review contributed to the meta-analyses with study data on singleton pregnancies (Alfirevic et al., 2017). In total, 2882/2923 women/newborns were included in the analyses.

Table 1. Risk of bias assessment (Low/High) of included original RCTs**.**

Singleton pregnancies		**Multifetal pregnancies**		**Mixed singleton and multifetal**	
Althuisius, 2001	High	Dor, 1982	High	Berghella, 2004	High
Lazar, 1984	High	Roman, 2020	Low	Macnaughton, 1993	Low
Otsuki, 2016	Low			Rust, 2000	High
Owen, 2009	Low				
Rush, 1984	High				
To, 2004	Low				
Ezechi, 2004	High				

Setting

The included trials were conducted in several different countries, including the USA (4), United Kingdom (2), France (2), the Netherlands (3), South Africa (2), Brazil, Slovenia, Greece, Chile, Nigeria, Hungary, Norway, Italy, Japan, Israel, Belgium, Zimbabwe, Iceland, Ireland, and Canada. Two trials were multinational (Macnaughton et al., 1993; To et al., 2004).

Population

The risk of preterm birth was assessed based on previous obstetric history (Ezechi et al., 2004; Macnaughton et al., 1993; Rush et al., 1984) and short cervical length (<25 mm) detected with serial ultrasound examinations (Owen et al., 2009). Lazar et al. (1984) used a mixed scoring system based on obstetric history and physical examination. Althuisius et al. (2001) assessed the risk of preterm birth based on previous obstetric history in 2/3 of the study population and short cervical length detected with serial ultrasound examinations of the cervix in 1/3.
Otsuki et al. (2016) and To et al. (2004) included a largely unselected obstetric population with the need for cerclage assessed with screening for short cervical length in the second trimester with transvaginal ultrasound examination (short cervical length defined as <25 mm and ≤15 mm, respectively, so-called one-off ultrasound). In addition, two trials included a mixed population, with the indication for cerclage based either on short cervical length detected with serial ultrasound examinations of the cervix in women at high risk of preterm birth or a one-off ultrasound examination in women at low risk (Berghella et al., 2004; Rust et al., 2000).

Intervention

All trials compared transvaginal cervical cerclage versus no cerclage. Blinding was not feasible due to the nature of the intervention. The intervention included either McDonald cerclage (seven trials) or Shirodkar cerclage (To et al., 2004). One trial used both types of cerclages (Otsuki et al., 2016). In one trial, the type of cerclage was not prespecified, but McDonald cerclage or similar was used in most cases (Macnaughton et al., 2003). Two trials required women in both the cerclage and no cerclage groups to undertake bed rest (Althuisius et al., 2001; Berghella et al., 2004). Modified bed rest in both groups was recommended in two trials (Owen et al., 2009; Rust et al., 2000). The other trials did not routinely recommend any restricted physical activity or did not state whether any recommendations were given. Three trials incorporated a rescue cerclage in the protocol for women randomised to the control group based on physical examination (Owen et al., 2009) or ultrasound detected changes of the cervix (Althuisius et al., 2001; Rust et al., 2000). No trial included adjuvant progesterone treatment in both groups as a routine.

Mean gestational age at study entry varied between 14.6 gestational weeks (Macnaughton et al., 1993) and 24.6 gestational weeks (Otsuki et al., 2016). Althuisius et al. (2001) included women before 27 gestational weeks and Lazar et al. (1984) before 28 gestational weeks. The cerclage suture was removed in six included trials between 36 and 37 gestational weeks in the absence of pregnancy complications. Four trials did not report gestational age for removal of the cerclage suture.
In the cerclage group, between 0 and 13% did not have a cerclage; in the control group, between 1 and 12%.

Directness, study limitations, and precision

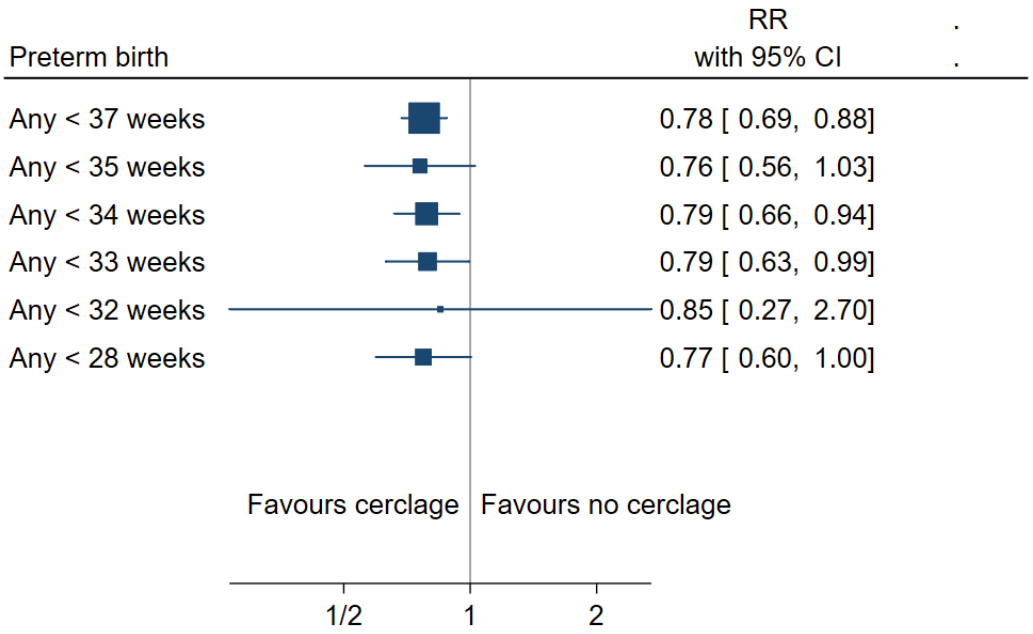
Some of the included trials had some problems with directness, which was affected by ethnicity (i.e., some included a high proportion of Black women). In addition, some trials were old, conducted, and published before 2000 (low risk of bias: Macnaughton et al., 1993; high risk of bias: Lazar et al., 1984; Rush et al., 1984).
Risk of bias in the individual trials is presented graphically in colour within the forest plots (legend in Table 2), and as an overall judgement of study limitations in the outcome tables in Appendix 4.2. The study limitation in all trials was the lack of blinding since blinding participants and personnel was not feasible.
The trials were generally underpowered for outcomes such as neonatal mortality and morbidity and maternal morbidity. One trial included miscarriages in numerator and denominator, which affected precision (Macnaughton et al., 1993).

Results per outcome

Preterm birth in singletons across gestational weeks

The pooled estimates from meta-analyses of trials reporting any preterm birth (<37, <35, <34, <33, <32, and <28 gestational weeks), from low risk of bias trials are summarised in Figure 1. No trial reported spontaneous preterm birth.

Figure 1. Summary graph of pooled estimates from meta-analyses comparing cerclage versus no cerclage in women with a singleton pregnancy and any type of risk factor for preterm birth from trials with low risk of bias regarding the outcome of any preterm birth before different gestational weeks.



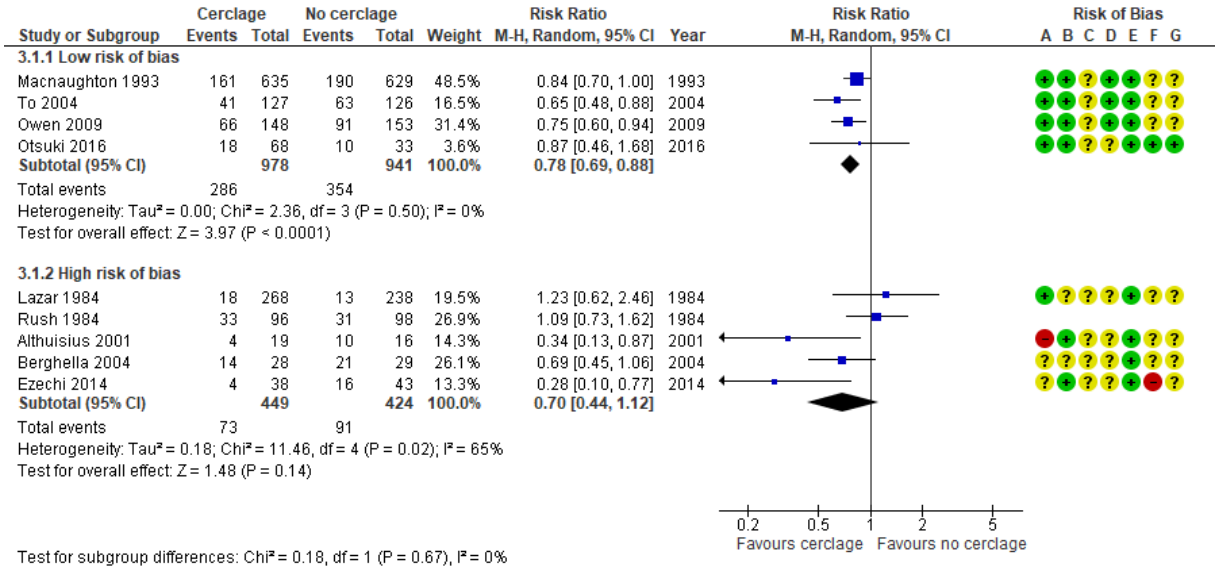
The pooled estimates (RR) ranged from 0.76 to 0.85 across the span of gestational weeks, indicating a favourable outcome of cerclage.

Table 2. Risk of bias legend to the colour plot within the following forests plots

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Conflict of interest bias

Any preterm birth <37 weeks (Appendix 4.2.1.a and Figure 2)
A meta-analysis of four trials with low risk of bias, including 1919 women, showed a significant reduction in the rate of any preterm birth, RR 0.78 (95% CI 0.69 to 0.88). A sensitivity analysis excluding Macnaughton et al., 1993 due to inclusion of miscarriages in numerator and denominator changed the result only marginally (RR 0.72 [95% CI 0.61 to 0.86]). The crude event rate across trials was 37.6% without cerclage. The pooled weighted RD was -9.9 percentage points (95% CI -17.2 to -2.7).

Figure 2. Outcome: Any preterm birth <37 weeks.

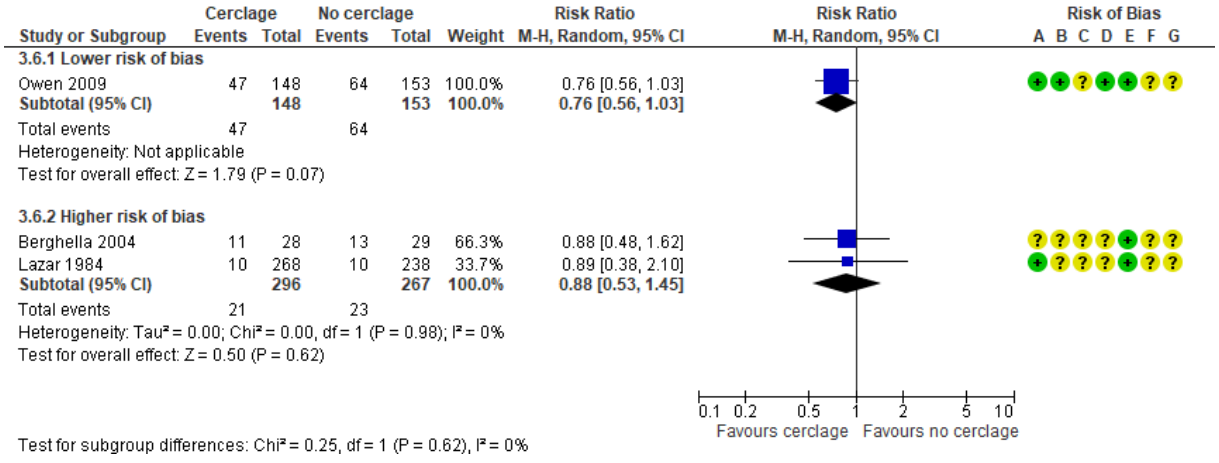


Conclusion: Cerclage compared with no cerclage probably reduces the risk of any preterm birth before 37 gestational weeks in women with a singleton pregnancy, not considering type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <37 weeks
No trial reported spontaneous preterm birth <37 weeks.

Any preterm birth <35 weeks (Appendix 4.2.2.a and Figure 3**)**
One trial with low risk of bias, including 301 women with a previous spontaneous preterm birth and short cervical length, showed no difference in the rate of any preterm birth, RR 0.76 (95% CI 0.56 to 1.03). The event rate was 41.8% without cerclage. The RD was -10.1 percentage points (95% CI -20.9 to 0.8).

Figure 3. Outcome: Any preterm birth before 35 weeks.

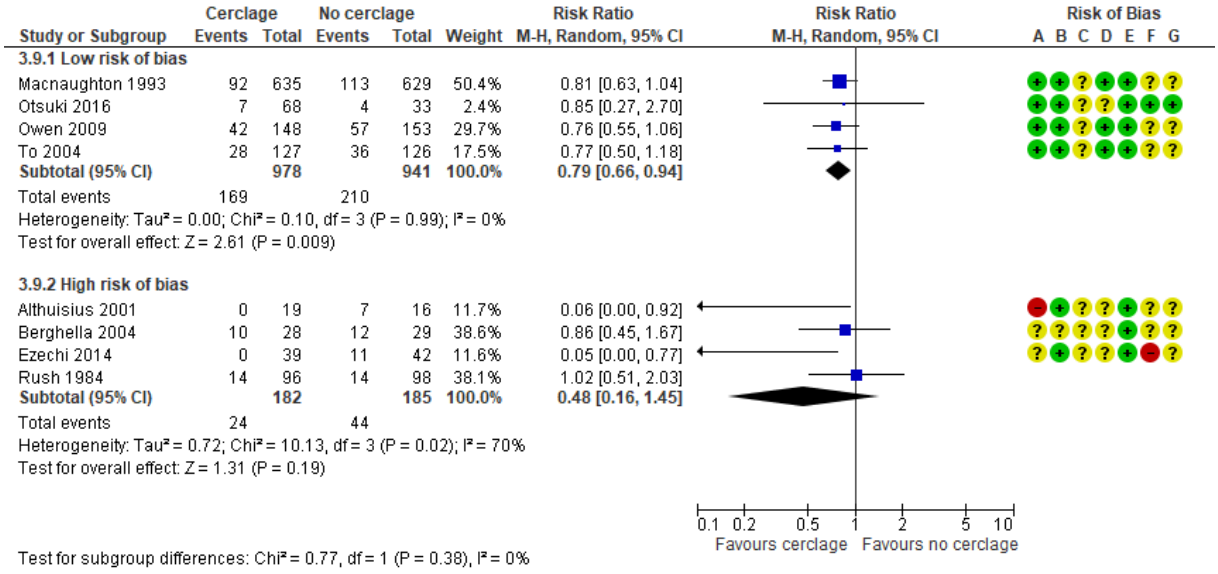


Conclusion: Cerclage compared with no cerclage may result in no difference in the risk of any preterm birth before 35 gestational weeks in women with a singleton pregnancy, previous spontaneous preterm birth, and short cervical length (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

Any preterm birth <34 weeks (Appendix 4.2.3.a and Figure 4)
A meta-analysis of four trials with low risk of bias, including 1919 women, showed a significant reduction in the rate of any preterm birth, RR 0.79 (95% CI 0.66 to 0.94). A sensitivity analysis excluding Macnaughton et al., 1993 due to inclusion of miscarriages in numerator and denominator changed the result marginally, but closer to non-significance (RR 0.77 [95% CI 0.60 to 0.99]). The crude event rate across trials was 22.3% without cerclage. The pooled weighted RD was -4.3 percentage points (95% CI -7.7 to -0.8).

Figure 4. Outcome: Any preterm birth before 34 weeks in singletons.

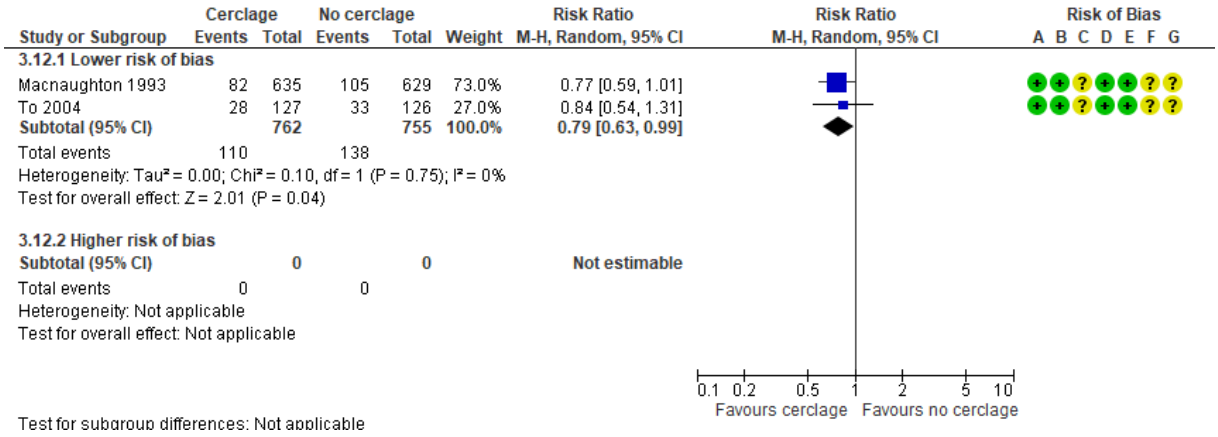


Conclusion: Cerclage compared with no cerclage probably reduces the risk of any preterm birth before 34 gestational weeks in women with a singleton pregnancy, not considering type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <34 weeks
No trial reported spontaneous preterm birth <34 weeks.

Any preterm birth <33 weeks (Appendix 4.2.4.a and Figure 5)
A meta-analysis of two trials with low risk of bias, including 1517 women, showed a significant reduction in the rate of any preterm birth, RR 0.79 (95% CI 0.63 to 0.99). Sensitivity analysis excluding Macnaughton 1993 due to inclusion of miscarriages included in numerator and denominator: RR 0.84 (95% CI 0.54, 1.31). The crude event rate across trials was 18.3% without cerclage. The pooled weighted RD was -3.8 percentage points (95% CI -7.5 to -0.2).

Figure 5. Outcome: Any preterm birth before 33 weeks in singletons.

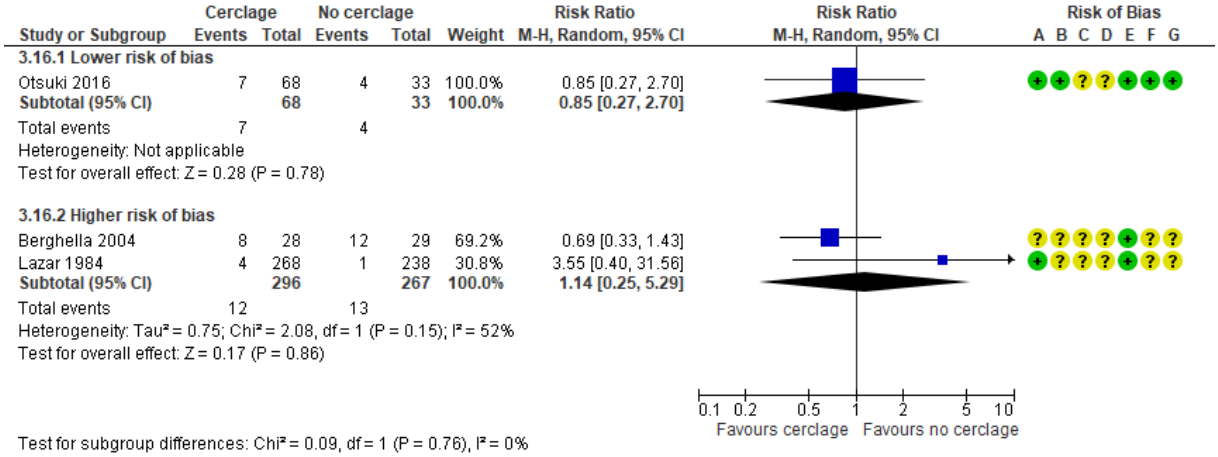


Conclusion: Cerclage compared with no cerclage probably reduces the risk of any preterm birth before 33 gestational weeks in women with a singleton pregnancy, not considering type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <33 weeks
No trial reportepontaneous preterm birth <33 weeks.

Any preterm birth <32 weeks (Appendix 4.2.5.a and Figure 6)
One trial with low risk of bias, including 101 women with short cervical length, showed no difference in the rate of any preterm birth, RR 0.85 (95% CI 0.27 to 2.70). The event rate was 12.1% without cerclage. The RD was -1.8 percentage points (95% CI -15.1 to 11.5).

Figure 6. Outcome: Any preterm birth before 32 weeks.

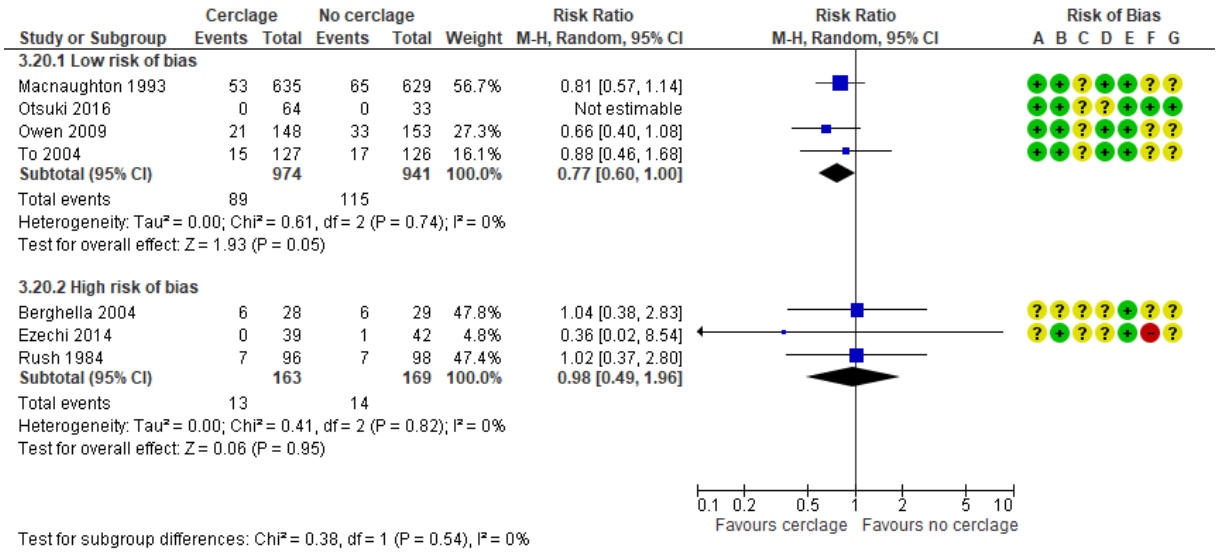


Conclusion: It is uncertain whether cerclage affects any preterm birth before 32 gestational weeks in women with a singleton pregnancy and short cervical length (GRADE ⊕◯◯◯).

Spontaneous preterm birth <32 weeks
No trial reported spontaneous preterm birth <32 weeks.

Any preterm birth <28 weeks (Appendix 4.2.6.a and Figure 7)
A meta-analysis of four trials with low risk of bias, including 1915 women, showed no difference in the rate of any preterm birth, RR 0.77 (95% CI 0.60 to 1.00). Sensitivity analysis excluding Macnaughton 1993 due to inclusion of miscarriages in numerator and denominator: RR 0.73 (95% CI 0.49, 1.09). The crude event rate across trials was 12.2% without cerclage. The pooled weighted RD was -1.8 percentage points (95% CI -4.3 to 0.6).

Figure 7. Outcome: Any preterm birth before 28 weeks in singleton pregnancies.

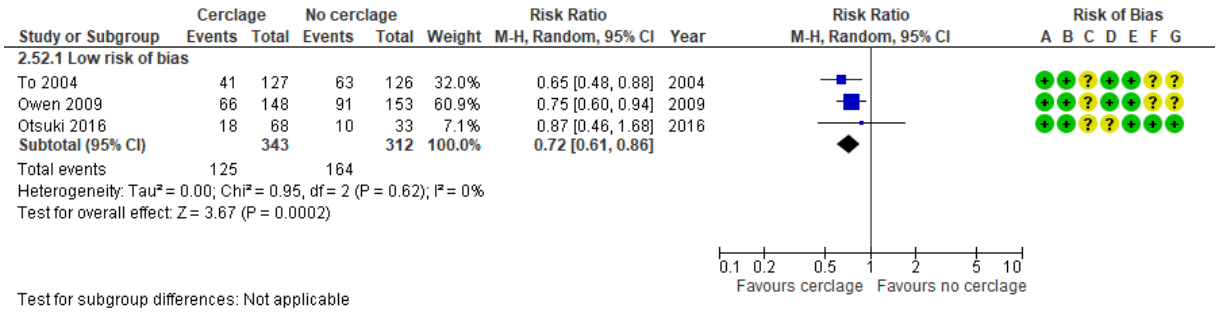


Conclusion: Cerclage compared with no cerclage probably results in no difference in the risk of any preterm birth before 28 gestational weeks not considering type of risk factor for preterm birth, although the CI for RR may imply a reduction (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <28 weeks
No trial reported spontaneous preterm birth <28 weeks.

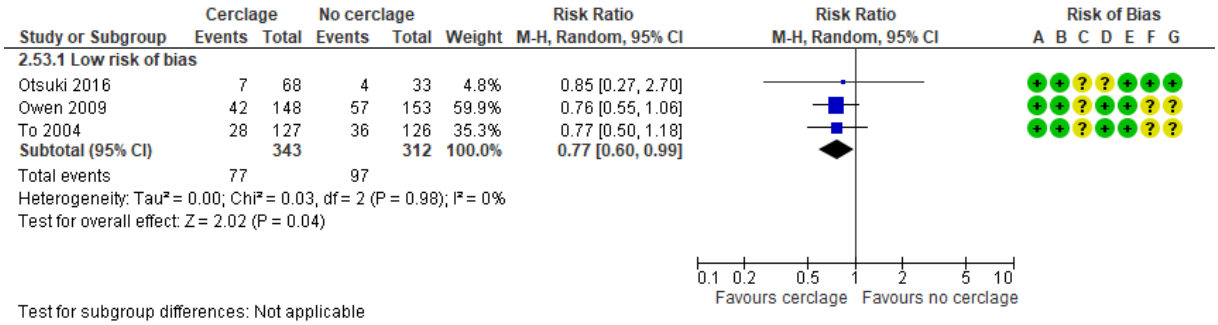
Subgroup analyses (Figures 8-9)
Pre-specified subgroup analyses for the specific risk factor short cervical length were performed. The meta-analyses of three trials with a total of 655 women, showed a significant reduction in the rate of any preterm birth <37 weeks, RR 0.72 (95% CI 0.61 to 0.86), and <34 weeks, RR 0.77 (95% CI 0.60 to 0.99).

Figure 8. Outcome: Any preterm birth <37 weeks among women with short cervical length.



Cut-off cervical length: To 2004 ≤15 mm, Owen 2009 <25 mm, Otsuki 2016 <25 mm.

Figure 9. Outcome: Any preterm birth <34 weeks among women with short cervical length.

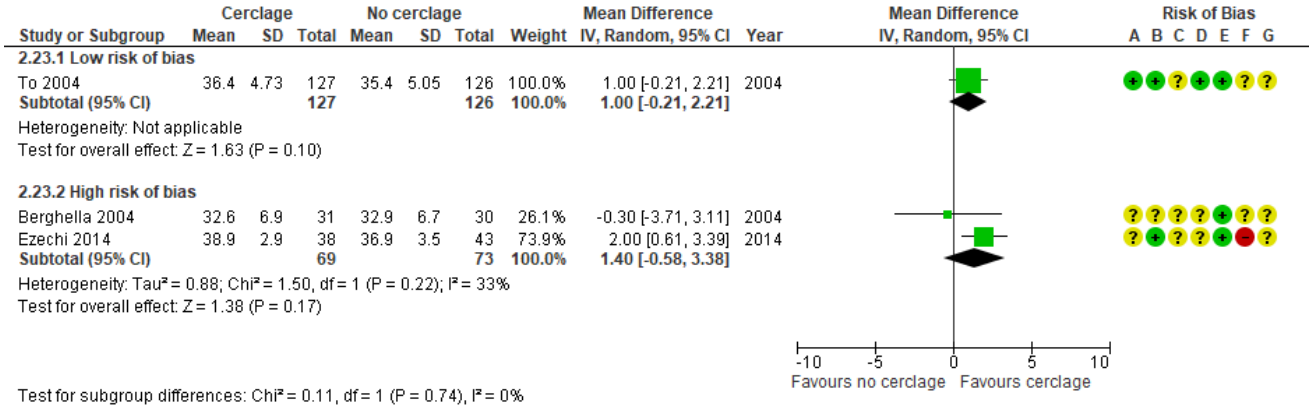


Cut-off cervical length: To 2004 ≤15 mm, Owen 2009 <25 mm, Otsuki 2016 <25 mm.

Only one trial had the specific inclusion criteria of previous spontaneous preterm birth (Owen et al., 2009) and no trial reported results in subgroups of patients with cervical surgical treatment for cervical intraepithelial neoplasia.

Gestational age in singletons (Appendix 4.2.7 and Figure 10)
One trial with low risk of bias, including 253 women with short cervical length, showed no mean difference in gestational age, 1.00 (-0.21 to 2.21) weeks, corresponding to seven days longer (one day less to 15 days longer) gestation in the cerclage group.

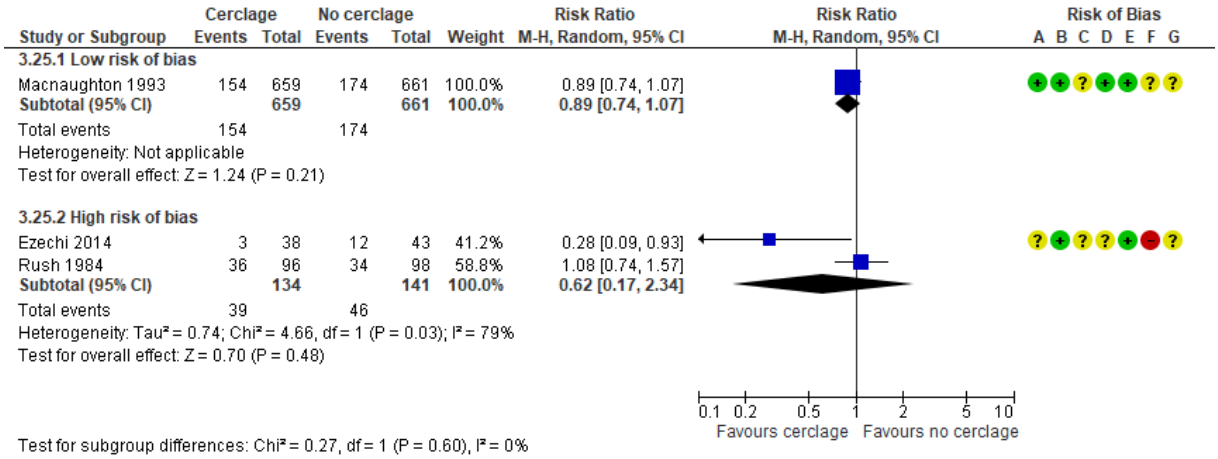
Figure 10. Outcome: Gestational age at delivery in singleton pregnancies.



Conclusion: Cerclage compared with no cerclage may result in no difference in gestational age at delivery in women with a singleton pregnancy and short cervical length, although the CI may imply an increase (GRADE ⊕⊕◯◯).

Low birth weight in singletons (Appendix 4.2.8 and Figure 11)
One trial with low risk of bias, including 1320 neonates, showed no difference in the rate of low birth weight, RR 0.89 (95% CI 0.74 to 1.07). The event rate was 26.3% without cerclage. The RD was -2.7 percentage points (95% CI -7.6 to 1.7). However, the analysis included twins (2%) since data could not be separated between singletons and twins for this outcome.

Figure 11. Outcome: Low birth weight (<2500g).

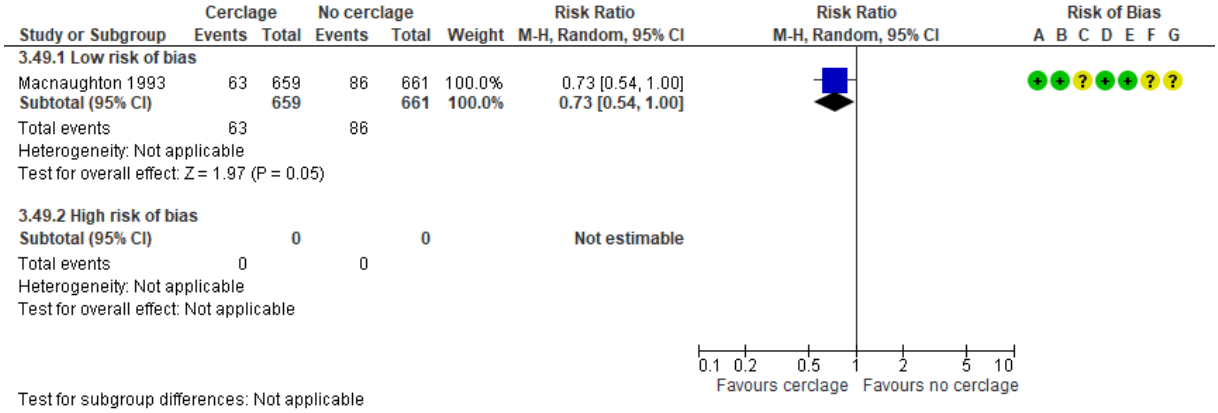


NB: Macnaughton 1993 includes 2% twins. Denominator includes miscarriages.

Conclusion: Cerclage compared with no cerclage may result in no difference in the risk of low birth weight in singletons not considering type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Very low birth weight in singletons (Appendix 4.2.9 and Figure 12)
One trial with low risk of bias, including 1320 neonates, showed no difference in very low birth weight rate, RR 0.73 (95% CI 0.54 to 1.00). The event rate was 13.0% without cerclage. The RD was-3.5 percentage points (95% CI -6.9 to -0.04). However, the analysis included twins (2%) since data could not be separated between singletons and twins for this outcome.

Figure 12. Outcome: Very low birth weight (<1500g).



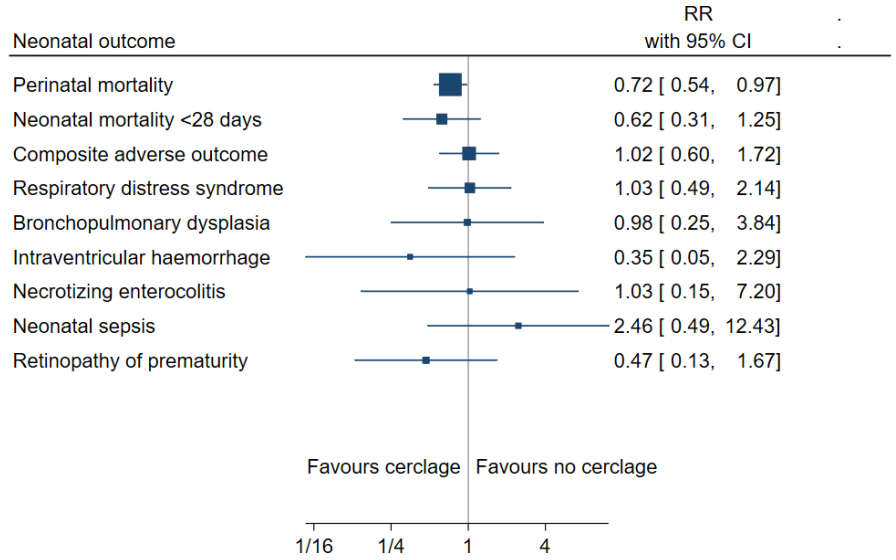
NB: Macnaughton 1993 includes 2% twins. Denominator includes miscarriages.

Conclusion: Cerclage compared with no cerclage may result in no difference in the risk of very low birth weight in singletons not considering the type of maternal risk factor for preterm birth, although the CI may imply a reduction (GRADE ⊕⊕◯◯).

Mortality and morbidity in neonates from singleton pregnancies

The pooled estimates from low risk of bias trials are summarised in Figure 13.

Figure 13. Summary graph of pooled estimates from meta-analyses comparing cerclage versus no cerclage in women with a singleton pregnancy and any type of risk factor for preterm birth from trials with low risk of bias, regarding neonatal outcomes.

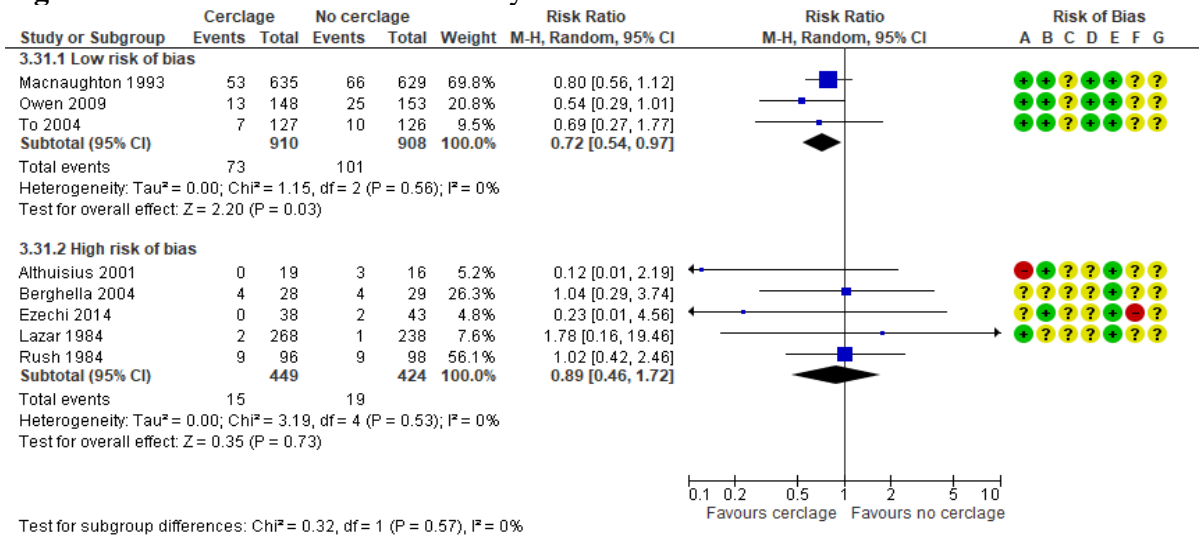


All outcomes but perinatal mortality displayed non-significant differences comparing cerclage versus no cerclage. Serious imprecision affected the certainty of evidence for all outcomes except for perinatal mortality.

Perinatal mortality (Appendix 4.2.10 and Figure 14)

A meta-analysis of three trials with low risk of bias, including 1818 singletons, showed a significant reduction in perinatal mortality rate, 8.0% (73/910) versus 11.1% (101/908), RR 0.72 (95% CI 0.54 to 0.97). The pooled weighted RD was -2.9 percentage points (95% CI -5.6 to -0.2). One trial included miscarriages in both the numerator and denominator (Macnaughton et al., 1993). A sensitivity analysis excluding Macnaughton et al., 1993 lowered the pooled estimate further, but increased the width of the CI (RR 0.58 [95% CI 0.35 to 0.98]).

Figure 14. Outcome: Perinatal mortality.

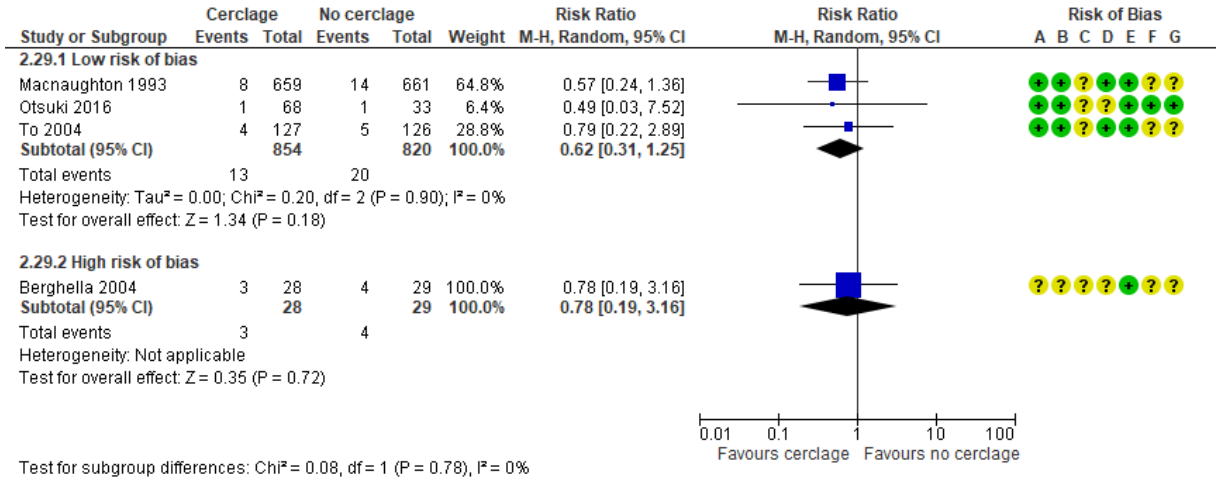


Conclusion: Cerclage compared with no cerclage may reduce the risk of perinatal mortality in singletons not considering the type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Neonatal mortality <7 days
No study reported neonatal mortality <7 days.

Neonatal mortality <28 days (Appendix 4.2.12 and Figure 15)
A meta-analysis of three trials with low risk of bias, including 1674 neonates, showed no difference in neonatal mortality rate <28 days, RR 0.62 (95% CI 0.31 to 1.25). A sensitivity analysis excluding Macnaughton 1993 due to inclusion of miscarriages in denominator, numerator 'liveborn died': RR 0.73 (95% CI 0.23, 2.33). The crude event rate across trials was 2.4% without cerclage. The pooled weighted RD was -0.9 percentage points (95% CI -2.2 to 0.4).

Figure 15. Outcome: Neonatal mortality <28 days.

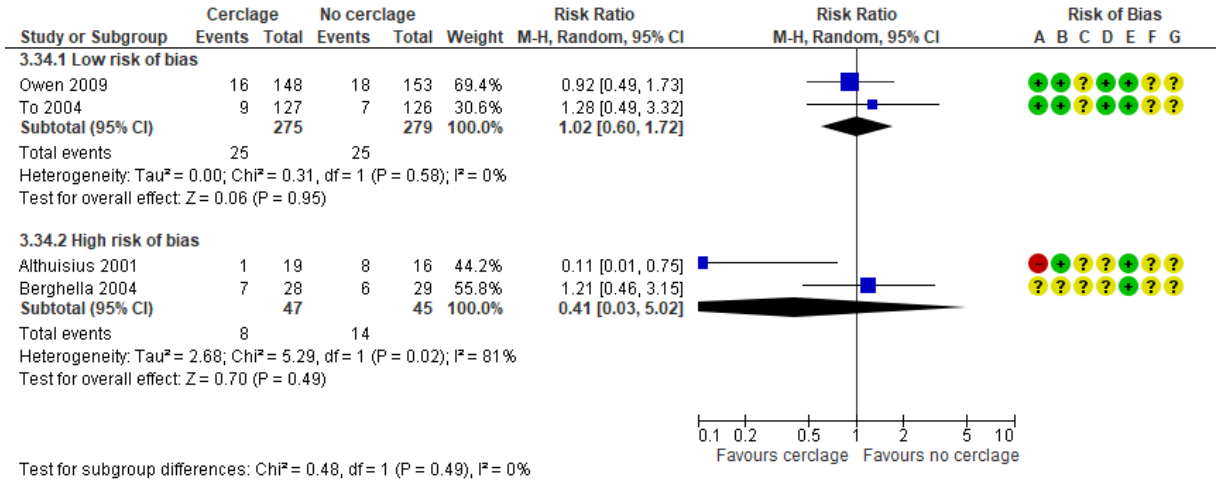


NB: Macnaughton 1993 includes 2% twins.

Conclusion: Cerclage compared with no cerclage may result in no difference in the risk of neonatal mortality <28 days in neonates not considering the type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Composite adverse neonatal outcome (Appendix 4.2.13 and Figure 16)
A meta-analysis of two trials with low risk of bias, including 554 neonates, showed no difference in composite adverse neonatal outcome rate, RR 1.02 (95% CI 0.60 to 1.72). The crude event rate across trials was 9.0% without cerclage. The pooled weighted RD was 0.5 percentage points (95% CI -4.1 to 5.1). However, composite adverse neonatal outcome (data from the systematic review of Alfirevic et al., 2017) was not defined (and there were no definitions in the original trials) but named serious neonatal morbidity; therefore, mortality was probably not included.

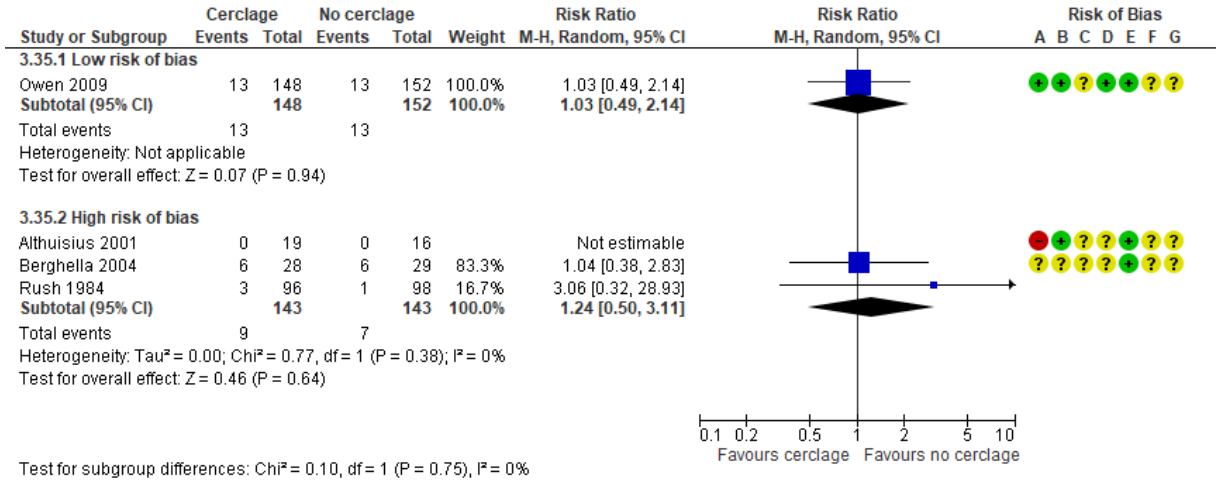
Figure 16. Outcome: Composite adverse neonatal outcome.



Conclusion: Cerclage compared with no cerclage may result in no difference in the risk of composite adverse neonatal outcomes in neonates, with the maternal risk factor short cervical length (GRADE ⊕⊕◯◯).

Respiratory distress syndrome (RDS) (Appendix 4.2.14 and Figure 17)
One trial with low risk of bias, including 300 neonates, showed no difference in RDS rate, RR 1.03 (95% CI 0.49 to 2.14). The event rate was 8.6% without cerclage. The RD was 0.2 percentage points (95% CI -6.1 to 6.6).

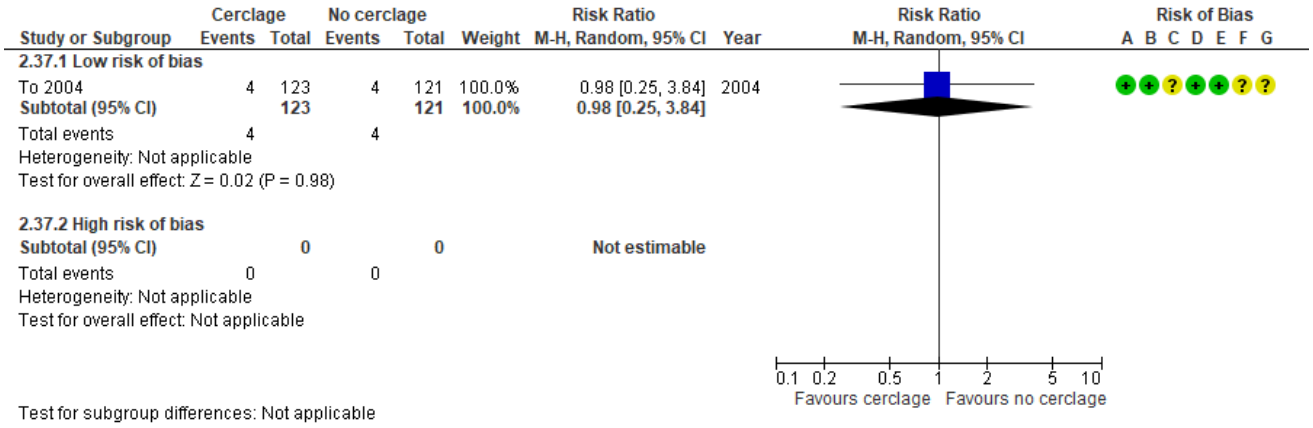
Figure 17. Outcome: Respiratory distress syndrome.



Conclusion: It is uncertain whether cerclage affects the risk of RDS in neonates with the maternal risk factors of previous spontaneous preterm birth and short cervical length (GRADE ⊕◯◯◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.2.15 and Figure 18)
One trial with low risk of bias, including 244 neonates showed no difference in BPD rate, RR 0.98 (95% CI 0.25 to 3.84). The event rate was 3.3% without cerclage. The pooled weighted RD was -0.1 percentage points (95% CI -4.5 to 4.4).

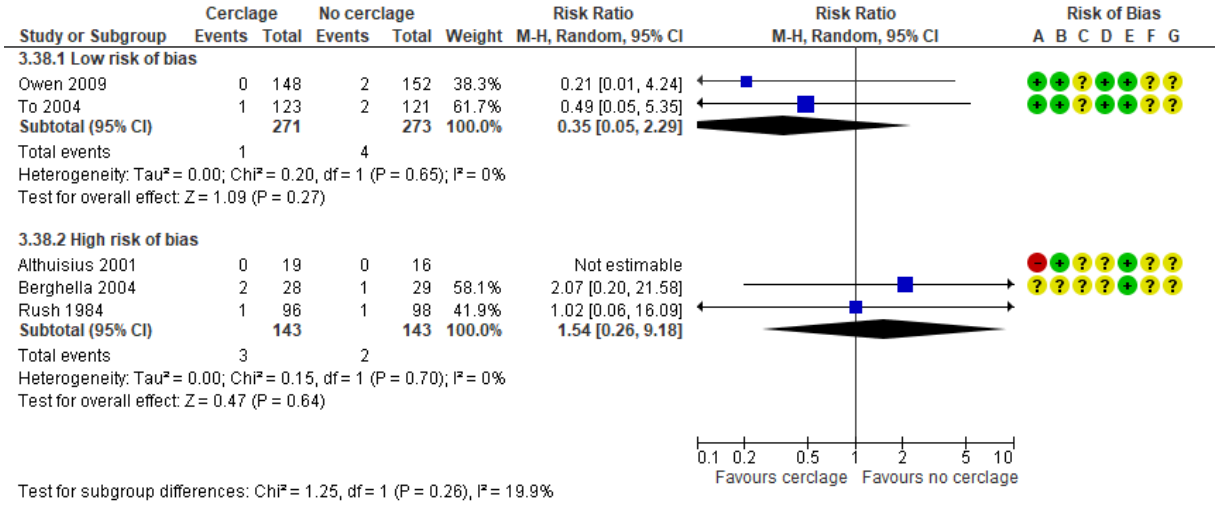
Figure 18. Outcome: Bronchopulmonary dysplasia.



Conclusion: It is uncertain whether cerclage affects the risk of BPD in neonates with the maternal risk factor short cervical length (GRADE ⊕○○○).

Intraventricular haemorrhage (IVH) (Appendix 4.2.16 and Figure 19)
A meta-analysis of two trials with low risk of bias, including 544 neonates, showed no difference in the rate of IVH, RR 0.35 (95% CI 0.05 to 2.29). The crude event rate across trials was 1.5% without cerclage. The pooled weighted RD was -1.1 percentage points (95% CI -2.9 to 0.6).

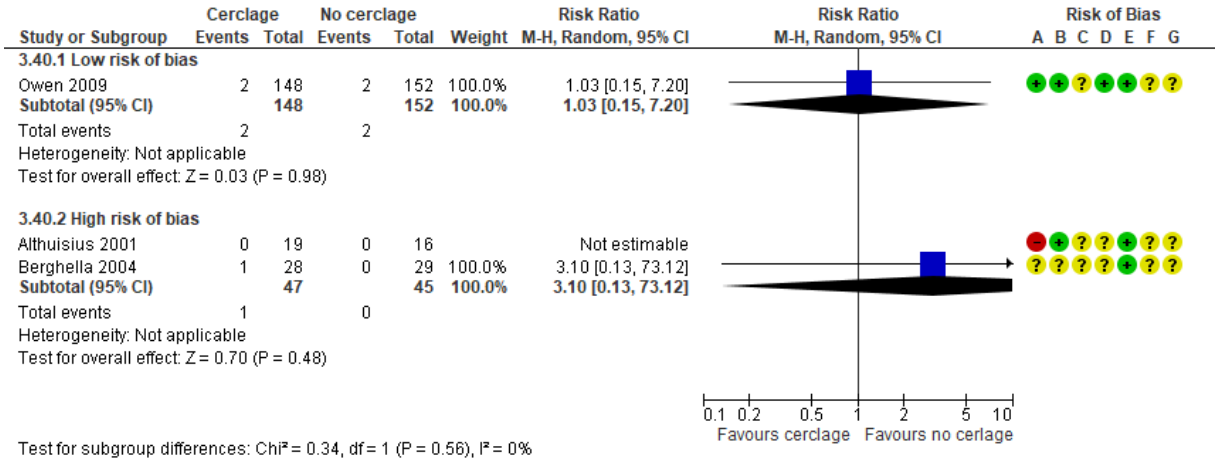
Figure 19. Outcome: Intraventricular haemorrhage.



Conclusion: It is uncertain whether cerclage affects the risk of IVH in neonates, with the maternal risk factor short cervical length (GRADE ⊕○○○).

Necrotizing enterocolitis (NEC) (Appendix 4.2.17 and Figure 20)
One trial with low risk of bias, including 300 neonates, showed no difference in the rate of NEC, RR 1.03 (95% CI 0.15 to 7.20). The event rate was 1.3% without cerclage. The pooled weighted RD was 0.04 percentage points (95% CI -2.6 to 2.6).

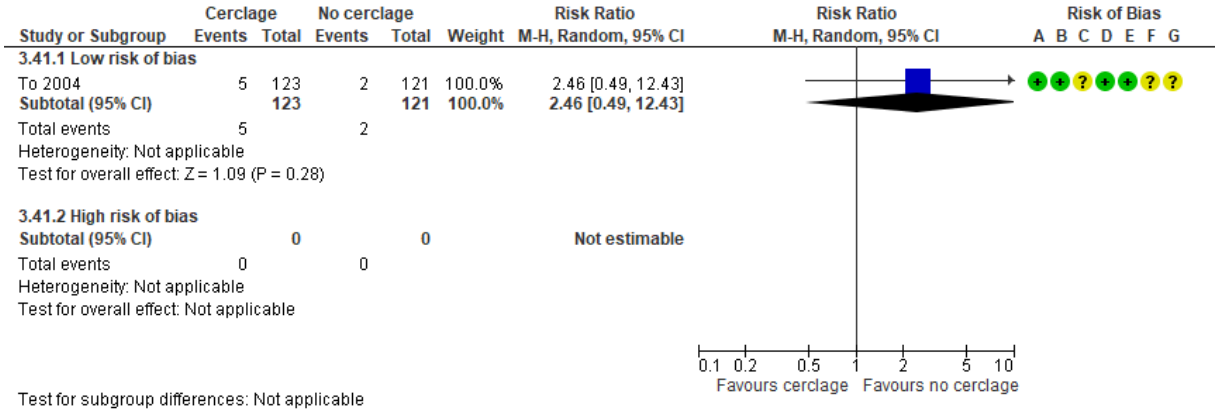
Figure 20. Outcome: Necrotizing enterocolitis.



Conclusion: It is uncertain whether cerclage affects the risk of NEC in neonates with the maternal risk factors previous spontaneous preterm birth and short cervical length (GRADE ⊕○○○).

Neonatal sepsis (Appendix 4.2.18 and Figure 21)
One trial with low risk of bias, including 244 neonates, showed no difference in the rate of neonatal sepsis, RR 2.46 (95% CI 0.49 to 12.43). The event rate was 1.7% without cerclage. The RD was 2.4 percentage points (95% CI -1.8 to 6.6).

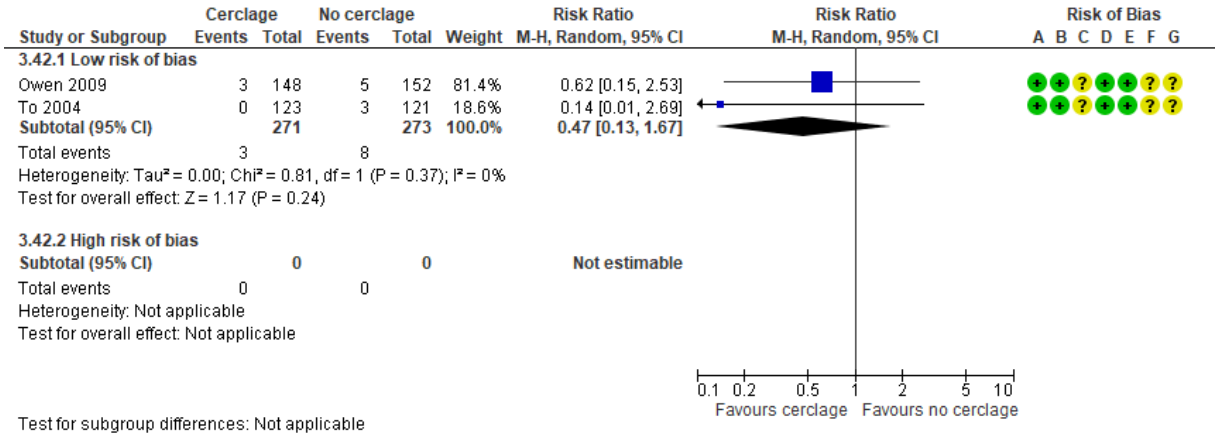
Figure 21. Outcome: Neonatal sepsis.



Conclusion: It is uncertain whether cerclage affects the risk of neonatal sepsis in neonates with the maternal risk factor short cervical length (GRADE ⊕○○○).

Retinopathy of prematurity (ROP) (Appendix 4.2.19 and Figure 22)
A meta-analysis of two trials with low risk of bias, including 544 neonates, showed no difference in the rate of ROP, RR 0.47 (95% CI 0.13 to 1.67). The crude event rate across trials was 2.9% without cerclage. The pooled weighted RD was -2.0 percentage points (95% CI -4.3 to 0.4).

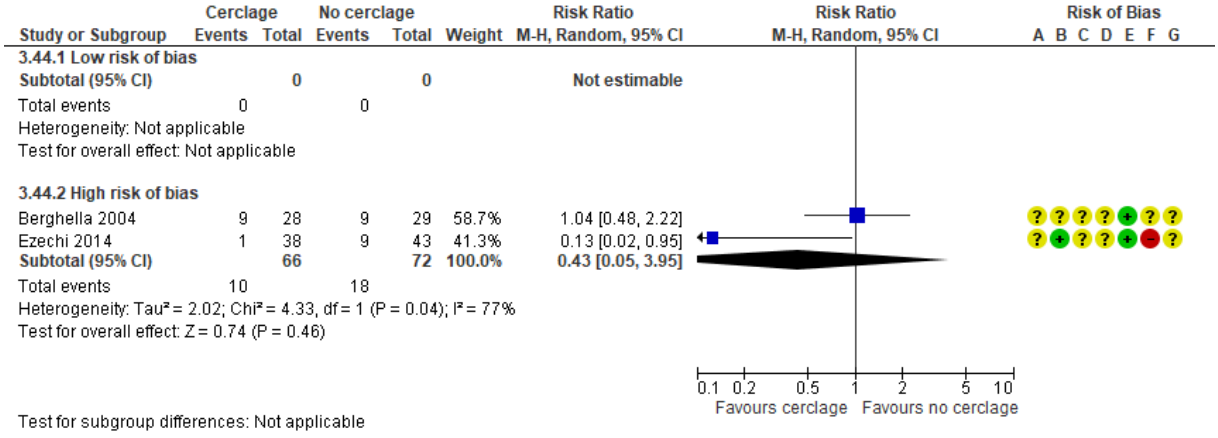
Figure 22. Outcome: Retinopathy of prematurity.



Conclusion: It is uncertain whether cerclage affects the risk of ROP in neonates, with the maternal risk factor short cervical length (GRADE ⊕○○○).

Admittance to neonatal intensive care unit (Appendix 4.2.20 and Figure 23)
No trial with low risk of bias reported on admittance to the neonatal intensive care unit.

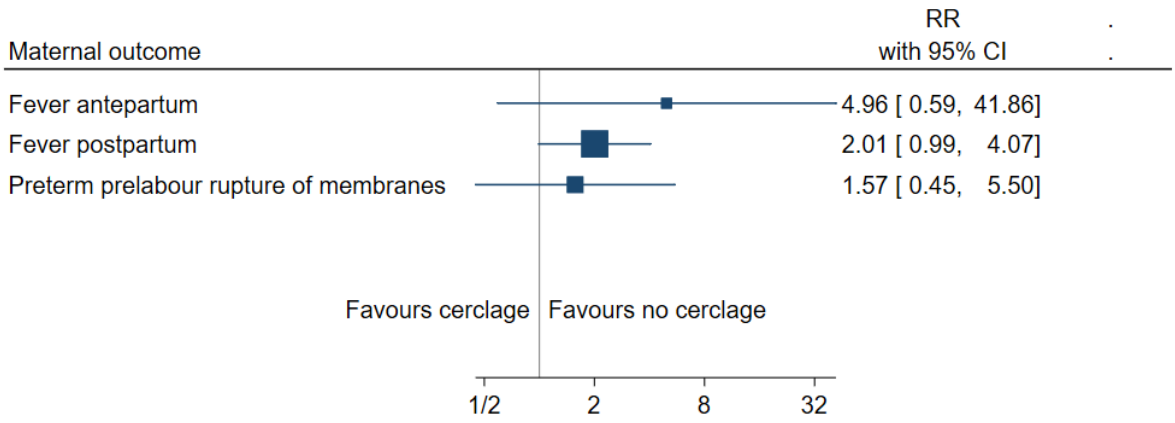
Figure 23. Outcome: Admittance to neonatal intensive care unit.



Long-term child outcomes
No trial reported long-term child outcomes.

Mortality and morbidity in women with singleton pregnancies
The pooled estimates from low risk of bias trials are summarised in Figure 24.

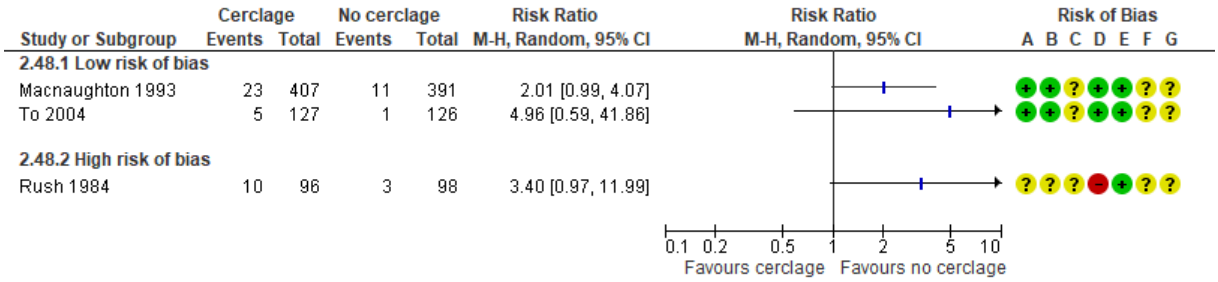
Figure 24. Summary graph of (pooled) estimates from trials or meta-analysis comparing cerclage versus no cerclage in women with a singleton pregnancy and any type of risk factor from trials with low risk of bias, regarding maternal outcomes.



Maternal mortality and morbidity
No trial reported maternal mortality, hypertensive disorders in pregnancy, gestational diabetes mellitus, or intrahepatic cholestasis.

Infection (maternal pyrexia) (Appendix 4.2.21 and Figure 25)
Two trials with low risk of bias, reported fever antepartum (RR 4.96 [95% CI 0.59 to 41.86]) and postpartum (RR 2.01 [95% CI 0.99 to 4.07]) respectively. No pooled estimate was calculated due to the clinical heterogeneity.

Figure 25. Outcome: Maternal pyrexia.

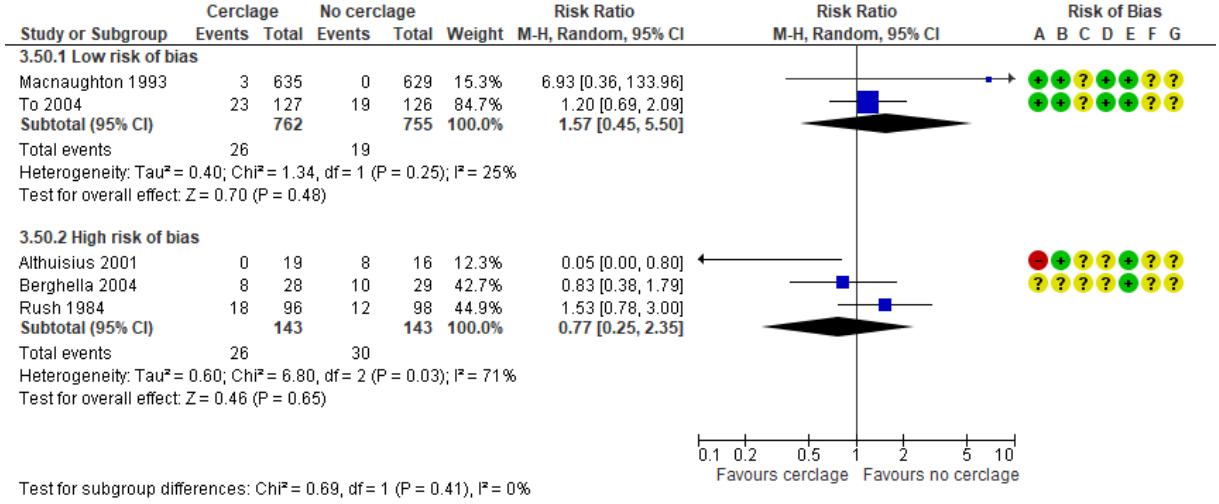


Macnaughton 1993 reports fever postpartum. To 2004 reports fever antepartum. Rush 1984 reports fever postpartum.

Conclusion: It is uncertain whether cerclage increases the risk of maternal pyrexia in women with a singleton pregnancy, not considering type of risk factor for preterm birth (GRADE ⊕○○○).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.2.22 and Figure 26)
A meta-analysis of two trials with low risk of bias, including 1517 women, showed no difference in the rate of PPROM, RR 1.57 (95% CI 0.45 to 5.50). The crude event rate across trials was 2.5% without cerclage. The pooled weighted RD was 1.1 percentage points (95% CI -4.6 to 6.9).

Figure 26. Outcome: Preterm prelabour rupture of membranes (PPROM).



Conclusion: Cerclage compared with no cerclage may result in no difference in PPROM in women with a singleton pregnancy, not considering the type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Results in multifetal pregnancies

Included studies

Two RCTs with only twin pregnancies were included. One was classified as having a low risk of bias and as having high risk of bias (Table 1). In addition, two RCTs, including both singleton and twin pregnancies, contributed with data on twin pregnancies (Macnaughton et al., 1993; Berghella et al., 2004). Above, in the singleton section, the setting, population, and intervention are presented for these two trials. No trial included triplet or higher order multiple births. In total, 107/214 women/newborns were included in the analyses.

Setting

The Dor trial (1982) was a single-center study conducted in Israel. The Roman trial (2020) was a multicenter study conducted at eight centers in the USA.

Population

The Dor trial (1982) included asymptomatic women at 13 weeks of gestation with twin pregnancies after ovulation induction. The Roman trial (2020) had a high-risk group of women between 16 and 23 weeks of gestation with diamniotic twin pregnancies, asymptomatic cervical dilation of 1 to 5 cm, and visible membranes identified by transvaginal ultrasound examination or physical examination.

Intervention

The trials compared McDonald cerclage versus no cerclage (Dor et al., 1982; Roman et al., 2020). Blinding was not feasible due to the nature of the intervention. In the Dor et al. trial (1982), women were followed at a high-risk pregnancy clinic. In the Roman et al. trial (2020), women in both arms were observed at the hospital until they were stable for discharge. After discharge, there were no study-specific recommendations for pregnancy care. In the Roman et al. trial (2020), 4/18 (22%) in the cerclage group did not receive any cerclage, and none (0/16) in the control group received any cerclage. The cerclage was removed at 36 weeks of gestation in one trial (Roman et al., 2020) and at 37 weeks in the other trial (Dor et al., 1982), or earlier in case of labour, preterm prelabour rupture of the membranes, or other pregnancy complications requiring delivery.

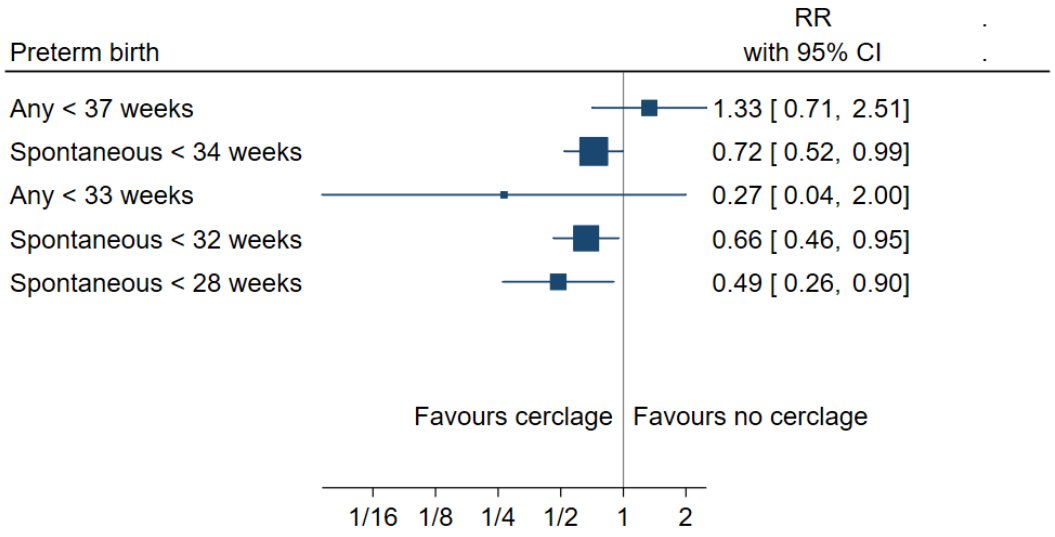
No trial included adjuvant progesterone treatment in both groups as a routine. Roman et al. (2020) reported use of vaginal progesterone in 52.9% in the cerclage group and 76.9% in the no cerclage group.

Directness, study limitations, and precision
One old trial included only twin pregnancies after infertility treatment (Dor et al., 1982). Risk of bias in the individual trials are presented graphically in colour within the forest plots (legends in Table 2) and as an overall judgment of study limitations in the outcome tables in Appendix 4.2. The main study limitation was the lack of blinding.
One trial was stopped early, affecting precision (Lazar et al., 1984). The trials were generally underpowered for all outcomes.

Results per outcome

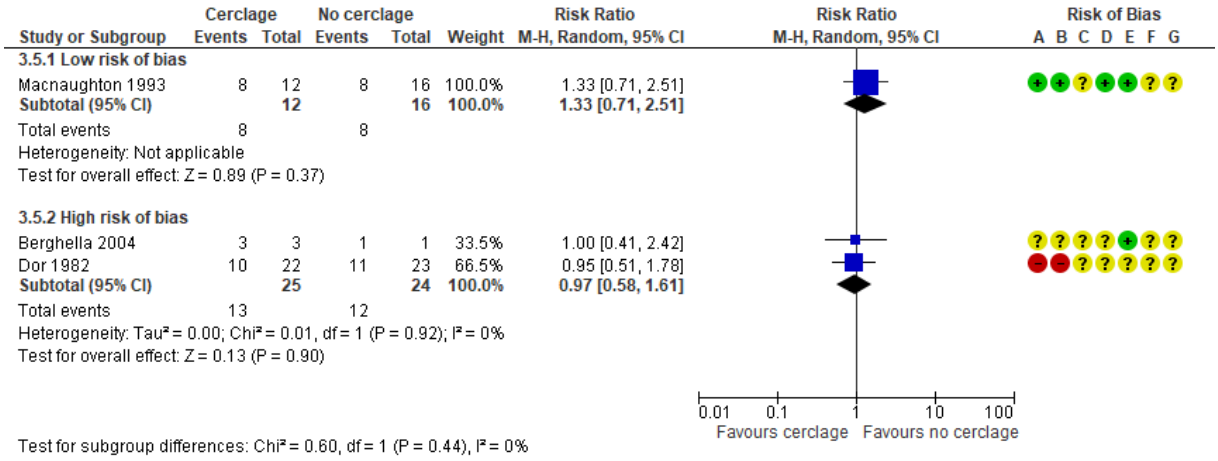
Preterm birth in multifetal pregnancies across gestational weeks
The pooled estimates from meta-analyses of trials reporting any or spontaneous preterm birth (<37, <35, <34, <33, <32, and <28 gestational weeks), from low risk of bias trials are summarised in Figure 27.

Figure 27. Summary graph of pooled estimates from meta-analyses comparing cerclage versus no cerclage in women with a multifetal pregnancy with or without additional risk factor(s) from trials with low risk of bias, regarding the outcome of any or spontaneous preterm birth before different gestational weeks.



Any preterm birth <37 weeks (Appendix 4.2.1.a and Figure 28)
One trial with low risk of bias, including 28 women with a twin pregnancy, showed no difference in the rate of any preterm birth, RR 1.33 (95% CI 0.71 to 2.51). The event rate was 50.0% without cerclage. The RD was 16.7 percentage points (95% CI -19.6 to 52.9).

Figure 28. Outcome: Any preterm birth before 37 weeks.



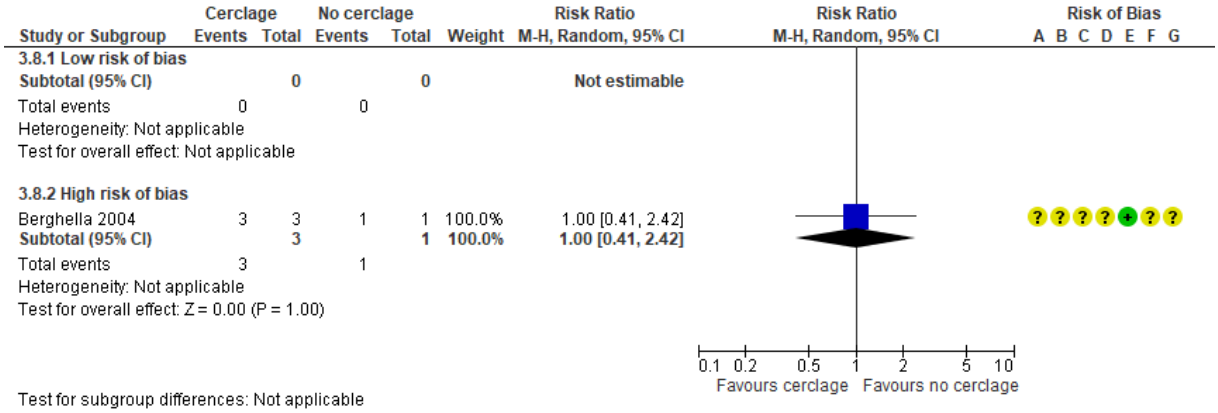
NB: Macnaughton 1993 includes miscarriages in numerator and denominator.

Conclusion: It is uncertain whether cerclage affects the risk of any preterm birth before 37 gestational weeks in women with a twin pregnancy with or without additional risk factor(s) for preterm birth (GRADE ⊕◯◯◯).

Spontaneous preterm birth <37 weeks
No trial reported spontaneous preterm birth <37 weeks.

Any preterm birth <35 weeks (Appendix 4.2.2.a and Figure 29**)**
No trial with low risk of bias reported spontaneous preterm birth <35 weeks.

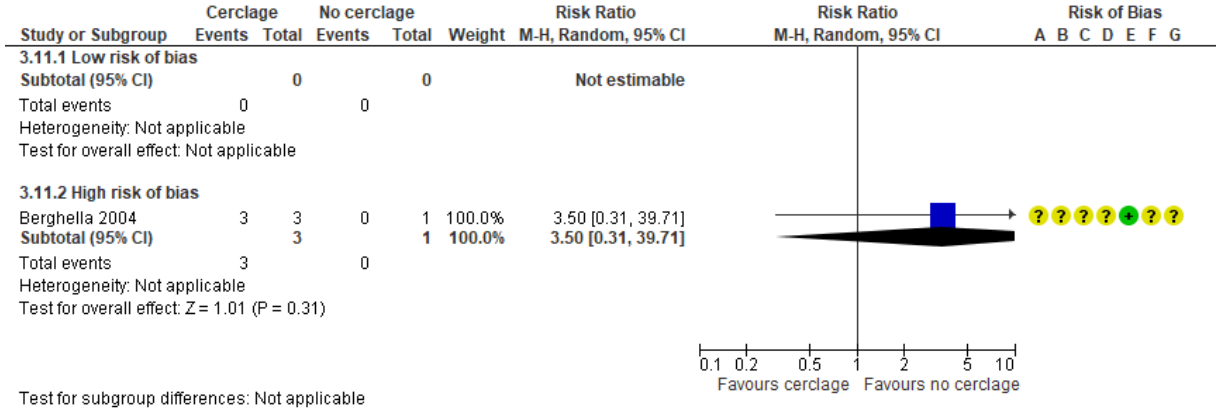
Figure 29. Outcome: Any preterm birth before 35 weeks.



Spontaneous preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

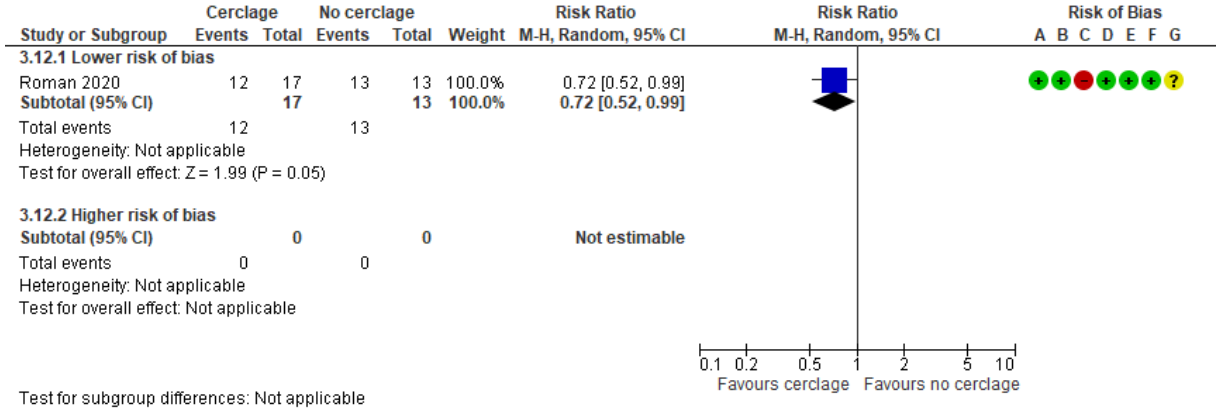
Any preterm birth <34 weeks (Appendix 4.2.3.a and Figure 30)
No trial with low risk of bias reported any preterm birth <34 weeks.

Figure 30. Outcome: Any preterm birth before 34 weeks.



Spontaneous preterm birth <34 weeks (Appendix 4.2.3.b and Figure 31)
One trial with low risk of bias, including 30 women with a twin pregnancy, showed a reduced rate of spontaneous preterm birth, RR 0.72 (95% CI 0.52 to 0.99). The event rate was 100% without cerclage. The RD was -29.4 percentage points (95% CI -52.8 to -6.0).

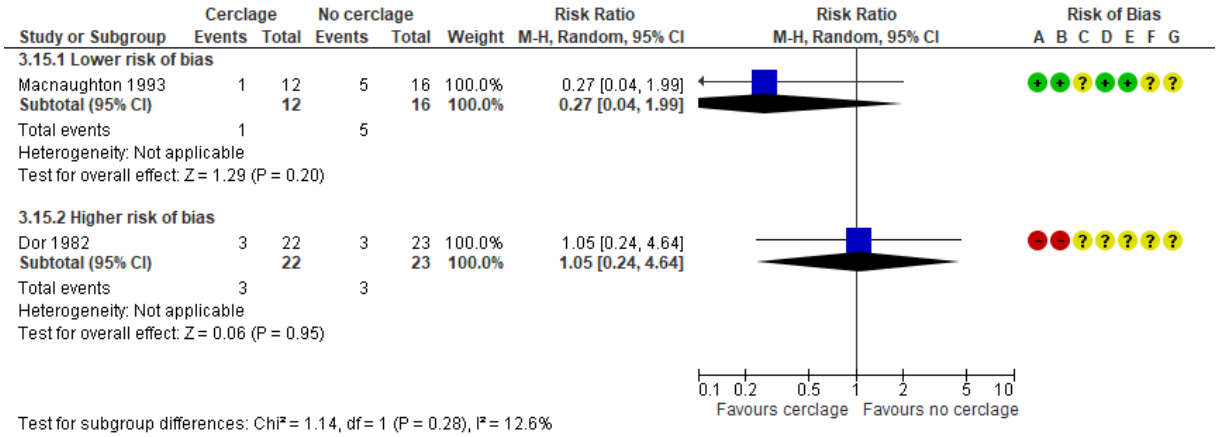
Figure 31. Outcome: Spontaneous preterm birth before 34 weeks.



Conclusion: It is uncertain whether cerclage reduces the risk for spontaneous preterm birth before 34 gestational weeks in asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕◯◯◯).

Any preterm birth <33 weeks (Appendix 4.2.4.a and Figure 32)
One trial with low risk of bias, including 28 women with a twin pregnancy, showed no difference in the rate of any preterm birth, RR 0.27 (95% CI 0.04 to 1.99). The event rate was 31.3% without cerclage. The RD was -22.9 percentage points (95% CI -50.5 to 4.7).

Figure 32. Outcome: Any preterm birth before 33 weeks.



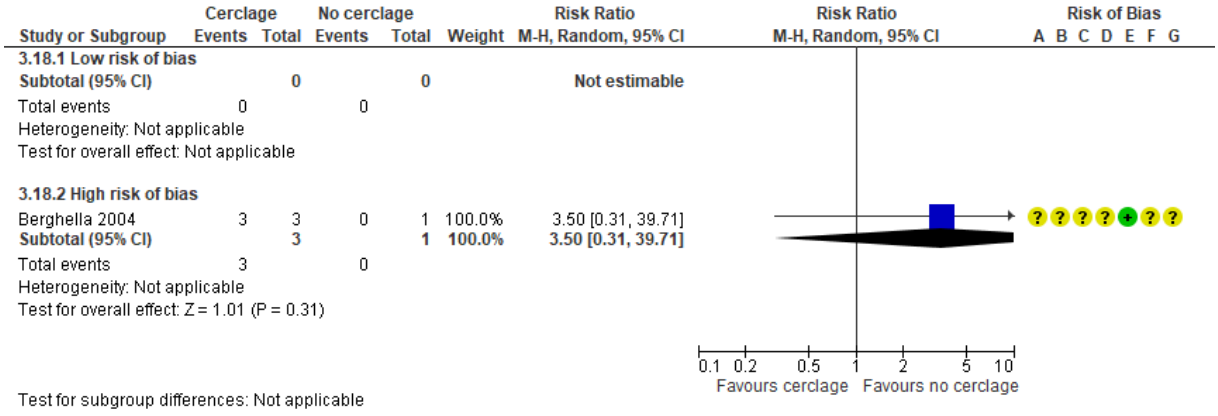
NB: Macnaughton 1993 includes miscarriages in numerator and denominator.

Conclusion: It is uncertain whether cerclage affects the risk of any preterm birth before 33 gestational weeks in women with a twin pregnancy with or without additional risk factor(s) for preterm birth (GRADE ⊕◯◯◯).

Spontaneous preterm birth <33 weeks
No trial reported spontaneous preterm birth <33 weeks.

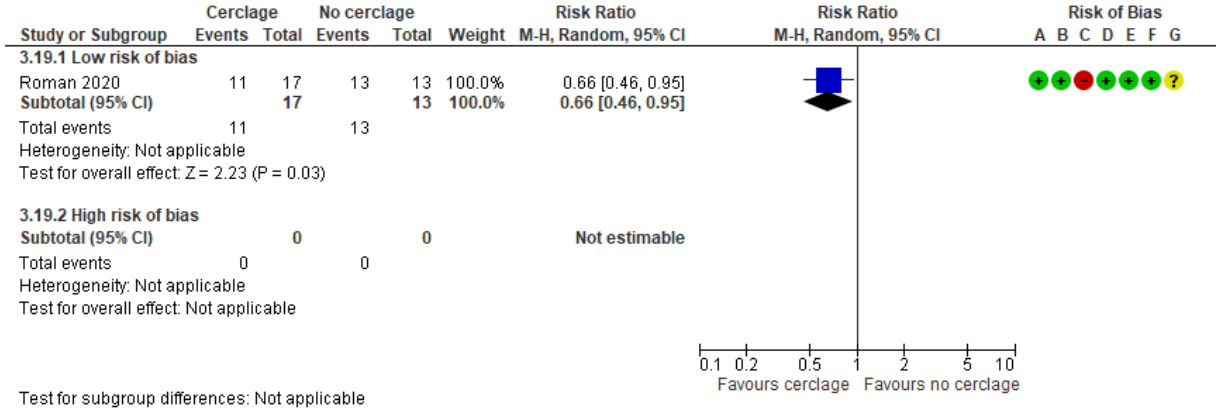
Any preterm birth <32 weeks (Appendix 4.2.5.a and Figure 33)
No trial with low risk of bias reported any preterm birth <32 weeks.

Figure 33. Outcome: Any preterm birth before 32 weeks.



Spontaneous preterm birth <32 weeks (Appendix 4.2.5.b and Figure 34)
One trial with low risk of bias, including 30 women with a twin pregnancy, showed a reduced rate of spontaneous preterm birth, RR 0.66 (95% CI 0.46 to 0.95). The event rate was 100% without cerclage. The RD was -35.3 percentage points (95% CI -59.2 to -11.1).

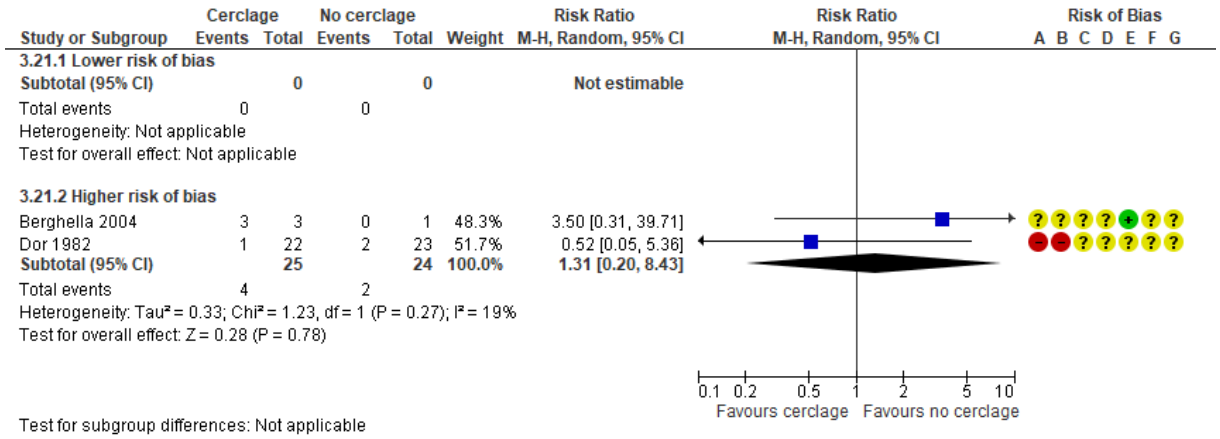
Figure 34. Outcome: Spontaneous preterm birth before 32 weeks.



Conclusion: It is uncertain whether cerclage reduces the risk for spontaneous preterm birth before 32 gestational weeks, in asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕◯◯◯).

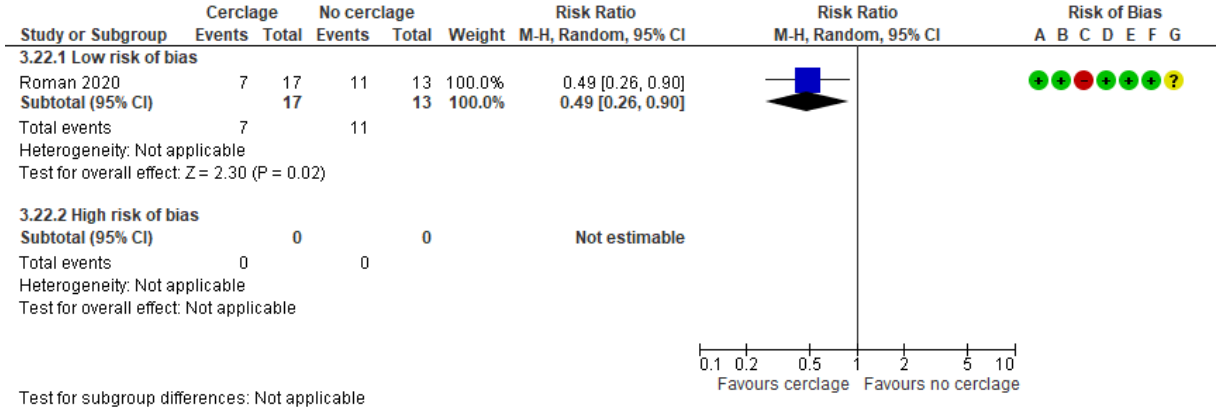
Any preterm birth <28 weeks (Appendix 4.2.6.a and Figure 35)
No trial with low risk of bias reportedny preterm birth <28 weeks.

Figure 35. Outcome: Any preterm birth before 28 weeks.



Spontaneous preterm birth <28 weeks (Appendix 4.2.6.b and Figure 36)
One trial with low risk of bias, including 30 women with a twin pregnancy, showed a reduced rate of spontaneous preterm birth, RR 0.49 (95% CI 0.26 to 0.90). The event rate was 84.6% without cerclage. The RD was -43.4 percentage points (95% CI -74.0 to -12.9).

Figure 36. Outcome: Spontaneous preterm birth before 28 weeks.



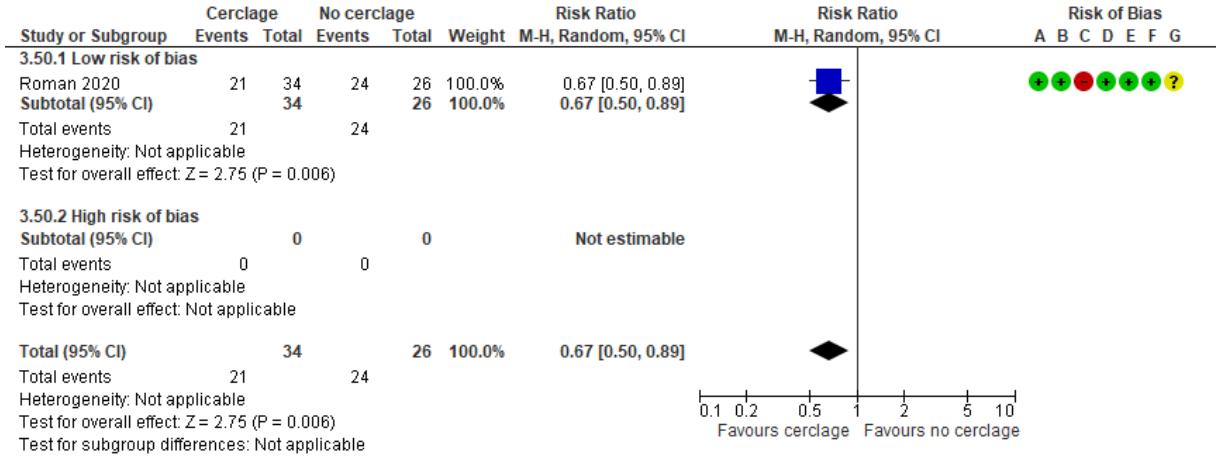
Conclusion: It is uncertain whether cerclage reduces the risk of spontaneous preterm birth before 28 gestational weeks, in asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Gestational age in multifetal pregnancies
No trial reported gestational age.

Low birth weight in multifetal pregnancies
No trial reported low birth weight.

Very low birth weight in multifetal pregnancies (Appendix 4.2.9 and Figure 37)
One trial with low risk of bias, including 60 neonates, showed a reduced rate of very low birth weight, RR 0.67 (95% CI 0.50 to 0.89). The event rate was 92.3% without cerclage. The RD was -30.5 percentage points (95% CI -49.8 to -11.3).

Figure 37. Outcome: Very low birth weight (<1500g).

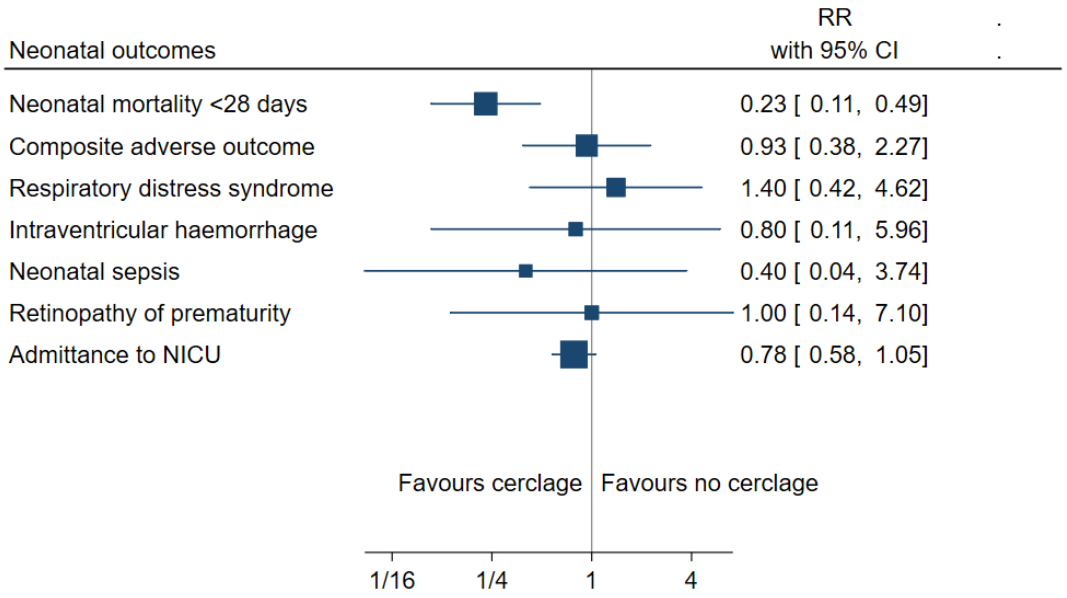


Conclusion: Cerclage may reduce the risk of very low birth weight, in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕⊕○○).

Mortality and morbidity in neonates from multifetal pregnancies

The pooled estimates from low risk of bias trials are summarised in Figure 38.

Figure 38. Summary graph of pooled estimates from meta-analyses comparing cerclage versus no cerclage in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth, from trials with low risk of bias, regarding neonatal outcomes.

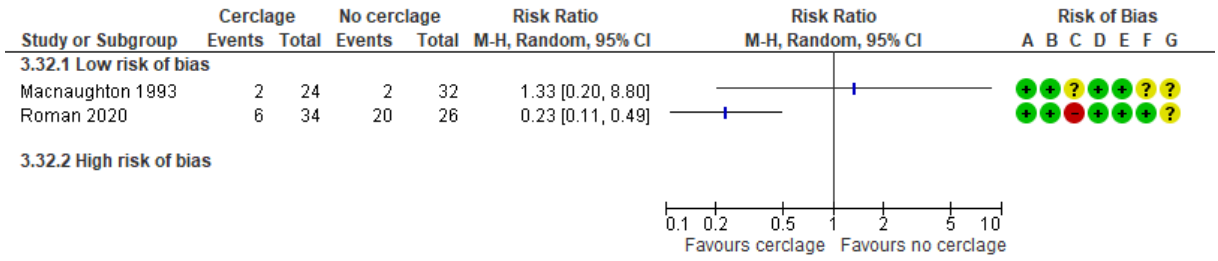


All outcomes but neonatal mortality displayed non-significant differences comparing cerclage versus no cerclage. Serious imprecision affected the certainty of evidence for all outcomes.

Perinatal mortality (Appendix 4.2.10 and Figure 39)

Two trials with low risk of bias reported perinatal mortality in twin pregnancies. Due to the heterogeneity of the trials, no meta-analysis was performed. The Roman et al. trial, including 60 neonates from women with a twin pregnancy with a very high risk for preterm birth, showed a reduced risk of perinatal mortality, RR 0.23 (95% CI 0.11 to 0.49). The event rate was 76.9% without cerclage. The RD was -59.3 percentage points (95% CI -79.9 to -38.6). There was no intrauterine detal death. The Macnaughton et al. trial, including 56 neonates, showed no difference in perinatal mortality rate, RR 1.33 (95% CI 0.20 to 8.80). The event rate was 6.3% without cerclage. The RD was 2.1 percentage points (95% CI -11.8 to 16.0).

Figure 39. Outcome: Perinatal mortality.



NB: Macnaughton 1993 includes all miscarriages in numerator and denominator.

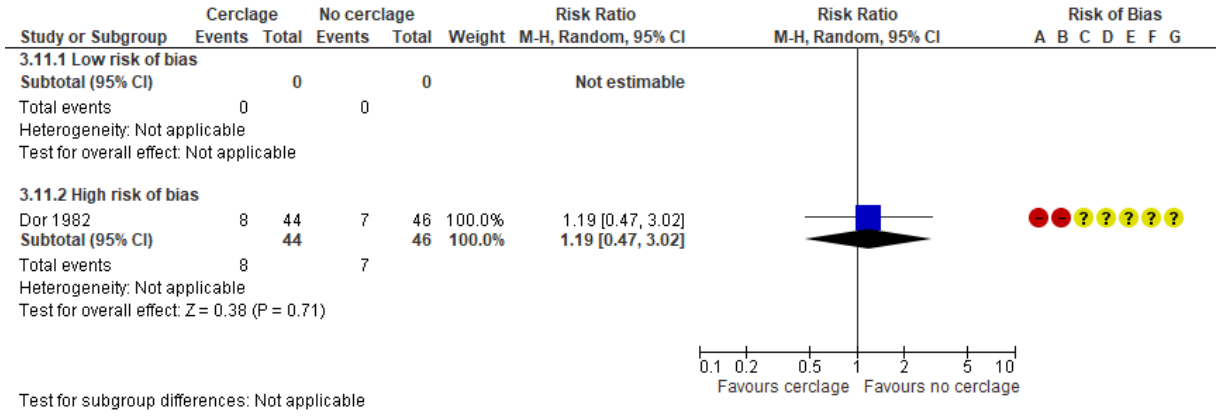
Conclusions:

-Cerclage may reduce the risk of perinatal mortality in asymptomatic women with twin pregnancies and a dilated cervix, and visible membranes (GRADE ⊕⊕◯◯) (based on Roman et al., 2020).

-It is uncertain whether cerclage affects the risk of perinatal mortality in twins with or without additional risk factor(s) for preterm birth (GRADE ⊕◯◯◯) (based on Macnaughton et al., 1993).

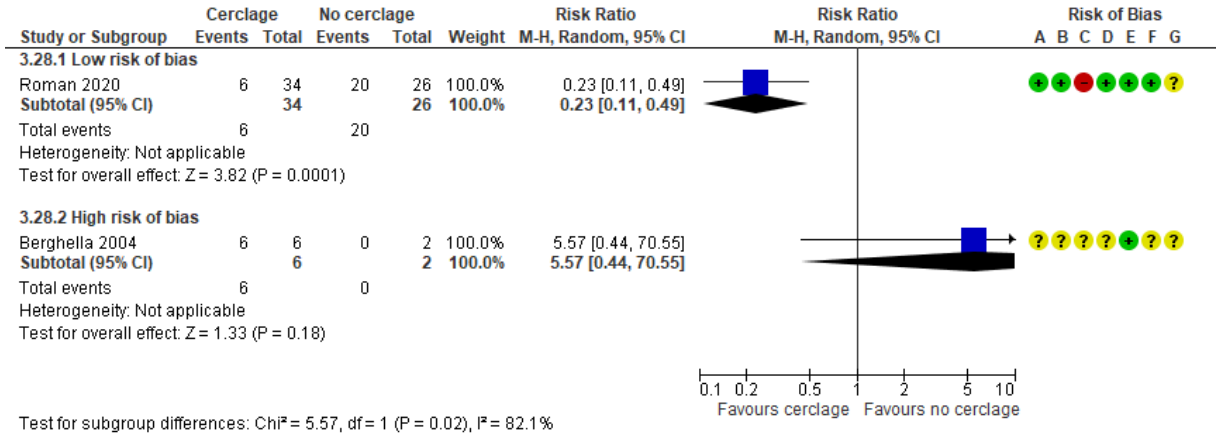
Neonatal mortality <7 days (Appendix 4.2.11 and Figure 40)
No trial with low risk of bias reported on neonatal mortality <7 days.

Figure 40. Outcome: Neonatal mortality <7days in twin pregnancies.



Neonatal mortality <28 days (Appendix 4.2.12 and Figure 41)
One trial with a low risk of bias, including 60 neonates, showed a reduced rate of neonatal mortality, RR 0.23 (95% CI 0.11 to 0.49). The event rate was 76.9% without cerclage. The RD was -59.3 percentage points (95% CI -79.9 to -38.6).

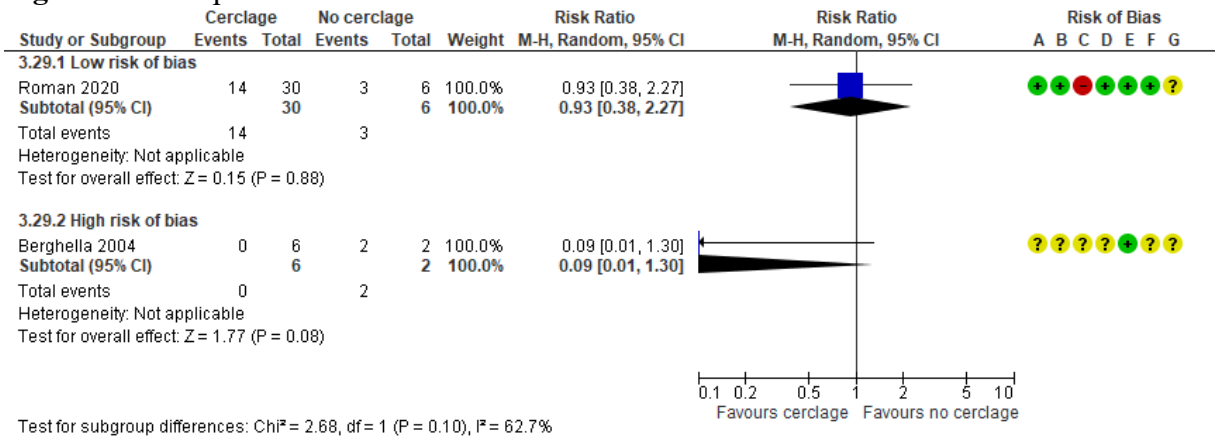
Figure 41. Outcome: Neonatal mortality <28 days.



Conclusion: Cerclage may reduce the risk of neonatal mortality <28 days in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕⊕◯◯).

Composite adverse neonatal outcome (Appendix 4.2.13 and Figure 42)
One trial with low risk of bias, including 36 neonates, showed no difference in composite adverse neonatal outcome rate, RR 0.93 (95% CI 0.38 to 2.27). Mortality was not included in the composite adverse outcome. The event rate was 50.0% without cerclage. The RD was -3.3 percentage points (95% CI -47.1 to 40.5).

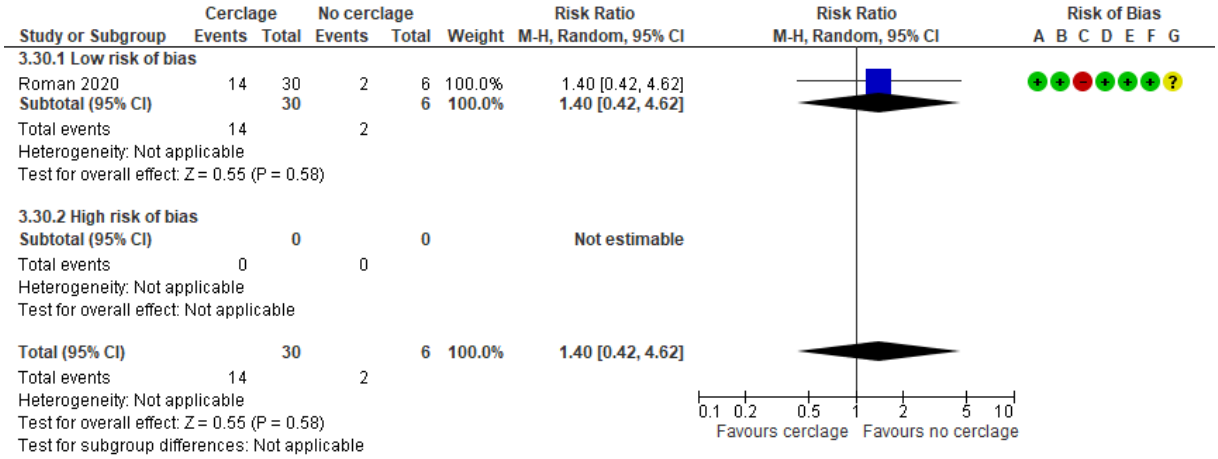
Figure 42. Composite adverse neonatal outcome.



Conclusion: It is uncertain whether cerclage compared with no cerclage, results in a reduced risk of composite adverse neonatal outcome, in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Respiratory distress syndrome (RDS) (Appendix 4.2.14 and Figure 43)
One trial with low risk of bias, including 36 neonates, showed no difference in RDS rate, RR 1.40 (95% CI 0.42 to 4.62). The event rate was 33.3% without cerclage. The RD was 13.3 percentage points (95% CI -28.4 to 55.1).

Figure 43. Outcome: Respiratory distress syndrome.

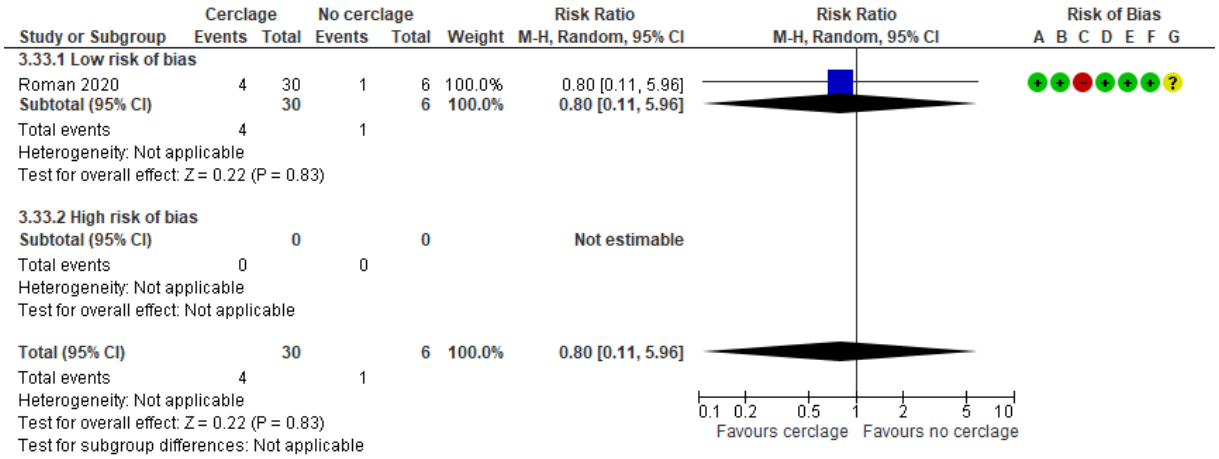


Conclusion: It is uncertain whether cerclage affects the risk of RDS in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Bronchopulmonary dysplasia (BPD)
No trial reported on BPD.

Intraventricular haemorrhage (IVH) (Appendix 4.2.16 and Figure 44)
One trial with low risk of bias, including 36 neonates, showed no difference in the rate of IVH, RR 0.80 (95% CI 0.11 to 5.96). The event rate was 16.7% without cerclage. The RD was -3.3 percentage points (95% CI -35.5 to 28.9).

Figure 44. Outcome: Intraventricular haemorrhage.



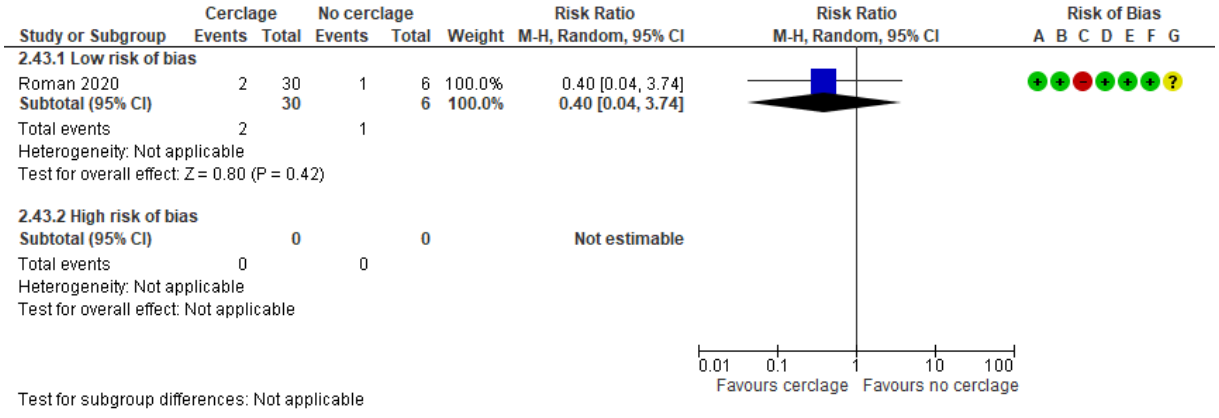
Conclusion: It is uncertain whether cerclage affects the risk of IVH in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Necrotizing enterocolitis (NEC) (Appendix 4.2.17)
One trial with low risk of bias, including 36 neonates reported zero events in both groups.

Conclusion: It is uncertain whether cerclage affects the risk of NEC in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Neonatal sepsis (Appendix 4.2.18 and Figure 45)
One trial with low risk of bias, including 36 neonates, showed no difference in the rate of neonatal sepsis, RR 0.40 (95% CI 0.04 to 3.74). The event rate was 16.7% without cerclage. The RD was -10.1 percentage points (95% CI -41.1 to 21.1).

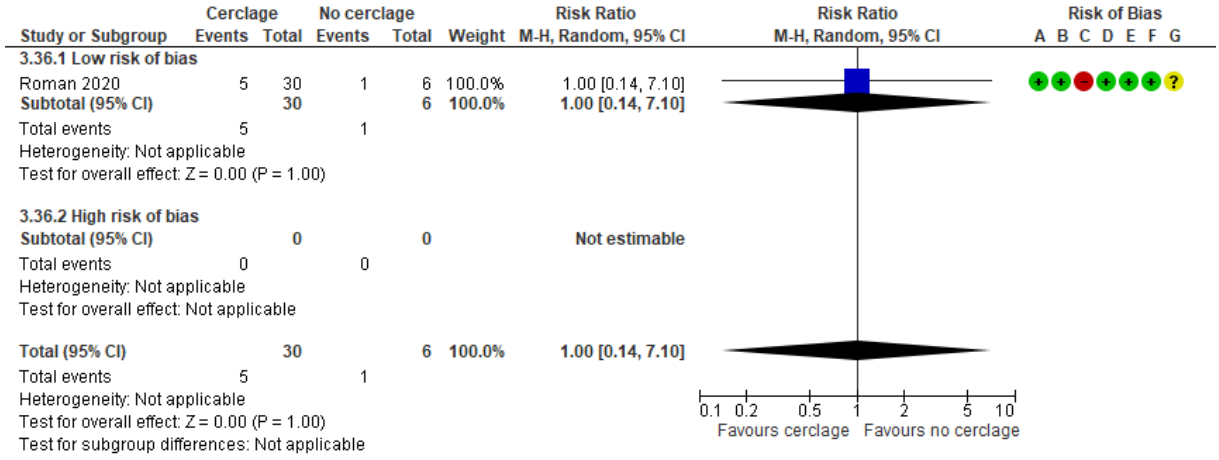
Figure 45. Outcome: Neonatal sepsis.



Conclusion: It is uncertain whether cerclage affects the risk of neonatal sepsis, in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕○○○).

Retinopathy of prematurity (ROP) (Appendix 4.2.19 and Figure 46)
One trial with low risk of bias, including 36 neonates, showed no difference in the rate of ROP, RR 1.00 (95% CI 0.14 to 7.10). The event rate was 16.7% without cerclage. The RD was 0.0 percentage points (95% CI -32.7 to 32.7).

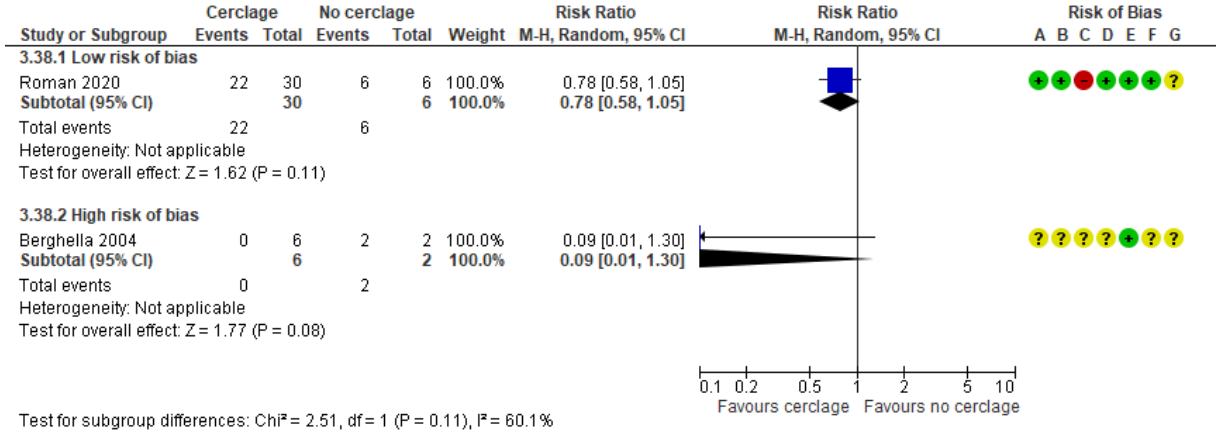
Figure 46. Outcome: Retinopathy of prematurity.



Conclusion: It is uncertain whether cerclage affects the risk of ROP in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕◯◯◯).

Admittance to neonatal intensive care unit (Appendix 4.2.20 and Figure 47)
One trial with a low risk of bias, including 36 neonates, showed no difference in the admittance rate to NICU, RR 0.78 (95% CI 0.58 to 1.05). The event rate was 100% without cerclage. The RD was -27.7 percentage points (95% CI -51.4 to -2.0).

Figure 47. Outcome: Admittance to neonatal intensive care unit.



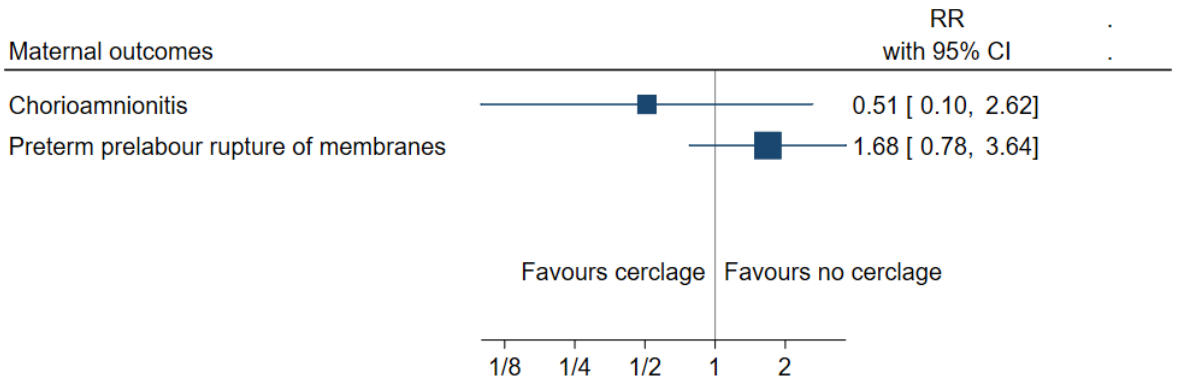
Conclusion: Cerclage compared with no cerclage, may result in no difference in the risk of NICU admittance in neonates from asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕⊕◯◯).

Long-term child outcomes
No trial reported long-term child outcomes.

Mortality and morbidity in women with multifetal pregnancies

The pooled estimates of low risk of bias trials are summarised in Figure 48.

Figure 48. Summary graph of pooled estimates from meta-analyses comparing cerclage versus no cerclage in women with a multifetal pregnancy with or without additional risk factor(s) from trials with a low risk of bias regarding maternal outcomes.



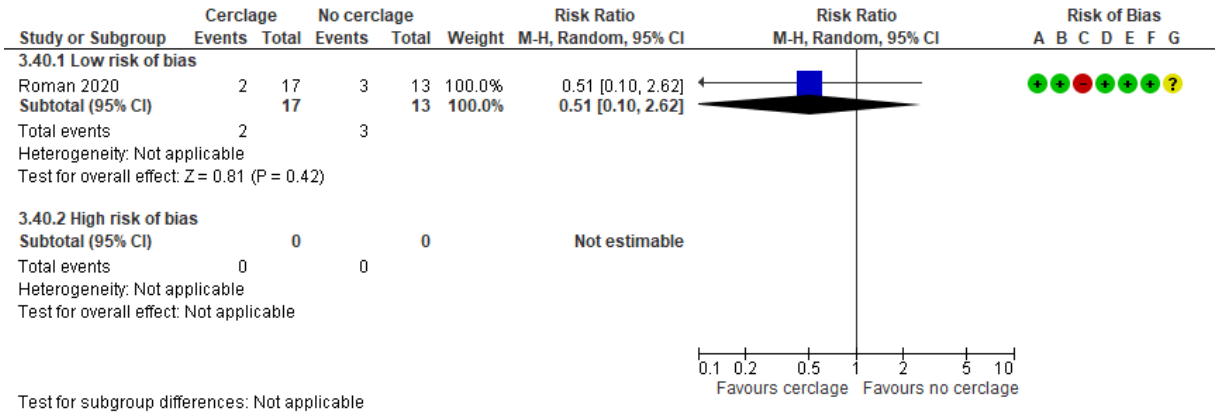
Maternal mortality and morbidity

No trial reported maternal mortality, hypertensive disorders in pregnancy, gestational diabetes, or intrahepatic cholestasis.

Infection (clinical chorioamnionitis) (Appendix 4.2.21 and Figure 49)

One trial with low risk of bias, including 30 women with a twin pregnancy, showed no difference in the rate of clinical chorioamnionitis, RR 0.51 (95% CI 0.10 to 2.62). The event rate was 23.1% without cerclage. The RD was -11.3 percentage points (95% CI -38.9 to 16.2).

Figure 49. Outcome: Chorioamnionitis.

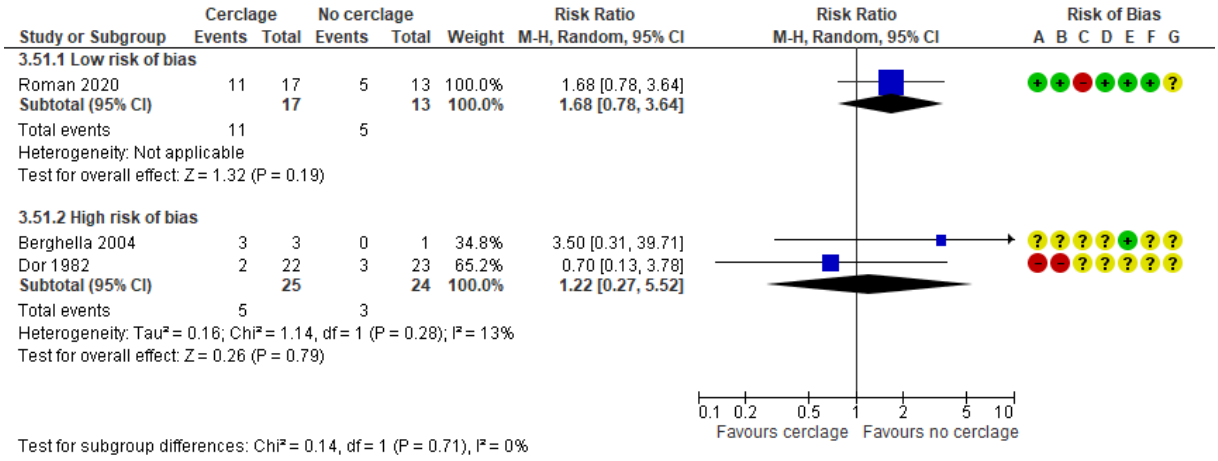


Conclusion: It is uncertain whether cerclage affects the risk of clinical chorioamnionitis in asymptomatic women with a twin pregnancy and dilated cervix, and visible membranes (GRADE ⊕◯◯◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.2.22 and Figure 50)

One trial with low risk of bias, including 30 women with a twin pregnancy, showed no difference in the risk of PPROM, RR 1.68 (95% CI 0.78 to 3.64). The event rate was 38.5% without cerclage. The RD was 26.2 percentage points (95% CI -8.6 to 61.1).

Figure 50. Outcome: Preterm prelabour rupture of the membranes (PPROM).



Conclusion: It is uncertain whether cerclage affects the rate of PPROM in asymptomatic women with a twin pregnancy, dilated cervix, and visible membranes (GRADE ⊕◯◯◯).

Project: Prevention of preterm birth
Appendix 4.2.1.a. Intervention cerclage
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ezechi, 2004 Nigeria	Not stated	History of PTB: 1 (63-69%) 2 (21-32%) 3 (5-9%)	I: 38 C: 43	McDonald cerclage 4/38 (10.5%) OR 0.20 (95% CI 0.05-0.74) p=0.012	No cerclage 16/43 (37.2%)	PO not defined Outcome stated as PTB, no definition but seems to be <37 w as described in text. Singletons/twins not stated but singletons correspond to neonatal outcomes.	-	?	?
Lazar, 1984 France	Singletons	Composite score of a combination of: History of PTB 29-36 w, history of previous miscarriage, prior threatening PTL treated by hospitalisation, uterine malformation, previous forced cervical dilatation, low lying placenta with bleeding, CL <2 cm, cx open for inner os	I: 268 C: 238	McDonald cerclage 18/268 (6.7%) p=0.35 RR not presented	No cerclage 13/238 (5.5%)	PO not defined	?	?	?
Otsuki, 2016 Japan	Singletons	General population screening: TVS CL <25 mm History of PTB 11-15%, history of previous abortion 20%	I1 (Shirodkar): 35 I2 (McDonald): 36 C: 35	I1: Shirodkar cerclage 7/34 (20%) p=0.50 RR not presented I2: McDonald cerclage 11/34 (32.4%) p=0.99 RR not presented	No cerclage, bedrest 10/33 (30.3%)	Not PO	?	?	?
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + short TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 66/148 (45%) p=0.01 RR not presented	No cerclage 91/153 (60%)	Not PO	?	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 and 2,3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 33/96 (34.4%) NS	No cerclage 31/98 (31.6%)	PO not defined	?	?	?

Project: Prevention of preterm birth
Appendix 4.2.1.a. Intervention cerclage
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
\- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins (28/1292, 2%) Twins: I: 12 C: 16	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647 C: 645	Cerclage (not prespecified) Singletons and twins: 169/647 (26%)* OR 0.80, 95% CI 0.63-1.02 p=0.07 Sensitivity analysis: Excluding early miscarriage (<13 w) in numerator and denominator (n=12) 157/635 (24.7%) No statistics in article Singletons (calculated, and same numbers as in Alfirevic, Cochrane, 2017) 161/635 (25.4%)* No statistics Twins 8/12 (67%)*, NS	No cerclage Singletons and twins: 198/645 (31%)* Sensitivity analysis: Excluding early miscarriage (<13 w) in numerator and denominator (n=9) 189/636 (29.7%) Singletons (calculated, and same numbers as in Alfirevic, Cochrane, 2017) 190/629 (30.2%)* Twins 8/16 (50%)*	PO, then PO changed to <33 w after study initiation *All miscarriages included in numerator and denominator I: 43/647 and C: 50/645	?	?	?
Rust, 2000 USA	Singletons and twins (7/61, 11.5% twins)	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I: 31 C: 30	McDonald cerclage and modified bedrest 18/31 (58.1%), p=0.4 RR not presented	Modified bedrest 3/30 (43.3%)	5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes. Not included in meta-analysis due to multifetal pregnancies >10%	-	-	?
Dor, 1982 Israel	Twins	Twin pregnancy after OI	I: 22/44 C: 23/46	McDonald cerclage 10/22 (45.4%), NS RR not presented	No cerclage 11/23 (47.8%)	PO not defined	?	-	-

Project: Prevention of preterm birth
Appendix 4.2.1.a. Intervention cerclage
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic, 2017 Cochrane	**Singletons**								
Althuisius, 2001 The Netherlands CIPRACT	Singletons	History of PTB <34 w, PPROM <32 w, cold knife conisation, diethylstilbestrol exposure, or uterine anomaly and TVS CL <25 mm	I: 20 C:16	McDonald cerclage and bedrest 4/19 (21.1%) No statistics	Bedrest 10/16 (62.5%)	Not PO	+	-	-
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	Short TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 41/127 (32.3%)	No cerclage 63/126 (50%)	Not PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons and twins (4/61) 7% twins	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregnancy) and or TVS CL <25 mm or significant funneling	I: 31 C: 30	McDonald cerclage with bedrest All 17/31 (54.8%) No statistics Singletons 14/28 (50.0%) No statistics Twins 3/3 (100%) No statistics	No cerclage, bedrest All 22/30 (73.3%) Singletons 21/29 (72.4%) Twins 1/1 (100%)	Not PO PTB in twins calculated from original article, 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw	+	?	-

C; control, CI; confidence interval, CL; cervical length, I; intervention, OI; ovulation induction, OR; odds ratio, PO; primary outcome, PPROM, preterm prelabour rupture of the membranes, PTB; preterm birth, RR; risk ratio, SO; secondary outcome, TVS; transvaginal scan, UK; United Kingdom, w; week

Project: Prevention of preterm birth
Appendix 4.2.2.a. Intervention cerclage
Outcome variable: Any preterm birth before 35 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n =	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Lazar, 1984 France	Singletons	Composite score of a combination of: History of PTB 29-36 w, history of previous miscarriage, prior threatening PTL treated by hospitalisation, uterine malformation, previous forced cervical dilatation, low lying placenta with bleeding, CL <2 cm, cx open for inner os	I: 268 C:238	McDonald cerclage 10/268 (3.7%) No statistics	No cerclage 10/238 (4.2%)	PO not defined	?	?	?
Owen, 2009 USA	Singletons	History of sPTB or PPROM and short TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 47/148 (32%) OR 0.67, 95% CI 0.42-1.07 p=0.09	No cerclage 64/153 (42%)	PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons and twins (twins 4/61, 7%)	≥1 of high-risk factors for preterm birth (≥1 preterm birth <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL < 25 mm or significant funneling	I: 31 C: 30	McDonald cerclage + bedrest All 14/31 (45%) RR 0.94 (95% CI 0.34-2.58) Singletons 11/28 (39.3%) No statistics Twins 3/3 (100%) No statistics	No cerclage, bedrest All 14/30 (47%) Singletons 13/29 (44.8%) Twins 1/1 (100%)	PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw	+	?	-

C; control, CI; confidence interval, CL; cervical length, I; intervention, OR; odds ratio, PO; primary outcome, PPROM; preterm prelabour rupture of the membranes, PTB; preterm birth, RR; risk ratio, TVS; transvaginal ultrasound, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.3.a. Intervention cerclage
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Althuisius, 2001 The Netherlands	Singletons	Previous PTB <34 w, PPROM<32 w or uterine anomaly, or prior cold knife conization and TVS CL <25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 0/19 (0%) p=0.002	No cerclage, bedrest 7/16 (43.8%)	One of 3 POs (together with neonatal morbidity/mortality and neonatal survival)	+	-	-
Otsuki, 2016 Japan 60 tertiary centers	Singletons	TVS CL <25 mm	I1 (Shirodkar): 35 I2 (McDonald): 36 C: 35	Shirodkar cerclage 1/34 (2.9%) p=0.34 RR not presented McDonald cerclage 6/34 (17.6%), p=0.78 RR not presented	No cerclage (bedrest) 4/33 (12.1%)	Not PO	+	?	-
Berghella, 2004 USA (2 centers)	Singletons and twins (4/61, 7% twins)	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregnancy) and or TVS CL < 25 mm or significant funneling	I: 31 C: 30	McDonald cerclage + bedrest All 13/31 (42%) RR 1.05 (95% CI 0.57-1.92) Singletons 10/28 (35.7%) No statistics Twins 3/3 (100%) No statistics	Bedrest All 12/30 (40%) Singletons 12/29 (41.4%) Twins 0/1 (0%)	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw	+	?	-
Rust, 2000 USA	Singletons and twins/triplets Singletons (n=54) and 5 sets of twins and 2 sets of triplets (11% multifetal pregnancies)	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multiple gestation and a TVS CL <25 mm or dilated internal os	I:31 C:30	McDonald cerclage + modified bedrest 12/31 (38.7%) p=0.6 RR not presented	No cerclage, modified bedrest 9/30 (30.0%)	No PO. 5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes. Not included in meta-analysis due to multifetal pregnancies >10%. Rust 2001 not included due to wrong intervention (risk factor analysis). Rust 2001 included an expanded study population from Rust 2000, I:55, C: 58	-	-	?

Project: Prevention of preterm birth
Appendix 4.2.3.a. Intervention cerclage
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic 2017	**Singletons**								
Ezechi, 2004 Nigeria	Not stated	Previous PTB; 1 (63-69%), 2 (21-32%), 3 (5-9%)	I:39 C:42	McDonald cerclage 0/39 (0%) No statistics	No cerclage 11/42 (26.2%)	PO not defined NB in original article 38 resp 43	-	?	?
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons (subanalysis from original paper)	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, twin, uterine anomaly	I: 635 C: 629 (singletons)	Cerclage (not prespecified) 92/635 (14.5%)* No statistics	No cerclage 113/629 (18.0%)*	Not PO *Includes all miscarriages in numerator and denominator According to Alfirevic, Cochrane 2017: Miscarriages in singletons I: 37/635, C: 42/629	?	?	?
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 42/148 (28.4%) No statistics	No cerclage 57/153 (37.3%)	Not PO	?	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2,3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 14/96 No statistics	No cerclage 14/98	Not PO	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodcar cerclage 28/127 (22.0%) No statistics	No cerclage 36/126 (28.6%)	Not PO	?	?	?

C; control, CI; confidence interval, CL; cervical length, gw; gestational week, I; intervention, PPROM; preterm prelabour rupture of membranes, PTB; preterm birth, RR; risk ratio, PO; primary outcome, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.3.b. Intervention cerclage
Outcome variable: Spontaneous preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Roman, 2020 Multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland.	Twins DA	Asymptomatic women with twin pregnancy, with dilated cervix 1-5 cm identified by pelvic examination and/or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 12/17 (70.6%) RR 0.71 (95% CI 0.52-0.96) p=0.05	No cerclage 13/13 (100%)	PO	+	?	-

C; control, CI; confidence interval, DA; diamniotic, I; intervention, PO; primary outcome, RR; risk ratio, US; United States of America, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.2.4.a. Intervention cerclage
Outcome variable: Any preterm birth before 33 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 28/127 (22%) RR 0.84, 95% CI 0.54-1.31 p=0.44	No cerclage 33/126 (26%)	PO	?	?	?
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins (2%) (Twins I:12 C:16)	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647 C: 645	Cerclage (not prespecified) Singletons and twins 83/647 (13%)* OR 0.72 (95% CI 0.53-0.97) p=0.03 Sensitivity analysis excluding early miscarriage (<13 w, n=12) in numerator and denominator 71/635 (11%) OR 0.67 (95% CI 0.49-0.92) p=0.015 Singletons (calculated) 82/635 (12.9%)* No statistics Twins 1/12 (8.3%)*, NS	No cerclage Singletons and twins 110/645 (17%)* Sensitivity analysis excluding early miscarriage (<13 w, n=9) in numerator and denominator 101/636 (16%) Singletons (calculated) 105/629 (16.7%)* Twins 5/16 (31.3%)*	PO (together with <37 w, changed to < 33 w after study initiation) All miscarriages (I: 43/647 and C: 50/645) included in numerator and denominator. In article also presented without early miscarriage (<13 w) for singletons and twins combined	?	?	?
Dor, 1982 Israel	Twins	Twin pregnancies after OI	I: 22/44 C: 23/46	Mc Donald cerclage 3/22 (13.6%) No statistics	No cerclage 3/23 (13.1%)	Not PO From Figure 1	?	-	-

C; control, CI; confidence interval, CL; cervical length, I; intervention, OI; ovulation induction, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal ultrasound, UK; United Kingdom, w; weeks.

Project: Prevention of preterm birth
Appendix 4.2.5.a. Intervention cerclage
Outcome variable: Any preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Lazar 1984, France	Singletons	Composite score of a combination of: History of PTB 29-36 w, history of previous miscarriage, prior threatening PTL treated by hospitalisation, uterine malformation, previous forced cervical dilatation, low lying placenta with bleeding, CL <2 cm, cx open for inner os	I: 268 C:238	McDonald cerclage 4/268 (1.5%) No p value or RR presented	No cerclage 1/238 (0.4%)	Primary outcome not defined	?	?	?
Otsuki 2016 Japan 60 tertiary centers	Singletons	TVS CL <25 mm	I1 (Shirodkar): 35 I2 (McDonald): 36 C: 35	Shirodkar cerclage: 1/34 (2.9%) p=0.79 RR not presented McDonald cerclage: 6/34 (17.6%) p=0.90 RR not presented	No cerclage, bedrest 4/33 (12.1%)	Not PO	?	?	?
Berghella 2004 USA (2 centers)	Singletons and twins (4/61, 7% twins)	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregnancy) and/or TVS CL <25 mm or significant funneling	I: 31 C: 30	McDonald cerclage+ bedrest All 11/31 (35%) RR 0.97 (95% CI 0.50-1.89) Singletons 8/28 (28.6%) No statistics Twins 3/3 (100%) No statistics	Bedrest All 11/30 (37%) Singletons 12/29 (41.4%) Twins 0/1 (0%)	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw	?	?	?

C; control, CI; confidence interval, CL; cervical length, I; intervention, RR; risk ratio, PO; primary outcome, PTB; preterm birth, TVS; transvaginal scan, w, weeks

Project: Prevention of preterm birth
Appendix 4.2.5.b. Intervention cerclage
Outcome variable: Spontaneous preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Roman, 2020 multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twin pregnancy, with dilated cervix 1-5 cm identified by pelvic examination and/or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 11/17 (64.7%) RR 0.65 (95% CI 0.46-0.92) p=0.02	No cerclage 13/13 (100%)	Not PO	+	+	-

C; control, CI; confidence interval, DA; diamniotic, I; intervention, RR; risk ratio, PO; primary outcome, US; United States of America, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.2.6.a. Intervention cerclage
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Otsuki, 2016 Japan 60 tertiary centers	Singletons	TVS CL <25 mm	I1 (Shirodkar): 35 I2 (McDonald): 36 C: 35	Shirodkar cerclage: 0/34 (0%) NS McDonald cerclage 0/34 (0%) NS	No cerclage, bedrest 0/33 (0%)	Not PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons and Twins (4/61, 7% twins)	≥1 of high-risk factors for preterm birth (≥1 preterm birth <35w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy), and/or TVS CL <25 mm or significant funneling	I: 31 C: 30	McDonald cerclage + bedrest 9/31 (29%) RR 1.45 (95% CI 0.59-3.58) Singletons 6/28 (21.4%) No statistics Twins 3/3 (100%) No statistics	Bedrest 6/30 (20%) Singletons 6/29 (20.7%) Twins 0/1 (0%)	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw	?	?	?
Rust, 2000 USA	Singletons and twins 11% multifetal pregnancies	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I: 31 C: 30	McDonald cerclage and modified bedrest 7/31 (22.6%) p=0.5 RR not presented	Modified bedrest 4/30 (13.3%)	Not PO 5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes Not included in meta-analysis due to multifetal pregnancies>10%	-	-	?
Dor 1982, Israel	Twins	Twin pregnancies after OI	I: 22/44 C: 23/46	Cerclage 1/22 (4.5%) No statistics	No cerclage 2/23 (8.7%)	Not PO From Figure 1	?	-	-

Project: Prevention of preterm birth
Appendix 4.2.6.a. Intervention cerclage
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles and not to the subgroups presented below									
Alfirevic 2017	**Singletons**								
Ezechi, 2004 Nigeria	Not stated	Previous PTB: 1 (63-69%), 2 (21-32%), 3 (5-9%)	I:39 C:42	McDonald cerclage 0/39 (0%) No statistics	No cerclage 1/42 (2.4%)	PO not defined NB in original article I:38 and C:43	-	?	?
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 635 C: 629 (singletons)	Cerclage (not prespecified) 53/635 (8.3%)* No statistics	No cerclage 65/629 (10.3%)*	No PO *All miscarriages included in numerator and denominator According to Alfirevic, Cochrane 2017: Miscarriage in singletons I: 37/635, C: 42/629	?	?	?
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + short TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 21/148 (14.2%) No statistics	No cerclage 33/153 (21.6%)	Not PO	?	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2,3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 7/96 (7.3%) No statistics	No cerclage 7/98 (7.1%)	Not PO	?	?	?
To, 2004 UK(6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodcar cerclage 15/127 (11.8%) No statistics	No cerclage 17/126 (13.5%)	Not PO	?	?	?

C; control, CL; cervical length, I; intervention, PPROM; preterm premature rupture of the membranes, PTB; preterm birth, RR; risk ratio, PO; primary outcome, sPTB; spontaneous PTB, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.6.b. Intervention cerclage
Outcome variable: Spontaneous preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Roman, 2020 Multicenter (8 centers, Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asympto-matic women with twin pregnancy, with dilated cervix 1-5 cm identified by pelvic examination and/or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 1/17 (41.2%) RR 0.49 (95% CI 0.26-0.89) p=0.02	No cerclage 11/13 (84.6%)	Not PO	+	+	-

C; control, CI; confidence interval, DA; diamniotic, I; intervention, RR; risk ratio, PO; primary outcome, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.2.7. Intervention cerclage
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention Mean (SD)	Control Mean (SD)				
Ezechi, 2004, Nigeria	Not stated	Previous PTB	I: 38 C: 43	McDonald cerclage Mean (SD) 38.9 (2.9) w p=0.001	No cerclage Mean (SD) 36.9 (3.5) w	Not PO Singletons/twins not stated.	-	?	?
To 2004 UK (6 countries 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage Mean (SE) 36.4 (0.42) w Difference in means 0.95 (95% CI -0.26 to 2.15) w p=0.12	No cerclage Mean (SE) 35.4 (0.45) w	Not PO	?	?	?
Berghella 2004 USA (2 centers)	Singletons and twins (4/61) (7%)	≥1 of high-risk factors for preterm birth (≥1 preterm birth <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL <25 mm or significant funneling	I: 31 C: 30	McDonald cerclage and bedrest Singletons and twins Mean (SD) 32.6 (6.9) w p=0.89	Bedrest Singletons and twins Mean (SD) 32.9 (6.7) w	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 w	+	?	-
Rust 2000 USA	Singletons and twins/triplets (7/61) (11%)	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I: 31 C: 30	McDonald cerclage Mean (SD) 33.5 (6.3) w p=0.4	Bedrest Mean (SD) 34.7 (4.7) gw	5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes.	-	-	?

C; control, CL; cervical length, I; intervention, PTB; preterm birth, RR; risk ratio, SD; standard deviation, SE; standard error, PO; primary outcome, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.8. Intervention cerclage
Outcome variable: Low birth weigth (<2500g)

* + No or minor problems
? Some problems
\- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ezechi, 2004 Nigeria	Not stated	Previous PTB; 1 (63-69%), 2 (21-32%), 3 (5-9%)	I: 38 C: 43	McDonald cerclage 3/38 (7.9%) OR 0.22 (95% CI 0.00-0.96) p=0.04	No cerclage 12/43 (27.9%)	Not PO Singletons/twins not stated. Singletons/twins not stated but singletons correspond to neonatal outcomes	-	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2,3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 36/96 (38%) No statistics	No cerclage 34/98 (35%)	Not PO	?	?	?
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins Twins 28/1292 (2%) Twins: I: 12 C: 16	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647/659 C: 645/661	Cerclage (not specified) Singletons and twins 154/659 (23.4%)* No statistics	No cerclage Singletons and twins 174/661 (26.3%)*	Not PO 2% twins in intervention group, 2.5% twins in no cerclage group This mix rendered the minus for directness *Miscarriages included in numerator and denominator (I: 43 and C: 50)	?	?	?

C; control, CI; confidence interval, I; intervention, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, PO; primary outcome, UK; United Kingdom, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.9. Intervention cerclage
Outcome variable: Very low birth weigth (<1500g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins 28/1292 (2%) Twins: I: 12 C: 16	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647/659 C: 645/661	Cerclage (not specified) Singletons and twins 63/659 (10%)* OR 0.70, 95% CI 0.50-0.99 No p value	No cerclage Singletons and twins 86/661 (13%)*	Not PO 2% twins in intervention group, 2.5% twins in no cerclage group This mix rendered the minus for directness *Miscarriages included in numerator and denominator (I: 43 and C: 50)	-	?	?
Roman, 2020 Multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland.	Twins DA	Asymtpmatic women with twins, dilated cervix 1-5 cm by pelvic examination and/or speculum examination and/or TVS	I: 17/34 C:13/26	Physical examination indicated McDonald cerclage 21/34 (61.7%) RR 0.67 (95% CI 0.50-0.89) p=0.007	No cerclage 24/26 (92.3)	Not PO	+	?	-

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, I; intervention, OR; odds ratio, PO; primary outcome PTB; preterm birth, RR; risk ratio, TVS; transvaginal ultrasound, UK; United Kingdom

Project: Prevention of preterm birth
Appendix 4.2.10. Intervention Cerclage
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations	Precision *
				Intervention	Control				
Althuisius, 2001 The Netherlands	Singleton	History of PTB <34 w, PPROM <32 w, cold knife conization, diethylstilbestrol exposure, or uterine anomaly and TVS CL <25 mm < 27 w	I: 19 C:16	McDonald cerclage, bedrest 0/19 (0%) p=0.002	No cerclage, bedrest 3/16 (18.8%)	One of 3 POs (together with neonatal morbidity/mortality and PTB <34 w) Defined as neonatal survival in the article, translated as perinatal mortality	+	-	-
Ezechi, 2004 Nigeria	Not stated	Previous PTB	I: 38 C: 43	McDonald cerclage 0/38 (0%) OR 0.00, 95% CI 0.0-4.68 p=0.53	No cerclage 2/43 (6.1%)	Not PO Singletons/twins not stated. Singletons/twins not stated but singletons correspond to neonatal outcomes	-	?	?
Lazar, 1984 France	Singletons	Composite score of a combination of: History of PTB 29-36 w, history of previous miscarriage, prior threatening PTL treated by hospitalisation, uterine malformation, previous forced cervical dilatation, low lying placenta with bleeding, CL <2 cm, cx open for inner os	I: 268 C:238	McDonald cerclage 2/268 (0.7%) No statistics	No cerclage 1/238 (0.4%)	Not PO Perinatal mortality not defined	?	?	?
Owen, 2009 USA	Singletons	History of sPTB + short TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 13/148 (8.8%) p=0.046	No cerclage 25/153 (16%)	Not PO One person in the cerclage group lost to follow up Defined as stillbirth or neonatal death prior to discharge	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 7/127 (6%) RR 0.69, 95% CI 0.27-1.77 p=0.44	No cerclage 10/126 (8%)	Not PO Perinatal death not defined in days	?	?	?

Project: Prevention of preterm birth
Appendix 4.2.10. Intervention Cerclage
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations	Precision *
				Intervention	Control				
Macnaughton MRC/RCOG, 1993 UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins (28 sets of twins, 2.2% I: n=12 C: n=16)	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647 (659 fetuses) C: 645 (661 fetuses)	Cerclage (not prespecified) Singletons and twins 55/659 (1.8%)* NS Singletons (calculated) 53/635 (8.3%)* No statistics Twins 2/24 (8.3%)* Fetal level as denominator	No cerclage Singletons and twins 68/661 (2.7%)* Singletons (calculated) 66/629 (10.4%)* No statistics Twins 2/32 (6.3%)* Fetal level as denominator	Not PO “Perinatal mortality” is the sum of all miscarriages, stillbirth and neonatal mortality, (neonatal mortality not defined in days) same as presented as all perinatal losses for singletons in Alfirevic, Cochrane, 2017 *Numerator and denominator include all miscarriages.	?	?	?
Roman, 2020 Multicenter (8 centra, Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, and dilated cervix 1-5 cm by pelvic examination and/or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 6/34 (17.6%) RR 0.23, 95% CI 0.1-0.49 p<0.001 (fetal level denominator)	No cerclage 20/26 (76.9%) (fetal level denominator)	Not PO Perinatal death not defined in days postpartum No case of fetal demise (i.e. PNM= NNM)	+	+	-

Project: Prevention of preterm birth
Appendix 4.2.10. Intervention Cerclage
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic, 2017 Cochrane	**Singletons**								
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2, 3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 9/96 No statistics	No cerclage 9/98	Not PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons	≥1 of high-risk factors for preterm birth (≥1 preterm birth <35 w, ≥2 curettages, diethylstilbestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL <25 mm or significant funneling	I: 28 C: 29	McDonald cerclage and bedrest 4/28 (14.3%)	No cerclage, bedrest 4/29 (13.8%)	Not PO Outcome defined as neonatal survival, no definition in days. No stillbirths. Cochrane data not corresponding to original article where it should be 3/28 after removing twins.	+	?	-

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, I; intervention, NS; non significant, PO; primary outcome, RR; risk ratio, TVS; transvaginal scan, UK; United Kingdom

Project: Prevention of preterm birth
Appendix 4.2.11. Intervention Cerclage
Outcome variable: Neonatal mortality < 7 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dor, 1982 Israel	Twins	Twin pregnancies after OI	I: 22/44 C: 23/46	8/44 (18.2%) No statistics	No cerclage 7/46 (15.2%)	Not PO Outcome defined as death within first week of life	?	-	-

C; control, CI; confidence interval, I; intervention, OI; ovulation induction, PO; primary outcome, RR; risk ratio

Project: Prevention of preterm birth
Appendix 4.2.12. Intervention Cerclage
Outcome variable: Neonatal mortality < 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Otsuki, 2016 Japan	Singletons	TVS CL <25 mm	I1 (Shirodkar): 35 I2 (McDonald: 36 C: 35	I1: Shirodkar cerclage 0/34 (0%), p=0.56 12: McDonald cerclage 1/34 (2.6%), p=0.99 RR not presented	No cerclage, bedrest 1/33 (5.7%)	Not PO	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS C ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 4/127 (3%)	No cerclage 5/126 (4%)	Not PO Neonatal mortality from table 2 PNM - stillbirths and text page 1851. No definition of perinatal mortality in days	?	?	?
Berghella, 2004 USA (2 centers)	Singletons and twins (4 sets of twins, 7%)	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstil-bestrol exposure, cone biopsy, Mullerian anomaly, or twin pregnancy) and/or TVS CL < 25 mm or significant funneling	I: 31 (34 fetuses) C: 30 (31 fetuses)	McDonald cerclage and bedrest All 9/34 (26%) p=0.22 Singletons 3/28 (10.7%) Twins 6/6 (100%)	No cerclage, bedrest All 4/31 (13%) Singletons 4/29 (13.8%) Twins 0/2 (0%)	Not PO 3 sets of twins (n=6) in intervention group, 1 set of twins (n=2) in the control group Outcome defined as neonatal survival, no definition in days	+	?	-
Macnaughton MRC/RCOG, 1993 multicenter UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons and twins (28 sets of twins, 2.2% I: n=12 C: n=16)	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 647 (659 fetuses) C: 645 (661 fetuses)	Cerclage (not prespecified) Singletons and twins 8/659 (1.2%)*, NS Fetal level as denominator	No cerclage Singletons and twins 14/661 (2.1%)* Fetal level as denominator	No discrimination about if neonatal deaths included twins or not Outcome defined as “liveborn died”, no definition in days *Denominator includes all miscarriages, numerator “liveborn died”	?	?	?

Project: Prevention of preterm birth
Appendix 4.2.12. Intervention Cerclage
Outcome variable: Neonatal mortality < 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rust, 2000 USA	Singleton and twins: Singletons (n=54) and 5 sets of twins and 2 sets of triplets, 11.5% multifetal pregnancies	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I: 31 C: 30	McDonalds cerclage, modified bedrest 4/31 (12.9%), p=0.9 Pregnancy level as denominator	No cerclage, modified bedrest 3/30 (10%) Pregnancy level as denominator	Not PO 5 sets of twins and 2 sets of triplets evenly distributed between the two groups, though not defined in the outcomes. Neonatal death defined as death <28 days after delivery Data reanalyzed without multifetal pregnancies NS (data not shown) Not included in metaanalysis due to multifetal pregnancies>10%	-	-	?
Roman, 2020 multicenter (8 centers, Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins and dilated cervix 1-5 cm by pelvic examination and/or speculum examination and/or TVS	I: 17 C: 13	Physical examination indicated McDonald cerclage Both twins died: 2/17 (11.7%) RR 0.15, 95% CI 0.04-0.58 p=0.005 1 twin died: 2/17 (11.7%) RR N/A, p=0.49 Denominator pregnancy level Fetal level as denominator (calculated): 6/34 (17.6%), No statistics	No cerclage Both twins died: 10/13 (76.9%) 1 twin died: 0/13 (0%) Denominator pregnancy level Fetal level as denominator (calculated): 20/26 (76.9%)	Not PO Outcome defined as neonatal survival, no definition in days	+	+	-

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, I; intervention, NS; non significant, PO; primary outcome, RR; risk ratio, TVS; transvaginal scan, UK; United Kingdom, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.13 Intervention cerclage
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Althuisius, 2001 The Netherlands	Singletons	Previous PTB <34 w, PPROM <32 w or uterine anomaly, or prior cold knife conisation and TVS CL <25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 1/19 (5.3%) RR 9.5, 95% CI 1.3-68.1 p=0.005	Bedrest 8/16 (50%)	Not PO Composite outcome: admission to NICU and/or neonatal death	+	-	-
Berghella, 2004 USA (2 centers)	Singletons and twins (4/61, 7%)	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstil bestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL <25 mm or significant funneling	I: 31 (34 fetuses) C: 30 (31 fetuses)	McDonald cerclage, bedrest All 7/34 (21%) p=0.80 Singletons 7/28 (25.0%) (3 singletons died) Twins 0/6 (all twins died)	Bedrest All 8/31 (13%) Singletons 6/29 (20.7%) (4 singletons died) Twins 2/2 (100%)	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw Defined as RDS, IVH III or IV, NEC or sepsis Denominator all neonates including deaths	+	?	-
Rust, 2000 USA	Singleton and twins: Singletons (n=54) and 5 sets of twins and 2 sets of triplets, 11.5% multiple pregnancies	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I:31 C:30	McDonalds cerclage , modified bedrest 3/31 (9.7%) p=0.6 Pregnancy level	Modified bedrest 1/30 (3.3%) Pregnancy level	5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes. Not PO Serious morbidity defined as mechanical ventilation, RDS, NEC, IVH, sepsis Data reanalyzed without multifetal pregnancies NS (data not shown) Not included in metaanalysis due to multifetal pregnancies>10%	-	-	?
Roman, 2020 multicenter (8 centra, Italy, US, Spain, Poland, Denmark, Switzerland.	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and/or speculum examination and/or TVS	I: 17 (34 fetuses) C: 13 (26 fetuses)	Physical examination indicated McDonald cerclage Child level 14/30 (46%) RR 0.93, 95% CI 0.4-2.2 p=1.0	No cerclage Child level 3/6 (50%)	Not PO Outcomes of neonates born alive. Composite neonatal outcome not defined but probably a summary of other morbidities listed, i.e. RDS, IVH, NEC, sepsis and ROP (laser therapy)	+	+	-

Project: Prevention of preterm birth
Appendix 4.2.13 Intervention cerclage
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic, 2017 **Cochrane**	**Singletons**								
Owen, 2009 USA	Singletons	History of sPTB <34 gw or PPROM + short TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 16/148 (10.8%) No statistics	No cerclage 18/153 (11.8%)	Not PO No definition i article or Cochrane	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodcar cerclage 9/127 (7.1%) No statistics	No cerclage 7/126 (5.6%)	Not PO No composite adverse neonatal outcome in article, but positive fetal blood culture, BPD, IVH/PVH and ROP are reported separately	?	?	?

BPD; bronchopulmonary dysplasia, Cx; cervix, CL; cervical lengh, C; control, DA diamniotic, I; intervention, IVH; intraventricular haemorrhage, NEC; necrotizing enterocolitis, NND; neonatal death, NICU; neonatal intensive care unit, NS; not significany, OR; odds ratio, PO; primary outcome, PPROM; preterm prelabour rupture of the membranes, PTB; preterm birth, RDS; respiratory distress syndrome, ROP; retinopathy of prematurity, RR; risk ratio, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.14 Intervention cerclage
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Roman, 2020 Multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with Ttwins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage Child level 14/30 (46.6%) RR 1.41, 95% CI 0.42-4.6 p=0.67	No cerclage Child level 2/6 (33.3%)	Not PO RDS defined as intubation or CPAP Outcomes of neonates born alive.	+	+	-
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles and not to the subgroups presented below									
Alfirevic 2017	**Singletons**								
Althuisius, 2001 Netherlands	Singletons	Previous PTB <34 w, PPROM<32 w or uterine anomaly, or prior cold knife conisation and TVS CL <25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 0/19 No statistics	No cerclage, bedrest 0/16	Not PO	+	-	-
Berghella, 2004 USA (2 centers)	Singletons	≥1 of high-risk factors for PTB (≥1 PTB <35w, ≥2 curettages, diethylstil-bestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL <25 mm or significant funneling	I: 28 C: 29	McDonald cerclage + bedrest Singletons 6/28 (21.4%) No statistics	No cerclage, bedrest Singletons 6/29 (20.7%)	Not PO	+	?	-
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 13/148 (8.8%) No statistics	No cerclage 13/152 (8.6%)	Not PO Control group: 153 in article	?	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2, 3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 3/96 (3.1%) No statistics	No cerclage 1/98 (1.0%)	Not PO	?	?	?

C; control, CL; cervical length, CPAP; continuous positive airway pressure, I; intervention, PO; primary outcome, PPROM; preterm prelabour rupture of the membranes, PTB; preterm birth, RDS; respiratory distress syndrome, RR; risk ratio, sPTB; spontaneous preterm birth, TVS; transcervical length, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.15 Intervention cerclage
Outcome variable: Bronchopulmonary dysplasia (BPD)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 4/123 (3%) RR 0.98 (95% CI 0.25-3.84) p=1.0	No cerclage 4/121 (3%)	Not PO	?	?	?

BPD; bronchopulmonary dysplasia, C; control, CL; cervical length, I; intervention, PO; primary outcome, RR; risk ratio, TVS; transvaginal scan, UK; United Kingdom

Project: Prevention of preterm birth
Appendix 4.2.16 Intervention cerclage
Outcome variable: Intraventricular haemorrhage (IVH) or periventricular leukomalacia

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 1/123 (1%) RR 0.49, 95% CI 0.05-5.35 p=0.62	No cerclage 2/121 (2%)	Not PO Outcome of neonates born alive IVH or PVH grade 3 and 4	?	?	?
Roman, 2020 multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage Child level 4/30 (13.3%) RR 0.80, 95% CI 0.1-5.9 p=1.0	No cerclage Child level 1/6 (16.6%)	Not PO Outcome of neonates born alive. IVH grade 3 and 4	+	+	-
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles and not to the subgroups presented below									
Alfirevic 2017	**Singletons**								
Althuisius 2001 Netherlands	Singletons	Previous PTB <34 w, PPROM<32 w or uterine anomaly, or prior cold knife conisation together with TVS CL<25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 0/19 (0%) No statistics	No cerclage, bedrest 0/16 (0%)	Not PO	+	-	-
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 0/148 (0%) No statistics	No cerclage 2/152 (1.3%)	Not PO Control group: 153 in article	?	?	?
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2, 3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 1/96 (1.0%) No statistics	No cerclage 1/98 (1.0%)	Not PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstil-bestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) nd/or TVS CL <25 mm or significant funneling	I: 28 C: 29	McDonald cerclage + bedrest 2/28 (7.1%) No statistics	No cerclage, bedrest 1/29 (3.4%)	Not PO	+	?	-

C; control, CI; confidence interval, CL; cervical length, I; intervention, IVH; intraventricular haemorrhage, PO; primary outcome, PTB; preterm birth, PVH; periventricular haemorrhage, TVS; transvaginal scan, RR; risk ratio, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.17 Intervention cerclage
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Roman, 2020 multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland.	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage Child level: 0/30 (0%), RR NA	No cerclage Child level: 0/6 (0%)	Not PO NEC grade 3 and 4	+	+	-
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic 2017	**Singletons**								
Althuisius, 2001 Netherlands	Singletons	Previous PTB <34 w, PPROM<32 w or uterine anomaly, or prior cold knife conisation and TVS CL <25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 0/19 No statistics	No cerclage, bedrest 0/16	Not PO	+	-	-
Berghella, 2004 USA (2 centers)	Singletons	≥1 of high-risk factors for PTB (≥1 PTB <35 w, ≥2 curettages, diethylstil-bestrol exposure, cone biopsy, Mullerian anomaly, or twin pregancy) and/or TVS CL <25 mm or significant funneling	I: 28 C: 29	McDonald cerclage + bedrest 1/28 (3.6%) No statistics	No cerclage, bedrest 0/29 (0%)	Not PO Denominator in Cochrane stated as 9, corrected to 29	+	?	-
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 2/148 (1.4%) No statistics	No cerclage 2/152 (1.3%)	Not PO Control group: 153 in article	?	?	?

C; control, CL; cervical length, DA; diamniotic, I; intervention, NA; not applicable, NEC; necrotizing enterocolitis, PO; primary outcome, PPROM; preterm prelabour rupture of the membranes, PTB; preterm birth, RR; risk ratio, sPTB; spontaneous PTB, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.18 Intervention cerclage
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 5/123 (4%) RR 2.46 (95% CI 0.49-12.43) p=0.44	No cerclage 2/121 (2%)	Not PO Positive fetal blood culture	?	?	?
Roman, 2020 multicenter (8 centers, Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 2/30 (6.6%) RR 0.40 (95% CI 0.04-3.74), p=0.43 (fetal level denominator)	No cerclage 1/6 (16.6%) (fetal level denominator)	Not PO Outcomes of neonates born alive	+	+	-

C; control, CI; confidence interval, CL; cervical length, DA, diamniotic, I; intervention, RR; risk ratio PO; primary outcome, TVS; transvaginal scan, UK; United Kingdom

Project: Prevention of preterm birth
Appendix 4.2.19 Intervention cerclage
Outcome variable: Retinopathy of prematurity (ROP)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm. Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 0/123 (0%) RR 0.14 (95% CI 0.01-2.69), p=0.12	No cerclage 3/121 (2%)	No PO Outcome of neonates born alive.	?	?	?
Roman, 2020 multicenter (8 centers, Italy, US, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated MacDonald cerclage Child level 5/30 (16.6%) RR 1.0 (95% CI 0.14-7.1), p=1.0	No cerclage Child level 1/6 (16.6%)	No PO Outcome of neonates born alive. ROP treated with laser therapy	+	+	-
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic, 2017	**Singletons**								
Owen, 2009 USA	Singletons	History of sPTB <34 w or PPROM + TVS CL <25 mm	I: 149 C: 153	McDonald cerclage 3/148 (2.0%) No statistics	No cerclage 5/152 (3.3%)	Not PO 153 women in the original paper	?	?	?

C; control, CI; confidence interval, CL; cervical length, I; intervention, PPROM; preterm prelabour rupture of the membranes, PO; primary outcome, PTB; preterm birth, ROP; retinopathy of prematurity, RR; risk ratio; sPTB; spontaneous preterm birth, TVS; transvaginal scan, UK; united Kingdom, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.20 Intervention cerclage
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ezechi, 2004, Nigeria	Not stated	Previous PTB	I: 38 C: 43	McDonald cerclage 1/38 (2.6%) OR 0.10 (95% CI 0.00-0.87) p=0.03	No cerclage 9/43 (20.9%)	Not PO Singletons/twins not stated but singletons correspond to neonatal outcomes	-	?	?
Berghella, 2004 USA (2 centers)	Singletons and twins (4 sets of twins, 7%)	Previous PTB <35w, cone biopsy, uterine malfor mation, and TVS CL <25 mm	I: 31 C: 30	McDonald cerclage All 9/34 (26%) p=0.53 Mean (SD) NICU stay 60.4 (62.1) days p=0.55 NICU admissions Singletons 9/28 (32%) Twins 0/6	No cerclage, bedrest All 11/31 (35%) Mean (SD) NICU stay 45.7 (44.6) days NICU admissions Singletons 9/29 (31%) Twins 2/2 (100%)	Not PO 3 sets of twins (n=6) in intervention group, 1 set of twins (n=2) in the control group Admission to NICU Length of NICU stay in days Denominator all neonates including deaths	+	?	-
Roman, 2020 multicenter (8 centers, Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I:17 C:13	Physical examination indicated McDonald cerclage Child level 22/30 (73.3%) RR 0.73 (95% CI 0.6-1.0) p=0.3 Mean (SD) NICU stay 68.2 (65.3) days Mean difference 29.8 days (95% CI -14.6 to 74.2)	No cerclage Child level 6/6 (100%) Mean (SD) NICU stay 92.3 (53.4) days	Not PO Denominator surviving neonates. Admission to NICU Length of NICU stay in days	+	+	-

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, I; intervention, NICU; neonatal intensive care unit, OR; odds ratio, PO; primary outcome, RR; risk ratio, SD; standarad deviation, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.21 Intervention cerclage
Outcome variable: Maternal morbidity, infections (fever or chorioamnionitis, not prespecified)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2, 3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage Maternal pyrexia 10/96 (10.4%) p=0.07	No cerclage Maternal pyrexia 3/98 (3.1%)	Not PO Fever ≥38° C on at least one occasion during puerperium Cochrane 11/96 resp 4/98	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage Maternal pyrexia 5/127 (4%) RR 4.92 (95% CI 0.58-41.93) p=0.21 Symptomatic vaginal discharge 8/127 (6%) RR 7.87 (95% CI 1.00-62.04) p=0.04	No cerclage Maternal pyrexia 1/126 (1%) Symptomatic vaginal discharge 1/126 (1%)	No PO Maternal pyrexia defined as fever of 38°C or more during antenatal hospital stay	?	?	?
Rust, 2000 USA	Singletons and twins Singletons (n=54), twins and triplets (7/61, 11.5%)	History of PTB, second trimester pregnancy loss, previous cervical surgery, uterine anomaly, multifetal pregnancy and a TVS CL <25 mm or dilated internal os	I:31 C:30	McDonald cerclage, modified bedrest Chorioamnionitis 5/31 (16.1%) p=0.4	No cerclage, modified bedrest Chorioamnionitis 2/30 (6.7%)	5 twin and 2 triplets evenly distributed between the two groups, though not defined in the outcomes Not included in MA due to >10% multifetal pregnancies	-	-	?
Roman, 2020 Multicentre (8 centres, Italy, US, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and or speculum examination and/or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage Clinical chorioamnionitis 2/17 (11.8%) RR 0.51 (95% CI 0.1-2.6) p=0.62	No cerclage Clinical chorioamnionitis 3/13 (23.1%)	Not PO	+	+	-

Project: Prevention of preterm birth
Appendix 4.2.21 Intervention cerclage
Outcome variable: Maternal morbidity, infections (fever or chorioamnionitis, not prespecified)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic, 2017 **Cochrane**	**Singletons**								
Macnaughton MRC/RCOG, 1993 Multicenter: UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 635 C: 629	Cerclage (not prespecified) Pyrexia 23/407 (5.7%) No statistics Chorioamnionitis 1/635 (0.2%) No statistics	No cerclage Pyrexia 11/391 (2.8%) Chorioamnionitis 0/629 (0%)	Not PO All miscarriages included in denominator unclear if included in numerator	?	?	?

C; control, CI; confidence interval, CL; cervical lengh, I; intervention, PO; primary outcome, PTB, preterm delivery, RR; risk ratio, TVS; transvaginal scan, UK; United Kingdom, w; weeks

Project: Prevention of preterm birth
Appendix 4.2.22 Intervention cerclage
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons /Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rush, 1984 South Africa	Singletons	History of previous late miscarriage or PTB out of at least one spontaneous between 14-36 w and 2, 3, or 4 previous pregnancies ending spontaneously before 37 w	I: 96 C: 98	McDonald cerclage 18/96 (18.8%) NS	No cerclage 12/98 (12.2%)	Not PO	?	?	?
To, 2004 UK (6 countries; UK, Brazil, South Africa, Slovenia, Greece, Chile; 12 hospitals)	Singletons	TVS CL ≤15 mm Previous cervical surgery: I: 6% C: 7%	I: 127 C: 126	Shirodkar cerclage 23/127 (18%) RR 1.20 (95% CI 0.69-2.09) p= 0.52	No cerclage 19/126 (15%)	No PO	?	?	?
Berghella, 2004 USA (2 centers)	Singletons and twins (4 sets of twins, 7%)	Previous PTB <35 w, cone biopsy, uterine malformation and/or short TVS CL <25 mm	I: 31 C: 30	McDonald cerclage + bedrest Singletons 8/28 (32.0%) No statistics Twins (calculated) 3/3 (100%) No statistics	No cerclage, bedrest Singletons 10/29 (34.5%) Twins calculated 0/1	Not PO 3 women with twin pregnancies in the intervention group, all early PTB at 20, 21 and 22 weeks. One woman with twin pregnancy in the bedrest group, PTB at 34 gw Information about singleton pregnancies from Alfirevic, Cochrane 2017	+	?	-
Dor, 1982 Israel	Twins	Twin pregnancy after OI	I: 22/44 C: 23/46	McDonald cerclage 2/22 (9.1%) NS RR not presented	No cerclage 3/23 (13.0%)	PO not defined	?	-	-
Roman, 2020 Multicenter (8 centers; Italy, USA, Spain, Poland, Denmark, Switzerland)	Twins DA	Asymptomatic women with twins, dilated cervix 1-5 cm by pelvic examination and/or speculum examination or TVS	I: 17 C:13	Physical examination indicated McDonald cerclage 11/17 (64.7%) RR 1.68 (95% CI 0.83-3.86) p=0.26	No cerclage 5/13 (38.5%)	Not PO PPROM defined<34 w	+	+	-

Project: Prevention of preterm birth
Appendix 4.2.22 Intervention cerclage
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons /Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Systematic reviews (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles									
Alfirevic 2017	**Singletons**								
Althuisius, 2001 Netherlands	Singletons	Previous PTB <34 w, PPROM<32 w or uterine anomaly, or prior cold knife conisation and TVS CL<25 mm at <27 w	I: 19 C:16	McDonald cerclage + bedrest 0/19 No statistics	No cerclage, bedrest 8/16 (50.0%)	Not PO	+	-	-
Macnaughton MRC/RCOG, 1993 Multicenter: UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada	Singletons	Included if uncertainty if cerclage or not for risk patients: Previous PTB, previous second trimester miscarriage, previous early abortion, cervical amputation, cone biopsy, uterine anomaly, twin pregnancy	I: 635 C: 629	Cerclage (not prespecified) 3/635 (0.5%) No statistics	No cerclage 0/629 (0%)	Not PO NB low rate of PPROM Miscarriage included in denominator	?	?	?

CL; cervical lengh, C; control, I; intervention, OI; ovulation induction, NS; not significant, PPROM; preterm prelabour rupture of membranes, RR; risk ratio, PO; primary outcome, TVS; transvaginal scan, UK; United Kingdom, w; weeks