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Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy (Review)

Rafael TJ, Berghella V, Alfirevic Z

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TABLE OF CONTENTS

[Intervention Review]

Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy

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ABSTRACT

Background

Cervical cerclage is a surgical intervention involving placing a stitch around the uterine cervix. The suture material aims to prevent cervical shortening and opening, thereby reducing the risk of preterm birth. The effectiveness and safety of this procedure in multiple gestations remains controversial.

Objectives

To assess whether the use of a cervical cerclage in multiple gestations, either at high risk of pregnancy loss based on just the multiple gestation (history-indicated cerclage), the ultrasound findings of 'short cervix' (ultrasound-indicated cerclage), or the physical exam changes in the cervix (physical exam-indicated cerclage), improves obstetrical and perinatal outcomes. The primary outcomes assessed were perinatal deaths, serious neonatal morbidity, and perinatal deaths and serious neonatal morbidity.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2014) and reference lists of retrieved studies.

Selection criteria

All randomised controlled trials (RCTs) of cervical cerclage in multiple pregnancies. Quasi-RCTs and RCTs using a cluster-randomised design were eligible for inclusion (but none were identified). Studies using a cross-over design and those presented only as abstracts were not eligible for inclusion.

We included studies comparing cervical cerclage with no cervical cerclage in multiple pregnancies.

Studies comparing cervical stitch versus any other preventative therapy (e.g. progesterone) in multiple pregnancies, and studies involving comparisons between different cerclage protocols (history-indicated versus ultrasound-indicated versus physical exam-indicated cerclage) were also eligible for inclusion but none were identified.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias. Two review authors extracted data. Data were checked for accuracy.

Main results

We included five trials, which in total randomised 1577 women, encompassing both singleton and multiple gestations. After excluding singletons, the final analysis included 128 women, of which 122 women had twin gestations, and six women had triplet gestations. Two trials (n = 73 women) assessed history-indicated cerclage, while three trials (n = 55 women) assessed ultrasound-indicated cerclage. The five trials were judged to be of average to above average quality, with three of the trials at unclear risk regarding selection and detection biases.

Concerning the primary outcomes, when outcomes for cerclage were pooled together for all indications and compared with no cerclage, there was no statistically significant differences in perinatal deaths (19.2% versus 9.5%; risk ratio (RR) 1.74, 95% confidence intervals (CI) 0.92 to 3.28, five trials, n = 262), serious neonatal morbidity (15.8% versus 13.6%; average RR 0.96, 95% CI 0.13 to 7.10, three trials, n = 116), or composite perinatal death and neonatal morbidity (40.4% versus 20.3%; average RR 1.54, 95% CI 0.58 to 4.11, three trials, n = 116).

Among the secondary outcomes, there were no significant differences between the cerclage and the no cerclage groups. To name a few, there were no significant differences among the following: preterm birth less than 34 weeks (average RR 1.16, 95% CI 0.44 to 3.06, four trials, n = 83), preterm birth less than 35 weeks (average RR 1.11, 95% CI 0.58 to 2.14, four trials, n = 83), low birthweight less than 2500 g (average RR 1.10, 95% CI 0.82 to 1.48, four trials, n = 172), very low birthweight less than 1500 g (average RR 1.42, 95% CI 0.52 to 3.85, four trials, n = 172), and respiratory distress syndrome (average RR 1.70, 95% CI 0.15 to 18.77, three trials, n = 116). There were also no significant differences between the cerclage and no cerclage groups when examining caesarean section (elective and emergency) (RR 1.24, 95% CI 0.65 to 2.35, three trials, n = 77) and maternal side-effects (RR 3.92, 95% CI 0.17 to 88.67, one trial, n = 28).

Examining the differences between prespecified subgroups, ultrasound-indicated cerclage was associated with an increased risk of low birthweight (average RR 1.39, 95% CI 1.06 to 1.83, $Tau^2 = 0.01$, $I^2 = 15\%$, three trials, n = 98), very low birthweight (average RR 3.31, 95% CI 1.58 to 6.91, $Tau^2 = 0$, $I^2 = 0\%$, three trials, n = 98), and respiratory distress syndrome (average RR 5.07, 95% CI 1.75 to 14.70, $Tau^2 = 0$, $I^2 = 0\%$, three trials, n = 98). However, given the low number of trials, as well as substantial heterogeneity and subgroup differences, these data must be interpreted cautiously.

No trials reported on long-term infant neurodevelopmental outcomes. There were no physical exam-indicated cerclages available for comparison among the studies included.

Authors' conclusions

This review is based on limited data from five small studies of average to above average quality. For multiple gestations, there is no evidence that cerclage is an effective intervention for preventing preterm births and reducing perinatal deaths or neonatal morbidity.

PLAIN LANGUAGE SUMMARY

Cervical stitch for preventing preterm birth in women with a multiple pregnancy

Background

Carrying more than one baby increases a woman's risk of delivering preterm. The risks increase with the number of babies being carried. Babies born prematurely are more likely to experience poor outcomes including serious ill health and death. Cervical cerclage is a surgical procedure carried out during pregnancy to try to prevent preterm birth by limiting shortening and opening of the cervix. It is performed by placing suture material around the cervix, which is accessed either by the vagina or through the mother’s abdomen. The effectiveness and safety of this procedure for multiple gestations remains uncertain. The likelihood of spontaneous preterm birth can be assessed by looking at the mother’s obstetric history, a physical examination, or transvaginal ultrasound examination in the second trimester.

Review question

To assess whether the use of a cervical stitch in women with multiple gestations at high risk of pregnancy loss improves obstetrical and perinatal outcomes.

Study Characteristics

We included five trials, which involved a total of 1577 women, comparing cerclage with no cerclage in women with either singleton and multiple gestations. After excluding singletons, our final analysis included 128 women, of which 122 were pregnant with twins, and six were pregnant with triplets. Cerclage was indicated by obstetric history in two trials (n = 73 women) and transvaginal ultrasound in three trials (n = 55 women).

Main findings

When cerclage was compared with no cerclage in women with multiple gestations, there was no difference in perinatal deaths or neonatal ill health, or preterm birth rates. However, the number of women included in the five studies was insufficient to provide meaningful conclusions.

The long-term effect of cerclage on neurodevelopmental outcomes in the surviving infants and maternal infection and side- effects could not be estimated. It was therefore unclear if cerclage for women with multiple pregnancies puts the health of either the mothers or the infants at risk in any way.

Quality of the evidence
The five included studies were generally considered to be of average to above average quality, but three of the studies were difficult to assess fully because of missing methodological information.

We did not find any studies comparing different indications for cerclage (obstetric history-indicated versus ultrasound-indicated cerclage) or comparing cerclage to another intervention (such as progesterone).

BACKGROUND

Description of the condition

The twin birth rate in the USA has risen over the last three decades, from 18.9 per 1000 births in 1980 to 33.3 per 1000 births in 2009. Although twin pregnancies currently represent only 1% to 3% of live births in most countries, they represent a substantial portion of preterm deliveries, with 10% of all preterm births in the USA attributable to twins (Martin 2012). In 2006 in the USA, the mean age at delivery for twins was 35.3 weeks compared with 38.8 weeks for singletons (Martin 2009), with 12.1% of twins delivering before 32 weeks compared to only 1.6% in singletons. Although less than 1% of singletons deliver before 28 weeks' gestation, 5% of twins are born before that extremely early gestational age. Similar rates are observed elsewhere worldwide, including Europe and Asia, where twin preterm birth rates (less than 37 weeks) range from 42% to 68% (Blondel 2006; Ooki 2010), with as many as 8% of twins delivering at less than 32 weeks (Ooki 2010; Papiernik 2010).

According to recent data from the USA, one in four very low birthweight infants (less than 1500 g), and one of every six infant deaths (within the first six months of life), come from twin pregnancies (Martin 2009; Mathews 2006). The burden of prematurity is worse for triplets and higher order gestations, with the median gestational age at delivery for triplets being 32 weeks. With premature infants being at higher risk of poor outcomes including death, preterm birth is, in effect, a surrogate for mortality and morbidity. Twins are five times, and triplets nearly 15 times more likely than singletons to die within one month of birth (Martin 2008), and those born preterm are at significantly greater risk of incurring serious neonatal morbidities (Refuerzo 2010).

The mechanism for early preterm birth in multiple gestations is unclear. While preterm birth usually represents the final common pathway of at least four distinct pathophysiologic processes (maternal and/or fetal stress, inflammation, abruption or decidual bleeding, and excessive mechanical stretching of uterus), it seems the latter, or overdistension of the uterus, is the most common aetiology causing twin preterm birth (Hodgson 2010). Given the different incidence of preterm birth and the different mechanisms leading to it in singleton and multiple pregnancies, we felt that safety and efficacy of interventions aimed at preventing preterm birth should be evaluated separately. The role of the cervix and/or cervical insufficiency, if any, is unclear in the aetiologies of preterm birth in multiple gestations.

Over the last 50 years, much has been learned about the cervix and its complex role involving both normal and abnormal parturition. In normal pregnancies approaching term, the cervix undergoes remodelling, ripening, and eventual dilatation, leading to normal labour and delivery. These events can occur prematurely, leading to either second trimester losses (e.g. between 16 and 24 weeks of gestation), or preterm births between 24 + 0 and 36 + 6 weeks of gestation. In the absence of uterine contractions, painless dilatation of the cervix leading to recurrent second trimester losses had been the classic definition of cervical insufficiency, previously referred to as cervical incompetence.

Transvaginal ultrasound examination of the cervix has emerged as an effective screening method for predicting pregnancies which will spontaneously deliver preterm. This is especially true for women with a prior preterm birth (Owen 2001). The earlier the short cervical length is detected, the higher the risk of preterm birth. Given this new information, the definition of cervical insufficiency needs to be updated to encompass women with prior preterm births with cervical shortening before 24 weeks in the current pregnancy (Berghella 2010). While the true incidence of cervical insufficiency is unknown, several risk factors for the condition have been reported in the literature, such as cervical excision surgery (loop electrosurgical excision procedure, cone biopsy) (Berghella 2004a; Jakobsson 2007; Noehr 2009), greater than one surgical termination of pregnancy (Liao 2011 ; Visintine 2008), diethylstilbestrol exposure (Ludmir 1987), and collagen tissue disorders.

Description of the intervention

Cervical cerclage represents one of the most well-known surgical interventions in obstetrics. It is performed by securing suture material around the cervix to prevent cervical shortening and opening. Both the transvaginal and transabdominal methods for cervical cerclage have been reported.

While there are various methods of placing a cerclage, the two most popular include the McDonald and Shirodkar methods. Usually these procedures require regional anaesthesia in the form of a spinal or epidural block. General anaesthetic remains an option. In 1955, Shirodkar reported the insertion of a cervical stitch (suture) at around 14 weeks of pregnancy, placing a purse string stitch around the cervix, requiring dissection of the bladder and rectum from the cervix prior to stitch placement (Shirodkar 1955). Two years later, McDonald described a simpler technique, whereby the stitch is inserted around the body of the cervix present in the vagina in three or four bites (McDonald 1957). The McDonald procedure is technically easier to perform, with less bleeding, and the stitch is easier to remove. These techniques were described as indicated just for women with both a prior preterm birth and a cervix that is shortening and/or dilating in the second trimester. Several other variations for cerclage technique have been described.

Stitches are normally inserted via the vaginal route, although transabdominal cerclage has also been proposed for women when vaginal stitches have failed to prevent a preterm birth, or when a woman has an extremely short, scarred cervix, making vaginal stitch insertion technically difficult (Anthony 1997; Gibb 1995). The transabdominal procedures can be carried out in early pregnancy around 12 weeks of gestation, or are scheduled before pregnancy. Regardless of the timing, during laparotomy, the suture is placed at the cervicoisthmic portion of the uterus. Recently a laparoscopic approach to transabdominal cerclage has been described as a safe and effective alternative approach to laparotomy (Carter 2009).

Vaginally inserted cervical stitches are usually taken out at 36 to 37 weeks' gestation, or when the woman presents in labour. Abdominal cervical stitches are left in place and the baby is delivered by caesarean section.

Risks associated with cerclage placement, albeit rare, include bleeding, infection, cervical lacerations, and iatrogenic rupture of membranes.

Definitions of cervical cerclage types, including those placed for multiple pregnancies and those considered to be at high risk for pregnancy loss, vary depending on indication:

- history-indicated cerclage - a planned procedure around 12 to 15 weeks based on previous obstetric history;
- ultrasound-indicated cerclage - a procedure carried out following the discovery of a shortened cervical length on transvaginal ultrasound examination;
- physical exam-indicated cerclage - a procedure carried out following detection of advanced cervical dilation during vaginal examination. This can been either an incidental finding or a finding in women with some symptoms of threatened preterm labour.

The safety and efficacy of cerclage should be evaluated separately for each of these groups, as they are different clinical situations and results would be expected to vary.

How the intervention might work

No matter when the cerclage is placed, the aim is to prevent or halt the process of cervical shortening that leads to established labour and eventual preterm birth. A history-indicated cerclage is placed early in pregnancy, typically at the end of the first trimester (12 to 15 weeks). These are placed in women with poor pregnancy histories (e.g. two to three second trimester losses, prior failed ultrasound-indicated cerclage, etc), regardless of any events in the current pregnancy, in an attempt to provide preemptive mechanical support before the cervix becomes 'insufficient' (Berghella 2007).

More recently, transvaginal ultrasonography measuring cervical length has shown that the finding of a short cervix is one of the best predictors for preterm birth (Berghella 1999; Iams 1996; Owen 2001), and ultrasound-indicated cervical cerclage is gaining popularity.

Rather than prevent cervical shortening prior to its commencement (history-indicated cerclage), an ultrasound-indicated cerclage looks to halt initial cervical length shortening by providing mechanical support to the cervix and lower uterine segment, and therefore prolonging pregnancy.

Interestingly, cerclage was originally described as being indicated for women with both second trimester loss/preterm birth and a dilated cervix (McDonald 1957; Shirodkar 1955).

Why it is important to do this review

While there is emerging evidence supporting the use of cerclage in women with both prior preterm birth and current mid-trimester cervical shortening, this evidence applies solely to singleton gestations.

In a previously published Cochrane review, Drakeley and colleagues showed a lack of reduction in total pregnancy loss, early pregnancy loss, or preterm delivery before 28 and 34 weeks in women receiving cerclage, compared with no cerclage (Drakeley 2003).

In their meta-analysis of individual patient data, Berghella et al concluded that cerclage does not prevent preterm birth in all women with a short cervix at ultrasound examination, but could be beneficial in singleton pregnancies with short cervix and prior preterm birth (Berghella 2005). This benefit in singleton pregnancies with short cervix and prior preterm birth was confirmed in a more recent randomised trial (Owen 2009) and a meta-analysis (Berghella 2011). Two meta-analyses (Berghella 2005; Jorgensen 2007) showed no benefit for multiple gestation pregnancies, with Berghella and colleagues demonstrating an increased risk for preterm birth before 35 weeks in those women with twin gestations who received an ultrasound-indicated cerclage (risk ratio 2.15, 95% confidence interval 1.15 to 4.01).

Despite published meta-analyses and other studies demonstrating the lack of efficacy of cerclage in multiple gestations (Rebarber 2005; Roman 2005), recent data from the USA indicate that roughly 10% of triplets, and 1.3% of twins are still receiving cerclages (Menacker 2008).

A separate Cochrane review (Alfirevic 2012) looks at singleton pregnancies. As the incidence of preterm birth and mechanisms that bring it about are so different in singleton and multiple pregnancies, we believe that safety and efficacy of interventions aimed at preventing preterm birth should be evaluated separately. This review and Alfirevic 2012 update the previously published review by Drakely (Drakeley 2003).

OBJECTIVES

To assess whether the use of a cervical stitch in multiple gestations at high risk of pregnancy loss based on woman's history, ultrasound findings of 'short cervix', or physical exam changes in the cervix, improves obstetrical and perinatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of cervical cerclage in multiple pregnancies. Quasi-RCTs and RCTs using a cluster-randomised design were eligible for inclusion (but none were identified). Studies using a cross-over design and those presented only as abstracts were not eligible for inclusion.

We included studies comparing cervical cerclage with no cervical cerclage in multiple pregnancies.

Studies comparing cervical stitch versus any other preventative therapy (e.g. progesterone) in multiple pregnancies, and studies involving comparisons between different cerclage protocols (history-indicated versus ultrasound-indicated versus physical exam-indicated cerclage) were also eligible for inclusion but none were identified.

Types of participants

All women with multiple gestations were included. We planned also to carry out a priori subgroup analyses (see Subgroup Analysis section).

Types of interventions

Cervical stitch (cerclage) inserted before or during pregnancy irrespective of the indication.

Comparisons

1. Cervical stitch versus no stitch
2. Cervical stitch versus any other preventative therapy (e.g. progesterone)

3. Any comparison of different cerclage protocols (history-indicated versus ultrasound-indicated versus physical exam-indicated cerclage)

Types of outcome measures

We selected outcome measures with the help of a proposed core data set of outcome measures (Devane 2007).

Primary outcomes

1. Perinatal deaths
2. Serious neonatal morbidity (defined by trialists)
3. Perinatal deaths and serious neonatal morbidity

We acknowledge that it is unusual to include a composite as the primary outcome when individual components may have significantly different consequences for families and healthcare providers. However, both perinatal deaths and severe neonatal morbidity are rare events even in these high-risk populations, and therefore meta-analysis may fail to detect clinically important differences.

As there are no internationally agreed definitions for severe neonatal morbidity, we will accept any reasonable definition by trialists, as long as it is applied consistently across the whole study population in an unbiased manner. The same applies for perinatal deaths. Although perinatal mortality is clearly defined (stillbirths and neonatal deaths within first week of life), some premature babies may die after the first week of life and it is important to include this information where available.

It may seem unusual not having preterm birth as the primary outcome. We believe that, in the context of this review, preterm birth is a merely a surrogate for mortality and morbidity. More importantly, there is a real possibility that prolongation of pregnancy may be misinterpreted as benefit, when in fact, it may be harmful to keep a baby in what can sometimes be a hostile uterine environment. Preterm birth (at various gestations) remains an important secondary outcome.

Secondary outcomes

Neonatal

1. Stillbirth (fetal demise after 20 weeks' gestation, prior to delivery)
2. Neonatal death (after birth, and before 29 days of neonatal life or discharge from hospital)
3. Preterm birth (as defined by trialists, e.g. less than 28, 32, 34, 35, 37 weeks)
4. Gestational age at delivery
5. Low birthweight defined as less than 2500 g
6. Very low birthweight defined as less than 1500 g
7. Respiratory distress syndrome (defined by trialists)
8. Intraventricular haemorrhage (defined by trialists)
9. Necrotising enterocolitis (defined by trialists)
10. Sepsis (defined by trialists)
11. Neonatal intensive care unit admission
12. Long-term infant neurodevelopmental outcomes

Maternal

1. Caesarean section (planned and emergency)
2. Maternal infection requiring intervention, e.g. antibiotics or delivery (including chorioamnionitis and endometritis)
3. Maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 June 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of the studies identified.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Zarko Alfirevic and Timothy Rafael) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. Disagreements were resolved through discussion.

Data extraction and management

We used a pre-designed form to extract data. For included studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2012) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Along those lines, in studies that included both singleton and multiple gestations, we made every effort to extract the data and results specific to the multiple gestation. Where outcomes were not reported specifically by subgroup, but rather as outcomes for singleton and multiple gestations combined, we attempted to contact the authors of the original reports to provide further details, e.g. original patient level data.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

We discussed whether missing data greater than 20% might impact on outcomes, acknowledging that with long-term follow-up, complete data are difficult to attain.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;

- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

We used as the denominator the number of babies of women who were randomised, even though some babies could not have attained the outcome; for example, if there was a stillbirth then this baby would not have been able to attain the outcome of 'admission to special care baby unit'. For outcomes dealing with the pregnancy as a whole (e.g. preterm birth less than 28 weeks, less than 32 weeks, etc), the unit of analysis was the pregnancy, and if the outcome occurred in either the fetus or neonate, we considered the pregnancy to have met the outcome.

Dichotomous data

For dichotomous data, we presented results as a summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review. However, if we identify any cluster-randomised trial in future updates of this review we will include them in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. We will meta-analyse effect estimates and their standard errors from correct analyses of cluster-randomised trials using the generic inverse-variance method in RevMan. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform sensitivity analyses to investigate the effects of the randomisation unit.

Cross-over trials

We considered cross-over designs inappropriate for this research question.

Dealing with missing data

For included studies, we planned to note levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using Sensitivity analysis.

For all outcomes, we planned to carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number of babies of women who were randomised.

We planned to exclude data on outcomes where there was greater than 20% missing data on short-term outcomes.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the Tau^2 was greater than zero and either an I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

In cases of substantial heterogeneity, we planned to explore the causes of it by pre-specified subgroup analysis provided that at least 10 studies contributed to the meta-analysis. We anticipated that for outcomes with fewer than 10 studies it would be difficult to assess subgroup effects with adequate power.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012).

We used a fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and discuss the clinical implications of treatment effects differing between trials.

Where we used random-effects analyses, we presented the results as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

We planned to carry out the following a priori subgroup analyses in the overall cerclage versus no cerclage analysis. It was felt that these subgroups specify five different clinical scenarios where the effect of cerclage may differ in the direction and effect size.

1. Twin only-indicated cerclage, e.g. the only indication for the cerclage was the twin pregnancy
2. Twin and history-indicated cerclage, e.g. a woman deemed to be at an increased risk for a preterm birth based on prior Ob/Gyn history: prior cone biopsy, previous termination of pregnancy or first trimester miscarriage, prior preterm birth, cervical abnormality on physical examination (known prior to pregnancy, or early during pregnancy - not referring to dilation), or uterine abnormality
3. Ultrasound-indicated cerclage, e.g. carried out following the discovery of a shortened cervical length on transvaginal ultrasound examination
4. Physical exam-indicated cerclage, e.g. carried out following the detection of advanced cervical dilation during vaginal examination, which could be either an incidental finding or a finding in women with symptoms of threatened preterm labour
5. Triplet cerclage

Outcomes to be used in the subgroup analyses are as follows.

1. Perinatal deaths
2. Serious neonatal morbidity
3. Composite - perinatal deaths and serious neonatal morbidity
4. Stillbirth (fetal demise after 20 weeks' gestation, prior to delivery)
5. Neonatal death (after birth and before 29 days of neonatal life or discharge from hospital)
6. Preterm birth less than 28 weeks
7. Preterm birth less than 32 weeks
8. Preterm birth less than 34 weeks
9. Preterm birth less than 35 weeks
10. Preterm birth less than 37 weeks
11. Mean gestational age at delivery
12. Low birthweight defined as less than 2500 g
13. Very low birthweight defined as less than 1500 g
14. Respiratory distress syndrome (defined by trialists)
15. Intraventricular haemorrhage (defined by trialists)
16. Necrotising enterocolitis (defined by trialists)
17. Sepsis (defined by trialists)
18. Neonatal intensive care unit admission
19. Long-term infant neurodevelopmental outcomes
20. Caesarean section (elective and emergency)
21. Maternal infection requiring intervention, e.g. antibiotics or delivery (including chorioamnionitis and endometritis)
22. Maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value. Should data from different subgroups come from the same trial (e.g. triplets who also had a short cervical length), the data were split in the mutually exclusive groups. This approach could cause some problems in a random-effects analysis because there may appear to be more trials than there actually are, which affects the estimate of the between-study variation, and hence the results. We addressed this issue in additional analysis.

Sensitivity analysis

We planned to perform sensitivity analysis on the primary outcomes based on trial quality, separating high-quality trials from trials of lower quality. 'High quality' was, for the purposes of this sensitivity analysis, defined as a trial having 'low risk of bias' for sequence generation and allocation concealment. While this sensitivity analysis was not carried out due to the low numbers of studies involved, this analyses will be carried out in future updates of this review as more data become available.

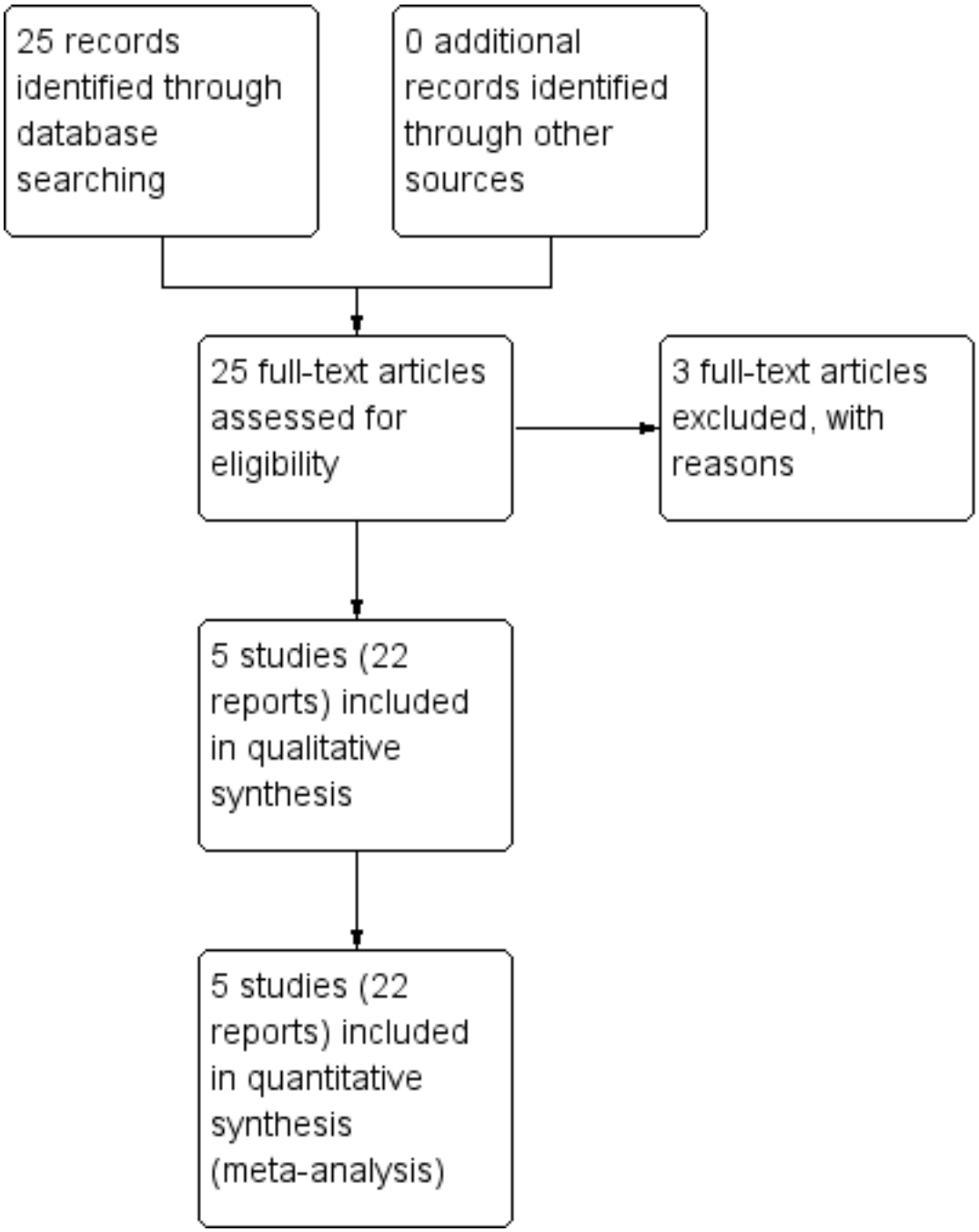
RESULTS

Description of studies

Results of the search

(See: Figure 1). The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 25 trial reports, of which five trials (22 reports) have been included, which in total randomised 1577 women, encompassing both singleton and multiple gestations. For the purposes of this review, after excluding singletons, the final analysis included 128 women (of which 122 women had twin gestations, and six women had triplet gestations). Three trials have been excluded. For further details of trial characteristics, please refer to the tables of Characteristics of included studies and Characteristics of excluded studies.

Figure 1. Study flow diagram.



Included studies

All of the included studies specified a cerclage versus no cerclage comparison (Althuisius 2001; Berghella 2004; Dor 1982; MRC/RCOG 1993; Rust 2001). Three of these studies required women to undertake some form of bedrest both in the intervention (cerclage) and control (no cerclage) groups (Althuisius 2001; Berghella 2004; Rust 2001).

In one trial, twins conceived via ovulation induction were included, with cerclage placement shortly at or after 13 gestational weeks (Dor 1982). This therefore represents assessment of cerclage based solely for the risk factor of multiple gestation (twin only-indicated cerclage).

In another trial, increased risk for preterm birth was based on prior obstetric history (MRC/RCOG 1993), with subsequent cervical cerclage placement occurring "as soon as possible". This study therefore assessed the effect of twin and history-indicated cerclage.

Three studies assessed women at high risk for preterm birth and identified those at higher risk based on short cervical length via transvaginal ultrasound (Althuisius 2001; Berghella 2004; Rust 2001), thus having cerclage placement in the early to mid second

trimester of pregnancy. These studies therefore assessed the effect of ultrasound-indicated cerclage.

One of these studies involved twins only (Dor 1982), while the remaining four studies contained both singleton and multiple pregnancies (Althuisius 2001; Berghella 2004; MRC/RCOG 1993; Rust 2001).

There were no studies comparing different indications for cerclage (e.g. history-indicated versus ultrasound-indicated cerclage). There were no studies comparing cerclage to another intervention (e.g. progesterone).

We were able to obtain the original databases from three of the five trials (Althuisius 2001; Berghella 2004; Rust 2001).

For further information, please refer to tables of Characteristics of included studies.

Excluded studies

Three studies were excluded. Two of these studies excluded multiple gestations (Blair 2002; Lazar 1984). The third trial (Nicolaides 2001) had only methodology and design published - the current status of this trial is unknown.

Risk of bias in included studies

The quality of the five included studies was difficult to assess due to lack of information in some studies regarding randomisation, selection bias, and detection bias.

Please see Figure 2 and Figure 3 for summary of 'Risk of bias' assessments.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

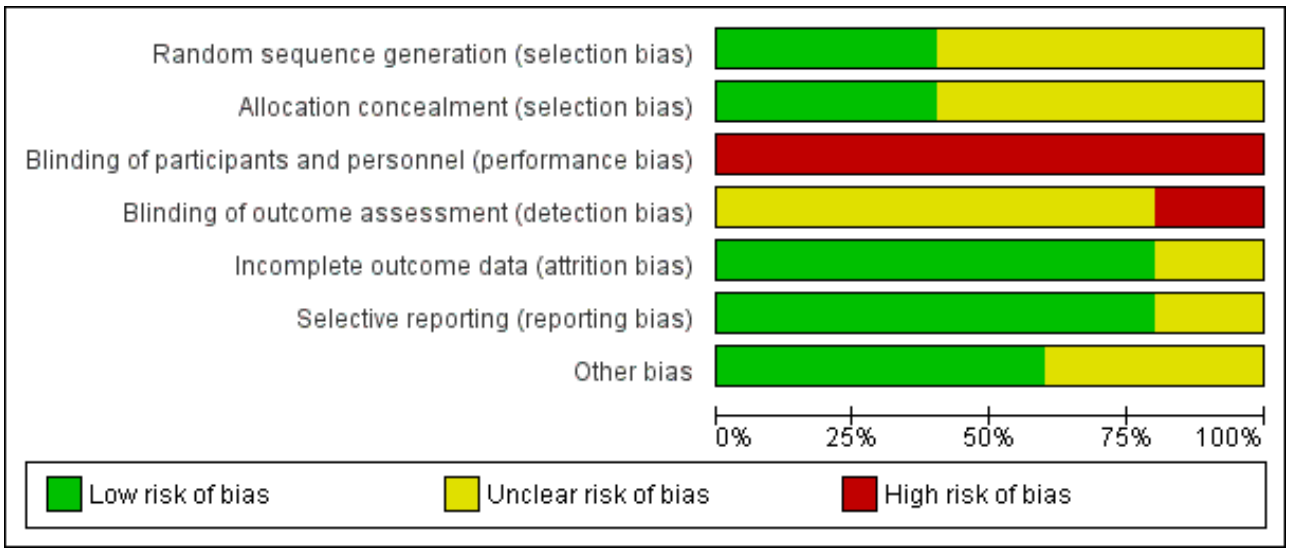
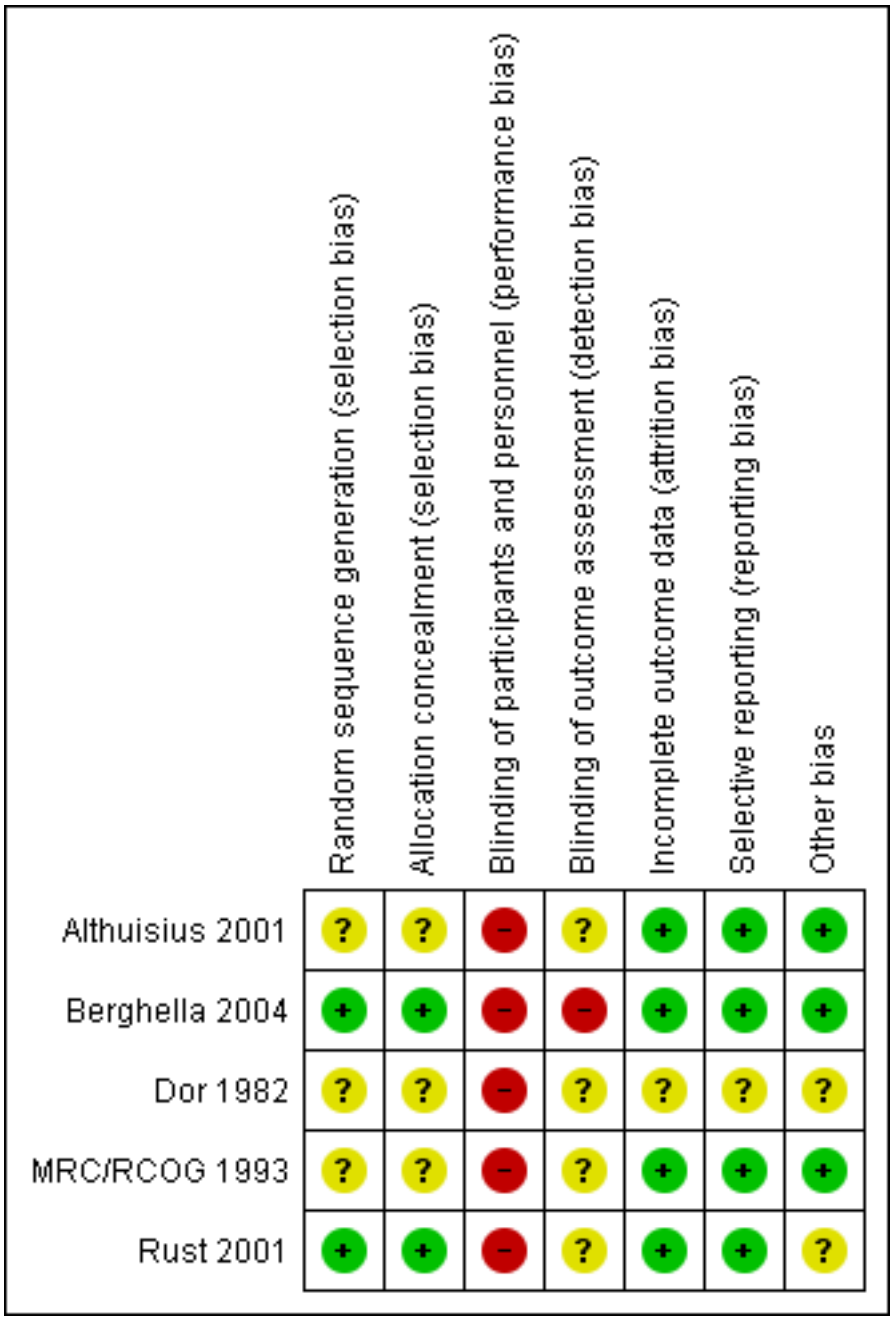


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two studies had both adequate random sequence generation and concealment allocation (Berghella 2004; Rust 2001). In the remaining three studies (Althuisius 2001; Dor 1982; MRC/RCOG 1993), both sequence generation and allocation concealment were unclear.

Blinding

Blinding of both participants and personnel was not possible given the nature of the intervention. Regarding detection bias, in one trial (Berghella 2004), the outcome assessors were not blinded; none of the remaining four trials were clear if the outcome assessors were blinded.

Incomplete outcome data

Four studies adequately addressed the issue of incomplete outcome data assessment (attrition bias) (Althuisius 2001; Berghella 2004; MRC/RCOG 1993; Rust 2001), while in the remaining study (Dor 1982), the quality of outcome data assessment (and incomplete outcome data) was unclear.

Selective reporting

None of the five study protocols were available, but in three of the five studies (Althuisius 2001; Berghella 2004; Rust 2001), the original

database was supplied by the primary first authors, thus those three seem to be free of selective reporting. In one of the studies (MRC/RCOG 1993), while the study protocol was not available, the authors provided the individual data on an extraction form, and thus was deemed low risk for reporting bias. There is an unclear risk of reporting bias in one of the studies (Dor 1982), as the full study protocol was not available.

Other potential sources of bias

Three studies were judged to be free of other sources of bias (Althuisius 2001; Berghella 2004; MRC/RCOG 1993), while the remaining two studies (Dor 1982; Rust 2001) were judged as unclear.

Effects of interventions

Comparison 1 - Cerclage versus no cerclage

Primary outcomes

When cerclage was compared with no cerclage in all trials, there was no statistically significant difference in perinatal deaths (19.2% versus 9.5%; risk ratio (RR) 1.74, 95% confidence intervals (CI) 0.92 to 3.28, five studies, n = 262) (Analysis 1.1) or serious neonatal morbidity (15.8% versus 13.6%; average RR 0.96, 95% CI 0.13 to 7.10, Tau^2 = 1.88, I^2 = 60%, three studies, n = 116) (Analysis 1.2). There was a higher rate of composite perinatal death and serious neonatal morbidity in the cerclage group compared with the no cerclage group (40.4% versus 20.3%, respectively), but the difference was also not statistically significant (average RR 1.54, 95% CI 0.58 to 4.11, Tau^2 = 0.41, I^2 = 44%, three studies, n = 116) (Analysis 1.3). The CIs for the primary outcomes are wide, thus it is not possible to exclude either benefit or harm to the liveborn baby from cerclage.

Secondary outcomes

Among the prespecified secondary outcomes, there were no significant differences between the cerclage and the no cerclage groups.

- **Stillbirth (fetal demise after 20 weeks' gestation, prior to delivery)** - RR 0.26, 95% CI 0.01 to 5.26, four studies, n = 188 (Analysis 1.4).
- **Neonatal death (after birth, and before 29 days of neonatal life or discharge from hospital)** - RR 1.60, 95% CI 0.69 to 3.74, four studies, n = 188 (Analysis 1.5).
- **Preterm birth less than 28 weeks** - RR 1.54, 95% CI 0.63 to 3.81, five studies, n = 128 (Analysis 1.6).
- **Preterm birth less than 32 weeks** - RR 1.43, 95% CI 0.72 to 2.83, four studies, n = 83 (Analysis 1.7).
- **Preterm birth less than 34 weeks** - average RR 1.16, 95% CI 0.44 to 3.06, Tau^2 = 0.67, I^2 = 58%, four studies, n = 83 (Analysis 1.8).
- **Preterm birth less than 35 weeks** - average RR 1.11, 95% CI 0.58 to 2.14, Tau^2 = 0.28, I^2 = 52%, four studies, n = 83 (Analysis 1.9).
- **Preterm birth less than 37 weeks** - RR 1.13, 95% CI 0.89 to 1.43, five studies, n = 128 (Analysis 1.10).
- **Mean gestational age at delivery** - Mean difference (MD) -0.95, 95% CI -2.64 to 0.75, four studies, n = 83 (Analysis 1.11).
- **Low birthweight less than 2500 g** - average RR 1.10, 95% CI 0.82 to 1.48, Tau^2 = 0.07, I^2 = 60%, four studies, n = 172 (Analysis 1.12).
- **Very low birthweight less than 1500 g** - average RR 1.42, 95% CI 0.52 to 3.85, Tau^2 = 0.73, I^2 = 66%, four studies, n = 172 (Analysis 1.13).
- **Respiratory distress syndrome** - average RR 1.70, 95% CI 0.15 to 18.77, Tau^2 = 3.13, I^2 = 70%, three studies, n = 116 (Analysis 1.14).
- **Intraventricular haemorrhage** - RR 0.88, 95% CI 0.25 to 3.12, three studies, n = 116 (Analysis 1.15).
- **Necrotising enterocolitis** - Not estimable, three studies, n = 116 (Analysis 1.16).
- **Sepsis** - RR 0.27, 95% CI 0.03 to 2.31, three studies, n = 116 (Analysis 1.17).
- **Neonatal intensive care unit admission** - average RR 0.35, 95% CI 0.06 to 2.12, Tau^2 = 0.99, I^2 = 48% , two studies, n = 42 (Analysis 1.18).
- **Long-term infant neurodevelopmental outcomes** - Not estimable, no studies (Analysis 1.19).
- **Caesarean section (elective and emergency)** - RR 1.24, 95% CI 0.65 to 2.35, three studies, n = 77 (Analysis 1.20).
- **Maternal infection requiring intervention, e.g. antibiotics or delivery (including chorioamnionitis and endometritis)** - Not estimable, two studies, n = 45 (Analysis 1.21).
- **Maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)** - RR 3.92, 95% CI 0.17 to 88.67, one study, n = 28 (Analysis 1.22).

These results remained non-significant when the Rust 2001 triplet cohort was combined with the ultrasound-indicated cohort, as above.

No trials reported on long-term infant neurodevelopmental outcomes.

Subgroup analysis

Examining the differences between prespecified subgroups, ultrasound-indicated cerclage was associated with an increased risk of low birthweight (average RR 1.39, 95% CI 1.06 to 1.83, Tau^2 = 0.01, I^2 = 15%, three studies, n = 98 (Analysis 1.12)), very low birthweight (average RR 3.31, 95% CI 1.58 to 6.91, Tau^2 = 0, I^2 = 0%, three studies, n = 98 (Analysis 1.13), and respiratory distress syndrome (average RR 5.07, 95% CI 1.75 to 14.70, Tau^2 = 0, I^2 = 0%, three studies, n = 98 (Analysis 1.14)). However, given the low number of trials, as well as substantial heterogeneity and subgroup differences (specifically among Analysis 1.12 and Analysis 1.13), these data must be interpreted cautiously.

We have tested the impact of analysing two subgroups (triplets; ultrasound-indicated cerclage) in the Rust 2001 as if they are coming from two separate studies. Our main analyses treated these two subgroups as different studies in order to graphically depict the subset of triplets as an analysis group. For completeness, the triplet and ultrasound-indicated subgroup from Rust 2001 were also combined given that these subgroups were in fact from a single trial. This was done so as not to affect the estimate of the between-study variation, and hence the results.

Neither the results for serious neonatal morbidity nor for composite perinatal death and serious neonatal morbidity were significantly altered, as the relative risks for the primary outcomes after combining the subgroups were:

- Perintal deaths - RR 1.75, 95% CI 0.93 to 3.29.
- Serious neonatal morbidity - RR 1.26, 95% CI 0.53 to 2.97.
- Composite perinatal deaths and serious neonatal morbidity - RR 1.70, 95% CI 0.95 to 3.05.

Cervical stitch versus any other preventative therapy (i.e. progesterone)

We did not identify any trials comparing cervical stitch versus any other preventative therapy (e.g. progesterone) in multiple gestations.

Comparisons between different cerclage protocols

We did not identify any trials comparing different cerclage protocols (history-indicated versus ultrasound-indicated versus physical exam-indicated cerclage) in multiple gestations.

DISCUSSION

Summary of main results

Examining the evidence from the five included randomised trials, in women with multiple gestations, placing a cerclage is not associated with a significant difference regarding perinatal deaths or neonatal morbidity. As only 128 women were randomised in the five included studies, the data are insufficient for meaningful conclusions, and this area deserves further study.

Unfortunately, none of the trials examined long-term neurodevelopmental outcomes among surviving neonates, and therefore the effect of cerclage could not be estimated for this outcome. Hence, the question of whether prolonging a pregnancy in what could be a 'hostile' intrauterine environment actually does more harm than good, remains unanswered. In addition, while among three studies (Berghella 2004; Dor 1982; MRC/RCOG 1993), it does not appear that cerclage has any effect on caesarean section; while in one study (MRC/RCOG 1993) cerclage did not appear to have an effect on maternal side-effects, maternal infection could not be estimated, so it's unclear if cerclage in multiple gestations puts maternal health at any degree of risk.

It was also not possible to evaluate cerclage versus other modalities (e.g. progesterone), nor was it possible to examine the effect of one cerclage modality versus another (e.g. history-indicated versus ultrasound-indicated cerclage), as there are no trials evaluating these comparisons.

As cerclage may have a different effect depending on the indication for the procedure, it is probably more clinically meaningful to evaluate the data according to the indication of cerclage in multiples, rather than analysing the totality of the data. Therefore, we prespecified five clinical scenarios (subgroups) based on the indications for cervical cerclage in current clinical practice.

We were only able to obtain the original databases from three of the five included studies (Althuisius 2001; Berghella 2004; Rust 2001), making these subgroup analyses somewhat limited. Given the low number of trials, as well as significant heterogeneity it is not possible to draw any meaningful conclusions from the currently available data. While an ultrasound-indicated cerclage appears to be associated with an increased risk for the composite adverse neonatal outcome, including respiratory distress syndrome, low and very low birthweight, given there is no evidence of a consistent subgroup effect, the observed results can most likely be attributed to chance.

Without adequately powered randomised clinical trials, questions will remain regarding any theoretical benefit (or harm) involving the indication of cerclage placement in multiple gestations.

The issue of prevention of preterm birth, especially among multiple gestations, is definitely a hot topic in the field of obstetrics today. Progesterone, in its various forms, has been shown to prevent preterm birth in singleton gestations, both in its synthetic caproate form among women with a prior preterm birth (Meis 2003), as well as in its micronised form among women with shortened cervical lengths (Hassan 2011). This prevention of preterm birth with progesterone use has not yet translated to those women with multiple gestations (Klein 2011; Rouse 2007). However, a recent individual patient data meta-analysis, although limited by small numbers of twin pregnancies, suggests that vaginal progesterone may have some role in multiple pregnancies with short cervix (Romero 2012).

Overall completeness and applicability of evidence

Given the limited numbers of trials, the overall numbers are small, and subgroup effects were difficult to assess with adequate power, which is a weakness of this meta-analysis. An additional limitation is the lack of long-term neonatal neurodevelopmental data, an important outcome to consider when implementing an antenatal intervention, regardless of the timing of this intervention. As there is considerable anxiety concerning preterm birth in multiple gestations, there is a pressure on clinicians to "do everything," which results in placing a cerclage, or mechanical support, as this seems intuitive. Thus far, however, despite the small numbers and potential biases in this analysis, there does not appear to be a benefit in multiple gestations with cerclage placement. More evidence needs to be obtained through properly conducted prospective trials to further address this clinical question.

Quality of the evidence

Overall, the included trials were of average to above average quality. Only two of the five included studies (Berghella 2004, Rust 2001) were judged to be at low risk for selection bias, with three of the trials at unclear risks regarding both selection and detection biases (Althuisius 2001; Dor 1982; MRC/RCOG 1993). Selective reporting of results is a concern when the trial protocols are not available for review. While this concern was alleviated with the providing of the original databases by three of the five study authors (Althuisius 2001; Berghella 2004; Rust 2001), the original databases were not available for review for the remaining two trials (Dor 1982; MRC/RCOG 1993). Additional data were entered into the collection sheets by the MRC/RCOG group.

Performance bias (blinding of both participants and personnel) is always (and will always be) an issue regarding cerclage trials, in that it is impossible to blind. The outcomes of interest, however, are unlikely to be affected by this inability to blind.

Potential biases in the review process

None identified.

Agreements and disagreements with other studies or reviews

Cervical cerclage in multiple gestations remains controversial, with no definitive evidence to date of its benefit at prolonging gestation or reducing neonatal mortality/morbidity. The current analysis demonstrates that overall cervical cerclage has no significant effect on perinatal death, neonatal death, or preterm birth. Interestingly, composite perinatal death and serious neonatal morbidity was significantly increased when limiting the analysis to the subgroup of ultrasound-indicated cerclage.

Concerning preterm birth, while another meta-analysis examining short cervical length and cerclage (Berghella 2005) demonstrated a 215% increase in the risk of preterm birth less than 35 weeks in twins receiving an ultrasound-indicated cerclage, the current meta-analysis did not demonstrate a significant difference in preterm birth comparing ultrasound-indicated cerclage with no cerclage. A retrospective analysis (Roman 2005) also did not demonstrate a reduction of spontaneous preterm delivery less than 28, 30, 32, or 34 weeks with the use of cerclage in multiple gestations (both twins and triplets). An additional large retrospective analysis of triplet gestations (Rebarber 2005) concluded that a prophylactic cerclage did not result in improved pregnancy or neonatal outcomes in triplet pregnancies without a history of cervical insufficiency.

A prospective, non-randomised trial (thus not included in this review) (Newman 2002), looked at cerclage versus no cerclage among twin pregnancies with a shortened mid-trimester cervical length, and did not find differences in length of gestation, birthweight, delivery at less than 34 weeks, preterm premature rupture of fetal membranes, or very low birthweight.

These current data, given the low numbers of participants, need to be interpreted with caution.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that there is no current evidence of benefit for cerclage placement in multiple gestations, regardless of the indication (e.g. multiple gestation alone, shortened cervical length, etc). These results are based on few studies, however; thus, cerclage placement in multiple gestations should be further evaluated through properly conducted prospective trials in order to determine its effect and safety.

Implications for research

Adequately powered randomised controlled trials involving twins and cervical cerclage are needed, involving in particular history-indicated cerclages, as well as ultrasound-indicated cerclages for shortened cervical length. It would seem that the two twin groups at highest risk for preterm birth would be those with 1) prior preterm birth (Ananth 2008), and/or 2) short cervical length. Regarding the former, the MRC/RCOG data encompassed those pregnancies with "higher risk" history (e.g. prior preterm birth, cervical conisation, etc); without the original database, however, it is impossible to ascertain which of these twin pregnancies actually had a prior preterm birth, and as such would be at a much higher risk of delivering preterm. Future prospective research involving cerclage is needed in this high-risk cohort. To our knowledge, direct comparisons between cerclage and other modalities (e.g. progesterone, bed rest, vaginal pessary) for the prevention of preterm birth in multiple gestations has yet to be carried out.

Future studies also need to address both short- and long-term neonatal/infant/child morbidity as an outcome.

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We are particularly grateful to Drs Sietske Althuisius and Orion Rust for providing access to individual patient databases, as well as to the MRC/RCOG group, who contributed additional data.

As part of the pre-publication editorial process, this review has been commented on by five peers (an editor and four referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Althuisius 2001

Methods	• RCT - balanced block randomisation. • July 1995 until July 2000. • University Hospital Vrije Universiteit and Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands.

Participants	**Participants**: A woman considered to be at high risk of preterm delivery, as diagnosed by a cervical length of < 25 mm before a gestational age of 27 weeks.
	
	Inclusion criteria:
	
	• Singletons and twins - total = 35 women (Only TWINS analysed for this review - 17 women, 34 possible neonates)
	• Analyses contain the data from 3 research lines:
	  ◦ 1) women with a previous preterm delivery before 34 weeks of gestation who met clinical criteria for the diagnosis of cervical incompetence or previous premature rupture of membranes before 32 weeks of gestation;
	  ◦ 2) women with a gynaecologic history with 1 or more accepted risk factors for cervical incompetence, such as cold knife conisation, exposure to diethylstilbestrol in utero, and uterine anomaly;
	  ◦ 3) women who met the inclusion criteria of the first or the second group but who had a gestational age of > 15 weeks with a cervical length of < 25 mm before 27 weeks of gestation or women who had symptoms of cervical incompetence.
	
	Exclusion criteria:
	
	• Prophylactic cerclage that was placed on the basis of historic high risk criteria.
	• Fetal congenital/chromosomal anomalies.
	• Preterm rupture of membranes.
	• Membranes bulging into the vagina.
	• Intrauterine infection (fever, uterine tenderness, fetal tachycardia, marked leukocytosis > 15,000 x 10^9/L, or elevated C-reactive protein > 15 mg/L).

Interventions	**Experimental intervention:** Therapeutic cerclage and bed rest. Women allocated to therapeutic cerclage received an indomethacin suppository (100 mg, 2 hours before and 6 hours after the operation).

Althuisius 2001 *(Continued)*

	Control/Comparison intervention: bed rest alone. Independent of the random allocation, women received amoxicillin/clavulanic acid 1 g intravenously every 6 hours and metronidazole 500 mg intravenously every 8 hours for 24 hours, followed by amoxicillin/clavulanic acid 500 mg orally every 8 hours and metronidazole 500 mg orally every 8 hours for 6 days.
Outcomes	**Primary:** • Preterm delivery before 34 weeks of gestation. • Neonatal morbidity defined as admission to the neonatal intensive care unit and/or neonatal death, and neonatal survival. **Secondary:** Not stated.
Notes	Additional information and the database for cross-checking of the published results were provided by the author. The trial did not make corrections for the non-independence of twins.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation was stratified for the different inclusion criteria and the 2 participating hospitals and organised in balanced blocks. It is not stated how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Assigned via telephone, but concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind for participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any loss of participants to follow-up at each data collection point: • 3 lost to follow-up. Any exclusion of participants after randomisation: • 1 participant was excluded because the membranes were bulging into the vagina. Was the analysis intention-to-treat? • Yes.
Selective reporting (reporting bias)	Low risk	The full study protocol was not available, but a pre-specified data extraction form, as well as database, were provided by the authors.
Other bias	Low risk	If the study was stopped early, explain the reasons: • The study was not stopped early. Describe any baseline imbalance: • None.

Berghella 2004

Methods	• RCT - randomisation in permuted blocks of 6. • Thomas Jefferson University Hospital from February 1998 until June 2003, and the University of Pennsylvania Hospital from February 2002 until June 2003.
Participants	**Participants:** • "Asymptomatic pregnant women who were identified...to have high risk factors for preterm birth were screened by transvaginal ultrasound of the cervix every 2 weeks between 14 weeks 0 days of gestation and 23 weeks 6 days of gestation." • Twin pregnancies also were screened prospectively. **Inclusion criteria:** • Singletons and twins - total = 61 women (Only TWINS analysed for this review - 4 women in total). • High risk for preterm birth (e.g. ≥ 1 preterm birth between 14 and 34 weeks of gestation, ≥ 2 curettage procedures for spontaneous/voluntary abortions, diethylstilbestrol exposure, cone biopsy, and Mullerian anomaly. • Screened twin pregnancies and non screened low-risk women who were identified incidentally, first on routine transabdominal anatomy ultrasound scanning, to have transvaginal ultrasound criteria for a short cervix (< 25 mm) or significant funnelling (> 25%) were also offered enrolment, with twin pregnancies randomly assigned separately. • Advanced cervical dilation or membranes bulging in the vagina in asymptomatic women was not an exclusion criteria. **Exclusion criteria:** • Prophylactic cerclage that was placed on the basis of historic high-risk criteria. • Last pregnancy delivered at term. • Major fetal anomaly. • Triplets or higher order multiple gestations. • Previous inclusion in another trial. • Current drug abuse. • Regular contractions that led to preterm labour after identification of abnormal cervix by ultrasound scanning. **Subgroup - cervical stitch based on:** • Serial ultrasound scans in high-risk groups (previous preterm birth or cervical surgery). • Subanalysis for cervical length or < 25 mm, ≤ 15 mm, previous preterm birth at < 35 or < 32 weeks, risk factors for preterm birth, no risk factors, twins.
Interventions	**Experimental intervention:** cerclage with bed rest. **Control/Comparison intervention:** bed rest alone.
Outcomes	**Primary:** • Preterm birth < 35 weeks. **Secondary:** • Gestational age at delivery. • Preterm labour. • Preterm rupture of membranes. • Interval from enrolment to delivery.

Berghella 2004 *(Continued)*

	• Neonatal outcomes: death; for the survivors, neonatal intensive care nursery admission, days in the neonatal intensive care unit, and composite morbidity (any of respiratory distress syndrome, intraventricular haemorrhage [III or IV], necrotising enterocolitis, or sepsis).
Notes	Additional information and the database for cross-checking of the published results were provided by the first author. The trial did not make corrections for the non-independence of twins.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation included allocation that was accomplished by computer-generated numbers in permuted blocks of 6.
Allocation concealment (selection bias)	Low risk	These were concealed in sequentially numbered, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind for participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessors were not blinded.

Incomplete outcome data (attrition bias)
All outcomes
	Low risk	Any loss of participants to follow-up at each data collection point:
		• No loss of participants.
		Any exclusion of participants after randomisation:
		• 1 woman was excluded in the low-risk group because of current drug abuse.
		• 14 of 333 in the high-risk group were excluded:
		  ○ 9 were already included in another study;
		  ○ 3 had persistent contractions;
		  ○ 2 had current drug abuse.
		• 1 of 92 in the twin group was excluded because of current drug abuse.
		Was the analysis intention-to-treat?
		• Yes.

Selective reporting (reporting bias)	Low risk	The full study protocol was not available, but pre-specified data extraction form, as well as database, were provided by the first author.
Other bias	Low risk	If the study was stopped early, explain the reasons: • The study was not stopped early. Describe any baseline imbalance: • 6/10 women in the twin group declined participation.

Dor 1982

Methods	• RCT - participants "selected at random".

Dor 1982 *(Continued)*

	• Infertility Clinic - Tel-Hashomer, Tel-Aviv, Israel, during the years 1975 to 1979.
Participants	**Participants:** • Infertile women who had conceived after induction of ovulation, either with clomiphene or gonadotropins. • Ultrasound was always performed between 6 and 10 weeks of gestation. • All patients had hysterography before treatment. • No patient had clinical or X-ray evidence of cervical incompetence, congenital uterine anomalies or threatened miscarriage during the studied pregnancy. • 55 multiple pregnancies were diagnosed by ultrasound of which 50 were twin pregnancies, 4 triplet, and 1 quadruplet. **Inclusion criteria:** • Twin pregnancy – 25 women with twin pregnancies (of the 50 total women) were selected at random, and underwent elective cervical suture at the 13th gestational week after informed consent. **Exclusion criteria:** • Singleton gestation. • Higher-order multiple gestation.
Interventions	**Experimental intervention:** Cervical suture (McDonald cerclage) at 13th gestational week; double silk stitches used; removed after the 37th gestational week, or when inevitable abortion, premature contraction or premature rupture of membranes occurred. **Control/Comparison intervention:** No cerclage.
Outcomes	**Primary:** • Preterm delivery < 37th week. **Secondary:** • Premature delivery preceded by premature contractions. • Premature delivery preceded by premature rupture of membranes. • Stillbirth. • Early neonatal death in the first week of life. • Neonatal deaths after first week of life.
Notes	This information and data came from the published paper, as the original database was not available. In the "Material and Methods" section, the authors make mention of 5 women (3 cerclage, 2 no cerclage) who "aborted" prior to 20 weeks' gestation, and are not included in the final analysis. While there is information on the gestational age at which they delivered, those patients, since they were not included in the final analysis in the paper, are not represented here. The trial did not make corrections for the non-independence of twins.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was no mention of how the randomisation sequence was generated, only that twin pregnancies were “selected at random”.
Allocation concealment (selection bias)	Unclear risk	There was no mention if there was any concealment at all.

Dor 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind for participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Any loss of participants to follow-up at each data collection point: • No participants lost to follow-up, although no mention of how many potential participants were screened, invited to participate in the trial, declined randomisation, etc. Any exclusion of participants after randomisation: • 3 cerclage patients who "aborted" at 14, 16, and 17 weeks were excluded both from the final analysis, and regarding patient demographic information. • 2 no-cerclage patients who "aborted" at 15 and 16 weeks were excluded both from the final analysis, and regarding patient demographic information. Was the analysis intention-to-treat? • Not stated; It appears all those allocated to receive cerclage actually received the cerclage, and vice versa.
Selective reporting (reporting bias)	Unclear risk	The full study protocol was not available.
Other bias	Unclear risk	No description available. It does not appear that the study was stopped early.

MRC/RCOG 1993

Methods	• RCT - balanced block randomisation. • 1981-1988. • Involved 12 countries in total, supervised by the MRC/RCOG Working Party on Cervical Cerclage and coordinated from the National Perinatal Epidemiology Unit in Oxford, UK.
Participants	**Participants:** • A total of 1318 women were recruited: 856 in the UK; 117 in France; 100 in Hungary; 73 in Norway; 68 in Italy; 34 in Belgium; 28 in Zimbabwe; and 42 in South Africa, Iceland, Ireland, the Netherlands and Canada. 26 (2%) women were lost to follow-up and the final analysis was based on 1292 women. **Inclusion criteria:** • A pregnant woman was eligible for entry to the trial if her obstetrician was uncertain whether to advise her to have a cervical cerclage; e.g. women deemed to be at increased risk of cervical incompetence: past history of 1 or more second trimester miscarriages or preterm deliveries, history of cervical amputation or cone biopsy, previous termination of pregnancy, previous first trimester miscarriage, cervical abnormality on physical examination, uterine abnormality, or twin pregnancy. • Both singleton and twin pregnancies were included (Only TWINS analysed for this review - total = 28 women). **Exclusion criteria:** • No discrete exclusion criteria are specified.

MRC/RCOG 1993 *(Continued)*

Interventions	**Experimental intervention:** a recommendation to insert a cervical suture (cerclage) as soon as possible (unless some clear contra-indication to it arose). **Control/Comparison intervention:** a recommendation to avoid cerclage (unless a clear indication arose).

Outcomes	**Primary:**
	
	• Length of pregnancy
	  ○ Delivery before 33 completed weeks.
	  ○ Delivery before 37 completed weeks.
	  ○ Vital status of the baby at the time of completion of the delivery form/questionnaire.
	
	Secondary:
	
	• Postpartum pyrexia (supplementary question was added after the first 360 cases).
	• Indications for caesarean section.
	• Usual technique of cervical cerclage.

Notes	The trial did not make corrections for the non-independence of twins.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Most obstetricians used the randomisation service provided by the Clinical Trial Service Unit in Oxford, but other randomisation centres were established in Hungary, Italy, and Zimbabwe. Randomisation was organised in balanced blocks, but no prognostic stratification was used.
Allocation concealment (selection bias)	Unclear risk	"Most women were entered and assigned a random allocation by telephone; a few were registered by post." "Once basic identifying and descriptive data had been given over the telephone, a random allocation was made to one of two clinical policies."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind for participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any loss of participants to follow-up at each data collection point: • 26 (2%) women were lost to follow-up. Any exclusion of participants after randomisation: • None stated. Was the analysis intention-to-treat?

MRC/RCOG 1993 *(Continued)*

		• Yes. 598/647 in the cerclage group received cerclage; 49/645 in the no cerclage group received cerclage.
Selective reporting (reporting bias)	Low risk	Study protocol was not available, but the authors provided the individual data after being supplied with the Cochrane Group data extraction form.
Other bias	Low risk	If the study was stopped early, explain the reasons: • The study was not stopped early. Describe any baseline imbalance: • No baseline imbalance.

Rust 2001

Methods	• RCT. • May 1998 until August 2000. • Lehigh Valley Hospital Outpatient Perinatal Testing Center.
Participants	**Participants:** • "Any patient between the gestational ages of 16 and 24 weeks with transvaginal ultrasound demonstration of (1) dilation of the internal os, (2) prolapsed of the membranes into the endocervical canal but not beyond the external os, (3) a shortened distal cervical length, and (4) exacerbation of these 3 findings associated with transfundal pressure was considered a candidate for enrolment." There were a total of 113 women who were randomised following exclusions, of which there were 6 women with triplet gestations, and 28 women with twin gestations, which were included in this review. **Inclusion criteria:** • "Consisted of demonstrable dilatation of the internal os and either prolapse of membranes at least 25% of the total cervical length or a distal cervical length of < 2.5 centimeters. Those patients, who met the inclusion criteria and provided informed consent, underwent an amniocentesis to rule out infection." • "A rescue arm of the study was designed for each group. Any patient at < 24 weeks gestation who had prolapsed membranes beyond the level of the cerclage or to the external os (without cerclage) was offered a revision, or rescue cerclage procedure." **Exclusion criteria:** • Included membrane prolapsed beyond the external os, any fetal lethal congenital or chromosomal anomaly, clinical evidence of abruption placenta, unexplained vaginal bleeding, chorioamnionitis (diagnosed by clinical or amniocentesis criteria and confirmed by histopathologic features), persistent uterine activity accompanied by cervical change (consistent with the diagnosis of preterm labour), or any other contraindication to a cerclage procedure.
Interventions	**Experimental intervention:** therapeutic cerclage and bed rest. Prior to randomisation, multiple urogenital cultures were obtained, and the patient was placed on inpatient bed rest for 48-72 hours. During this time, the patient received empiric antibiotic therapy with clindamycin (900 mg intravenous every 8 hours) and indomethacin therapy (100 mg loading dose per rectum followed by 50 mg orally every 6 hours). **Control/Comparison intervention:** bed rest alone. Independent of the random allocation, both groups were treated with an identical protocol with the exception of cerclage placement. Indomethacin and antibiotic therapy were withdrawn beginning ap-

Rust 2001 *(Continued)*

	proximately 24 hours after randomisation for both groups. All patients had bed rest modified to allow feeding, clothing, and performing basic bodily functions. Outpatient therapy included modified bed rest at home, weekly sonographic reevaluation of the lower uterine segment, and education about the signs and symptoms of preterm labour.

Outcomes	**Primary:**
	• Gestational age at delivery.
	• Perinatal death rate.
	Secondary:
	• Neonatal morbidity
	  ○ Minimal – defined as an intensive care unit admission without life-threatening complication.
	  ○ Severe – defined as life-threatening illness (such as respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage, sepsis, or other serious morbidity.
	• Maternal readmission for preterm labour.
	• Chorioamnionitis.
	• Placental abruption.
	• Rescue or revision procedures.
	• Cervical laceration.

Notes	Additional information and the database for cross-checking of the published results were provided by the first author. The trial did not make corrections for the non-independence of multiple gestations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence. Note--"The study protocol was approved by the Institutional Review Board, was identical to the protocol published by Rust et al" referring to: *Rust OA, et al. A randomized trial of cerclage versus no cerclage among patients with ultrasonographically detected second-trimester preterm dilatation of the internal os. Am J Obset Gynceol 2000;183:830-5.*
Allocation concealment (selection bias)	Low risk	Placed in sealed opaque envelopes (as per "identical" nature to the above cited reference).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind for participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any loss of participants to follow-up at each data collection point: • 135 patients met the inclusion criteria. • 20/135 declined randomisation. Any exclusion of participants after randomisation: • 2/135 were excluded because of chorioamnionitis that was diagnosed by amniocentesis.

Rust 2001 *(Continued)*

		Was the analysis intention-to-treat? • Yes - "A rescue arm of the study was designed for each group. Any patient at <24 weeks' gestation who had prolapsed membranes beyond the level of the cerclage or to the external os(without cerclage) was offered a revision or rescue cerclage procedure. Data were analysed on the basis of intention to treat."
Selective reporting (reporting bias)	Low risk	The study protocol was not available. The full database was provided by the first author, so any selective reporting bias is unlikely.
Other bias	Unclear risk	If the study was stopped early, explain the reasons: • The study was not stopped early. Describe any baseline imbalance: • None apparent.

cm: centimetre
g: gram
L: litre
mg: milligram
mm: millimetre
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Blair 2002	Outpatient cerclage versus inpatient cerclage; excluded those with multiple pregnancies.
Lazar 1984	Excluded multiple gestations.
Nicolaides 2001	Design and methodology only; unknown status of trial.

DATA AND ANALYSES

Comparison 1. Cerclage versus no cerclage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal deaths	5	262	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.92, 3.28]
1.1 Twin only-indicated	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.47, 3.02]
1.2 Twin and history-indicated (prior Ob/Gyn history)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.20, 8.80]
1.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [0.83, 8.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Triplets	1	18	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.38, 23.68]
2 Serious neonatal morbidity (defined by trialists)	3	116	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.13, 7.10]
2.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Random, 95% CI)	2.59 [0.85, 7.86]
2.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Triplets	1	18	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.80]
3 Composite – Perinatal deaths and serious neonatal morbidity	3	116	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.58, 4.11]
3.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Random, 95% CI)	2.52 [1.20, 5.30]
3.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Triplets	1	18	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.20, 1.79]
4 Stillbirth (fetal demise after 20 weeks' gestation, prior to delivery)	4	188	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 5.26]
4.1 Twin only-indicated	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Twin and history-indicated (prior Ob/Gyn history)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 5.26]
4.3 Ultrasound-indicated	2	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Neonatal death (after birth, and before 29 days of neonatal life or discharge from hospital)	4	188	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.69, 3.74]
5.1 Twin only-indicated	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.47, 3.02]
5.2 Twin and history-indicated (prior Ob/Gyn history)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Ultrasound-indicated	2	42	Risk Ratio (M-H, Fixed, 95% CI)	5.57 [0.44, 70.55]
5.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Preterm birth less than 28 weeks	5	128	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.63, 3.81]
6.1 Twin only-indicated	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.36]
6.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.09, 19.23]
6.3 Ultrasound-indicated	3	49	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [0.72, 9.51]
6.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 Triplets	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.10, 9.61]
7 Preterm birth less than 32 weeks	4	83	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.72, 2.83]
7.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.61]
7.3 Ultrasound-indicated	3	49	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.96, 6.37]
7.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Triplets	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.32, 3.10]
8 Preterm birth less than 34 weeks	4	83	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.44, 3.06]
8.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.04, 1.99]
8.3 Ultrasound-indicated	3	49	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.72, 6.63]
8.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 Triplets	1	6	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.31, 1.66]
9 Preterm birth less than 35 weeks	4	83	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.58, 2.14]
9.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.61]
9.3 Ultrasound-indicated	3	49	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.88, 3.02]
9.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.5 Triplets	1	6	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.31, 1.66]
10 Preterm birth less than 37 weeks	5	128	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.89, 1.43]
10.1 Twin only-indicated	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.51, 1.78]
10.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.71, 2.51]
10.3 Ultrasound-indicated	3	49	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.91, 1.53]
10.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Triplets	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.59, 1.69]
11 Mean gestational age at delivery	4	83	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-2.64, 0.75]
11.1 Twin only-indicated	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Mean Difference (IV, Fixed, 95% CI)	0.70 [-3.50, 4.90]
11.3 Ultrasound-indicated	3	49	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-3.13, 0.66]
11.4 Physical exam-indicated	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.5 Triplets	1	6	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-11.23, 7.23]
12 Low birthweight defined as less than 2500 grams	4	172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.82, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Twin and history-indicated (prior Ob/Gyn history)	1	56	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.34]
12.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.06, 1.83]
12.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.5 Triplets	1	18	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.16]
13 Very low birthweight defined as less than 1500 grams	4	172	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.52, 3.85]
13.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Twin and history-indicated (prior Ob/Gyn history)	1	56	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.45]
13.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Random, 95% CI)	3.31 [1.58, 6.91]
13.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.5 Triplets	1	18	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.52, 1.92]
14 Respiratory distress syndrome (defined by trialists)	3	116	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.15, 18.77]
14.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Random, 95% CI)	5.07 [1.75, 14.70]
14.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.5 Triplets	1	18	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.80]
15 Intraventricular hemorrhage (defined by trialists)	3	116	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.25, 3.12]
15.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

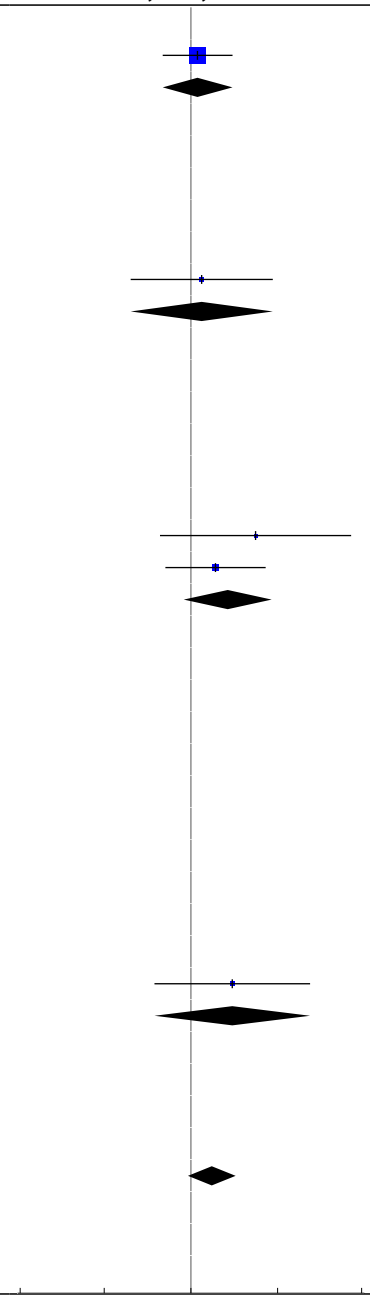
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.27, 4.74]
15.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.5 Triplets	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.24]
16 Necrotising enterocolitis (defined by trialists)	3	116	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.5 Triplets	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Sepsis (defined by trialists)	3	116	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.03, 2.31]
17.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Ultrasound-indicated	3	98	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.58]
17.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.5 Triplets	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.24]
18 Neonatal intensive care unit admission	2	42	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.06, 2.12]
18.1 Twin only-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.3 Ultrasound-indicated	2	42	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.06, 2.12]
18.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.5 Triplets	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Long-term infant neurodevelopmental outcomes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Twin and history-indicated (prior Ob/Gyn history)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 Ultrasound-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Caesarean section (elective and emergency)	3	77	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.65, 2.35]
20.1 Twin only-indicated	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.61, 2.98]
20.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.36, 3.14]
20.3 Ultrasound-indicated	1	4	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Maternal infection requiring intervention, e.g. antibiotics or delivery (including chorioamnionitis and endometritis)	2	45	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Ultrasound-indicated	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [0.17, 88.67]
22.1 Twin only-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Twin and history-indicated (prior Ob/Gyn history)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [0.17, 88.67]
22.3 Ultrasound-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.4 Physical exam-indicated	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.5 Triplets	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Cerclage versus no cerclage, Outcome 1 Perinatal deaths.

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Twin only-indicated					
Dor 1982	8/44	7/46		52.47%	1.19[0.47,3.02]
Subtotal (95% CI)	**44**	**46**		**52.47%**	**1.19[0.47,3.02]**
Total events: 8 (Cerclage), 7 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
1.1.2 Twin and history-indicated (prior Ob/Gyn history)					
MRC/RCOG 1993	2/24	2/32		13.14%	1.33[0.2,8.8]
Subtotal (95% CI)	**24**	**32**		**13.14%**	**1.33[0.2,8.8]**
Total events: 2 (Cerclage), 2 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.77)					
1.1.3 Ultrasound-indicated					
Althuisius 2001	0/16	0/18			Not estimable
Berghella 2004	6/6	0/2		5.37%	5.57[0.44,70.55]
Rust 2001	5/26	3/30		21.36%	1.92[0.51,7.28]
Subtotal (95% CI)	**48**	**50**		**26.72%**	**2.66[0.83,8.54]**
Total events: 11 (Cerclage), 3 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					
1.1.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.5 Triplets					
Rust 2001	3/9	1/9		7.67%	3[0.38,23.68]
Subtotal (95% CI)	**9**	**9**		**7.67%**	**3[0.38,23.68]**
Total events: 3 (Cerclage), 1 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
Total (95% CI)	**125**	**137**		**100%**	**1.74[0.92,3.28]**
Total events: 24 (Cerclage), 13 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=1.81, df=4(P=0.77); I^2=0%					
Test for overall effect: Z=1.72(P=0.09)					



Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=1.47, df=1 (P=0.69), I²=0%					

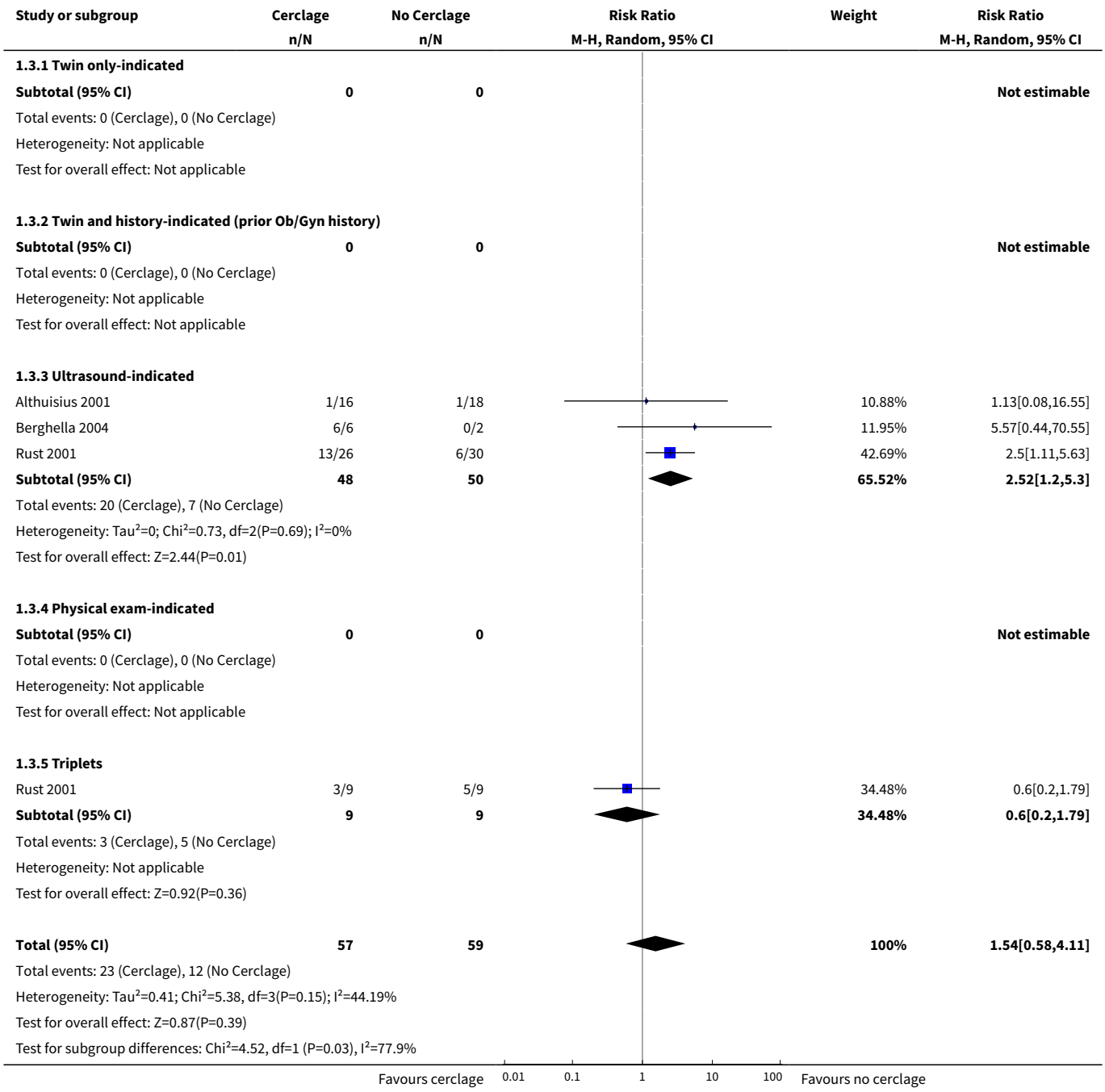
Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Analysis 1.2. Comparison 1 Cerclage versus no cerclage, Outcome 2 Serious neonatal morbidity (defined by trialists).

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Twin only-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.2 Twin and history-indicated (prior Ob/Gyn history)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.3 Ultrasound-indicated					
Althuisius 2001	1/16	1/18		27.59%	1.13[0.08,16.55]
Berghella 2004	0/6	0/2			Not estimable
Rust 2001	8/26	3/30		45.8%	3.08[0.91,10.41]
Subtotal (95% CI)	**48**	**50**		**73.4%**	**2.59[0.85,7.86]**
Total events: 9 (Cerclage), 4 (No Cerclage)					
Heterogeneity: Tau²=0; Chi²=0.45, df=1(P=0.5); I²=0%					
Test for overall effect: Z=1.68(P=0.09)					
1.2.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.5 Triplets					
Rust 2001	0/9	4/9		26.6%	0.11[0.01,1.8]
Subtotal (95% CI)	**9**	**9**		**26.6%**	**0.11[0.01,1.8]**
Total events: 0 (Cerclage), 4 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
Total (95% CI)	**57**	**59**		**100%**	**0.96[0.13,7.1]**
Total events: 9 (Cerclage), 8 (No Cerclage)					
Heterogeneity: Tau²=1.88; Chi²=5.04, df=2(P=0.08); I²=60.28%					
Test for overall effect: Z=0.04(P=0.97)					
Test for subgroup differences: Chi²=4.23, df=1 (P=0.04), I²=76.38%					

Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Analysis 1.3. Comparison 1 Cerclage versus no cerclage, Outcome 3 Composite – Perinatal deaths and serious neonatal morbidity.

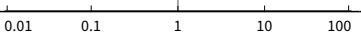


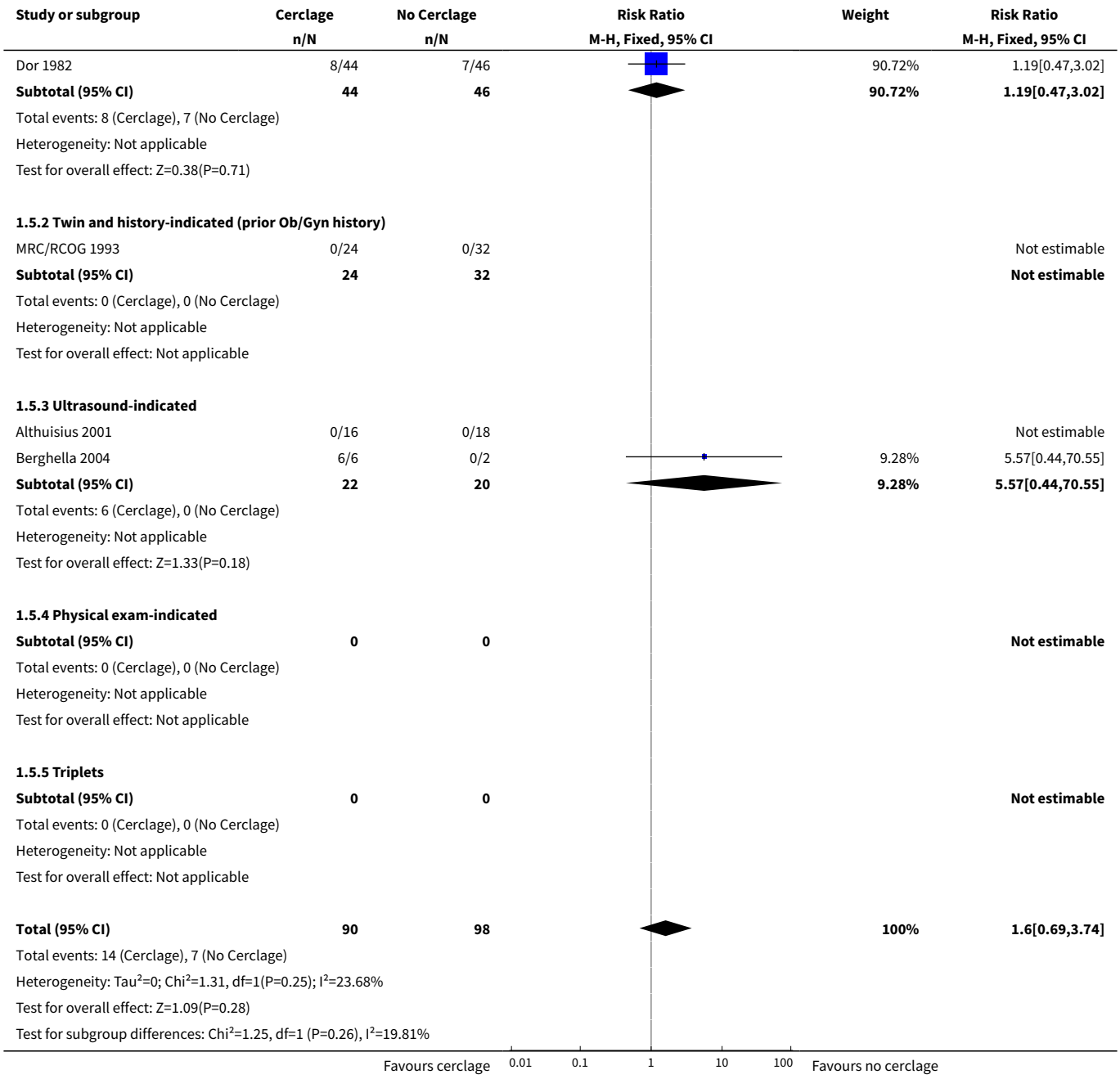
Analysis 1.4. Comparison 1 Cerclage versus no cerclage, Outcome 4 Stillbirth (fetal demise after 20 weeks' gestation, prior to delivery).

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Twin only-indicated					
Dor 1982	0/44	0/46			Not estimable
Subtotal (95% CI)	**44**	**46**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.4.2 Twin and history-indicated (prior Ob/Gyn history)					
MRC/RCOG 1993	0/24	2/32		100%	0.26[0.01,5.26]
Subtotal (95% CI)	**24**	**32**		**100%**	**0.26[0.01,5.26]**
Total events: 0 (Cerclage), 2 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					
1.4.3 Ultrasound-indicated					
Althuisius 2001	0/16	0/18			Not estimable
Berghella 2004	0/6	0/2			Not estimable
Subtotal (95% CI)	**22**	**20**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.4.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.4.5 Triplets					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**90**	**98**		**100%**	**0.26[0.01,5.26]**
Total events: 0 (Cerclage), 2 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Not applicable					

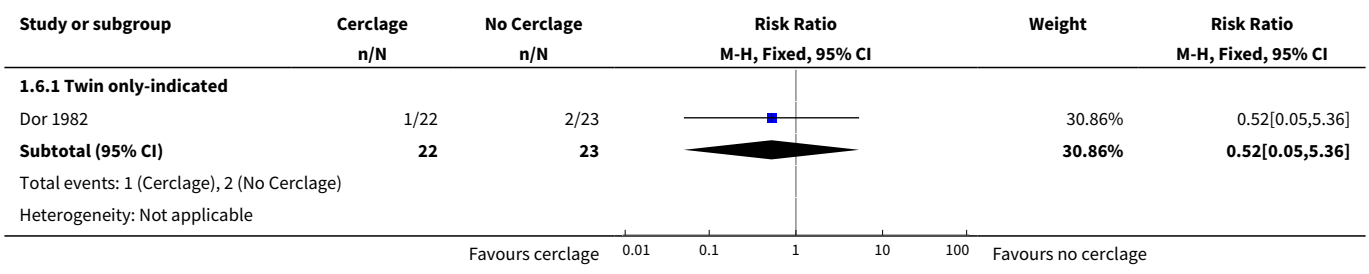
Analysis 1.5. Comparison 1 Cerclage versus no cerclage, Outcome 5 Neonatal death (after birth, and before 29 days of neonatal life or discharge from hospital).

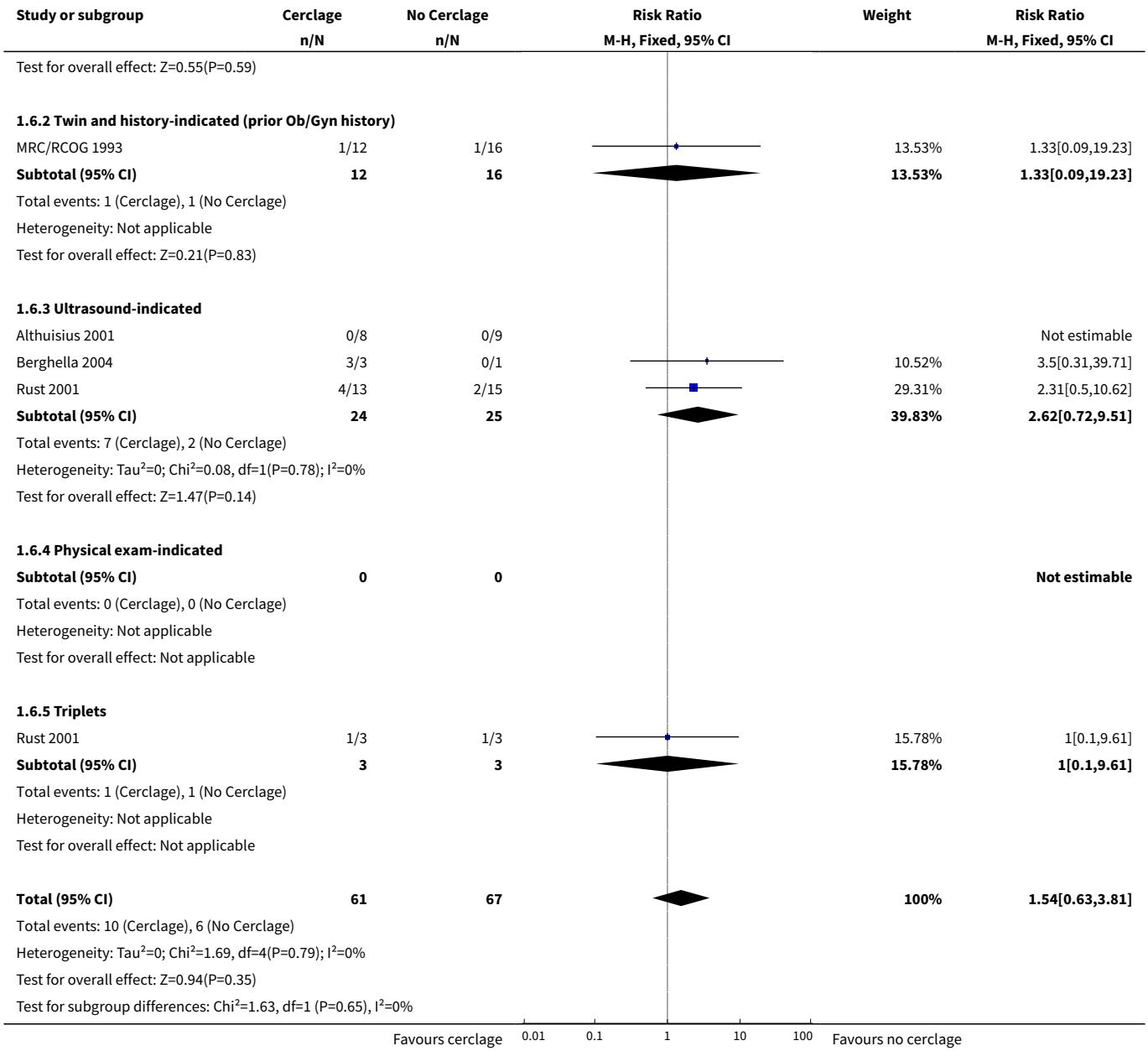
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Twin only-indicated					



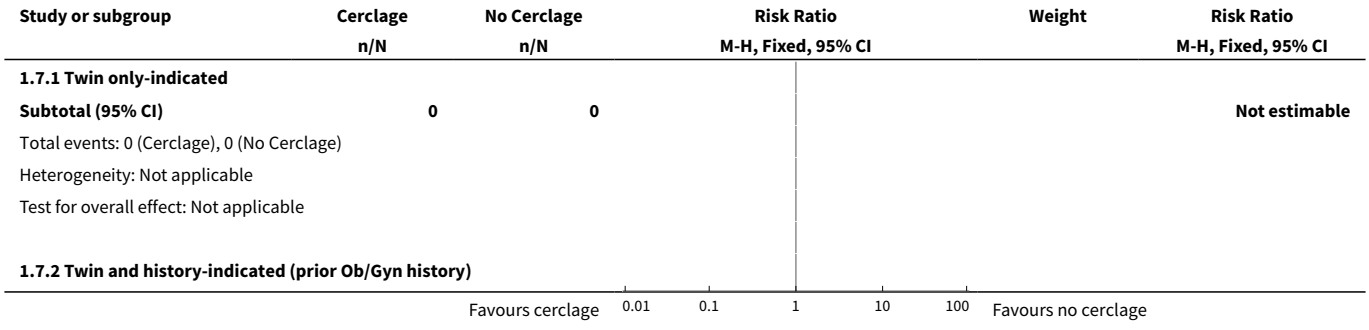


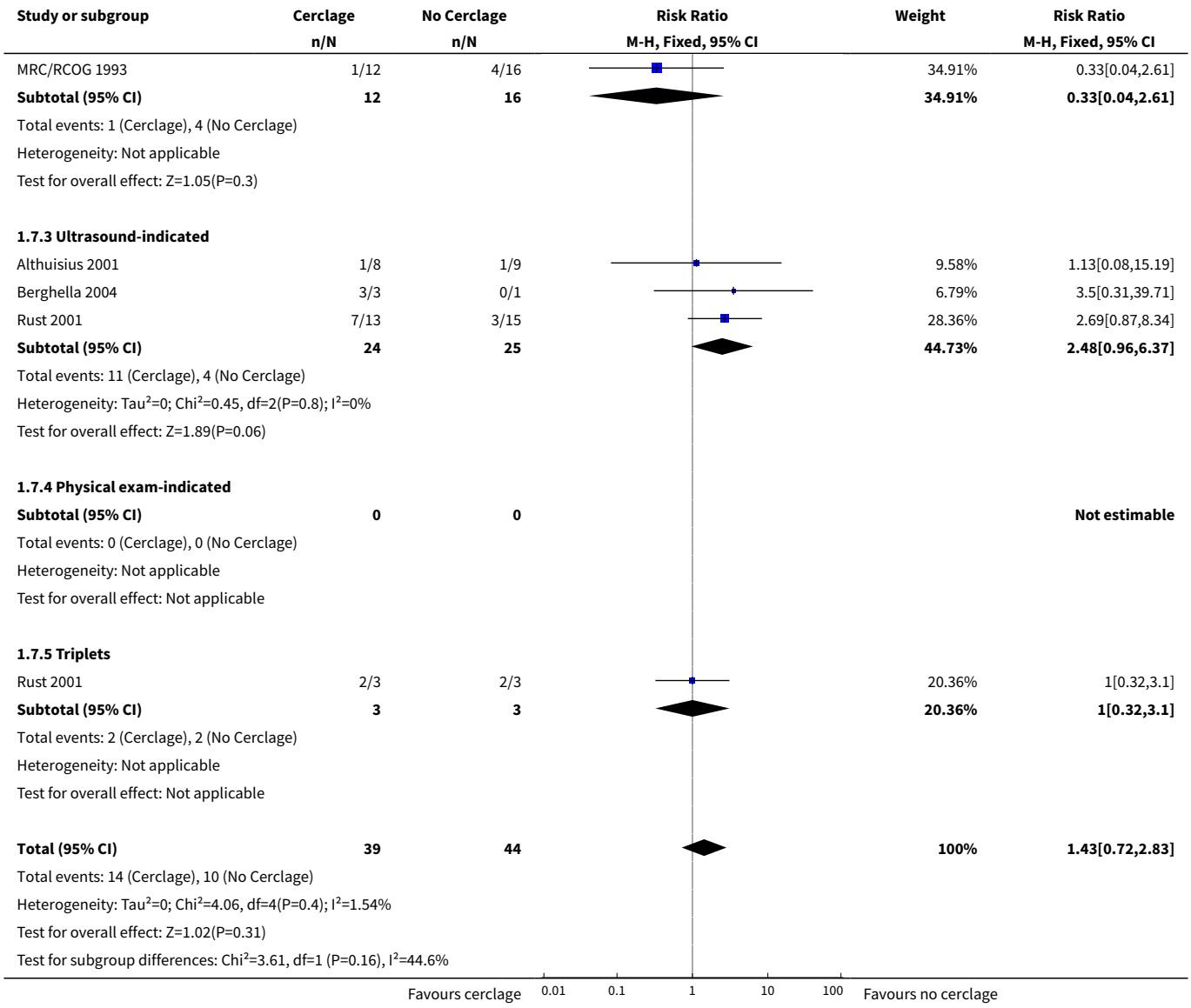
Analysis 1.6. Comparison 1 Cerclage versus no cerclage, Outcome 6 Preterm birth less than 28 weeks.



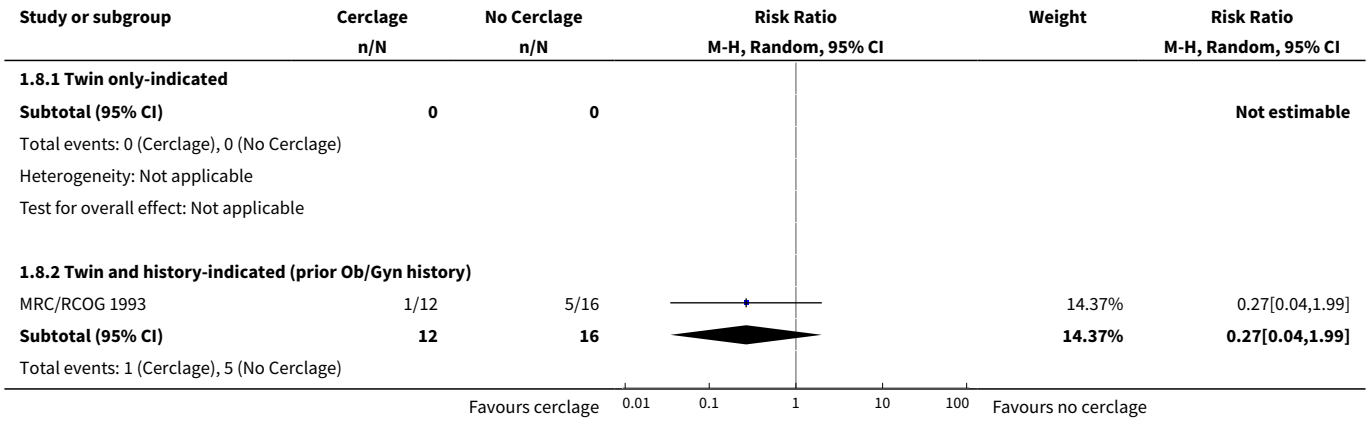


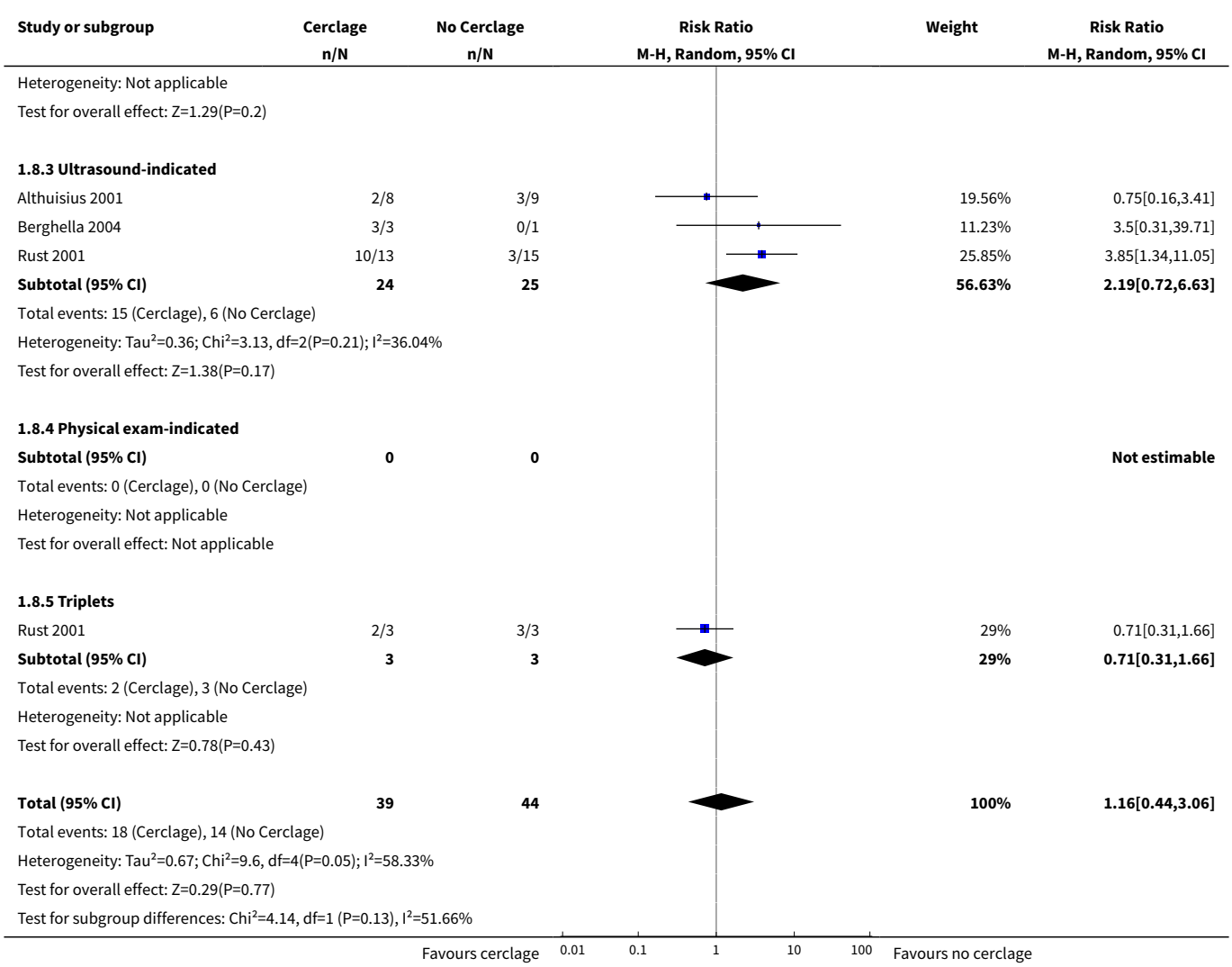
Analysis 1.7. Comparison 1 Cerclage versus no cerclage, Outcome 7 Preterm birth less than 32 weeks.



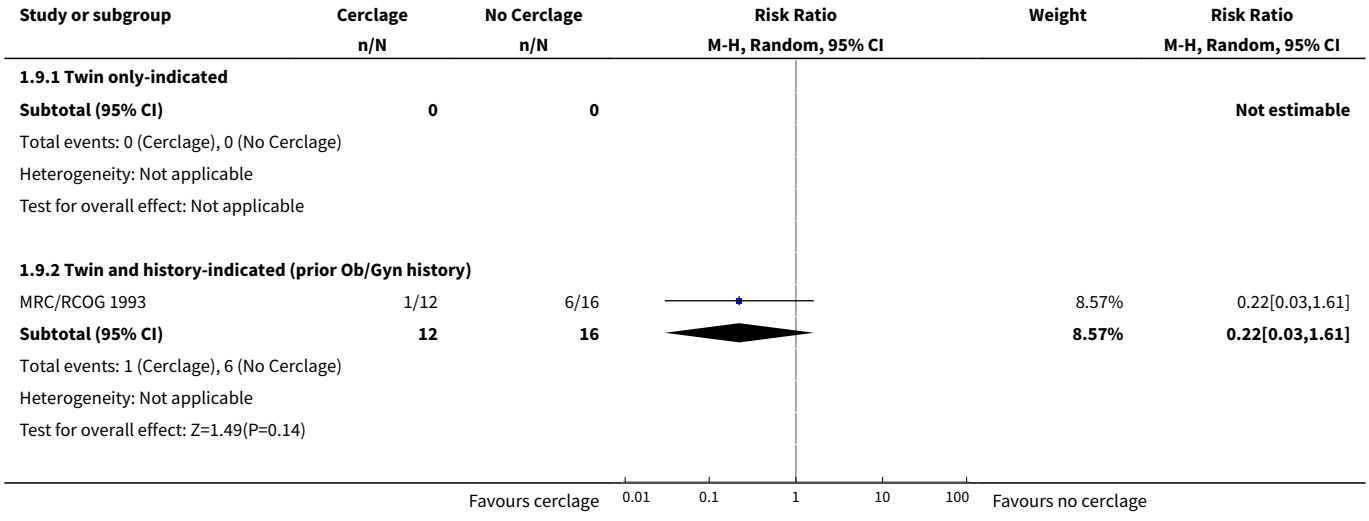


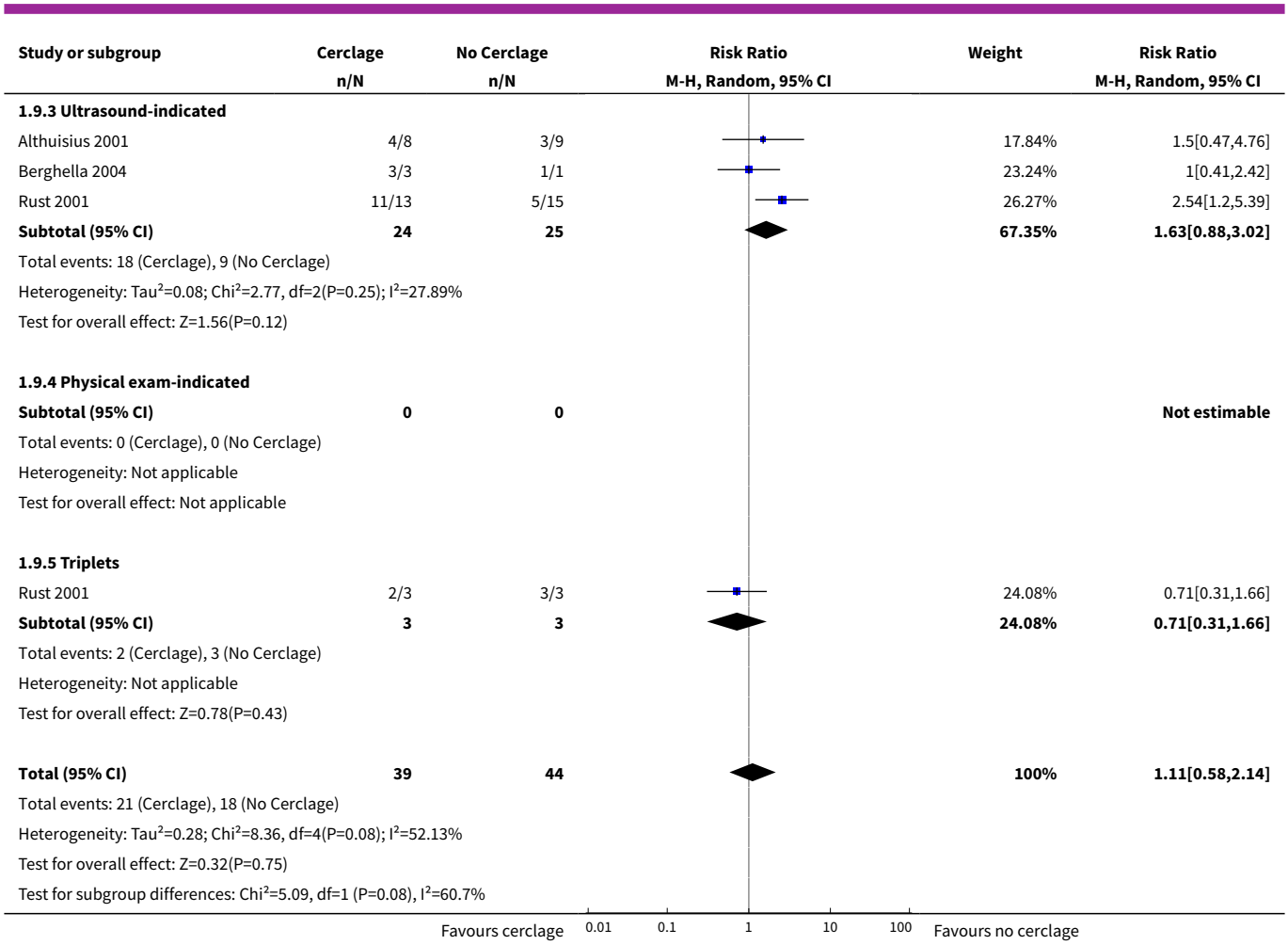
Analysis 1.8. Comparison 1 Cerclage versus no cerclage, Outcome 8 Preterm birth less than 34 weeks.



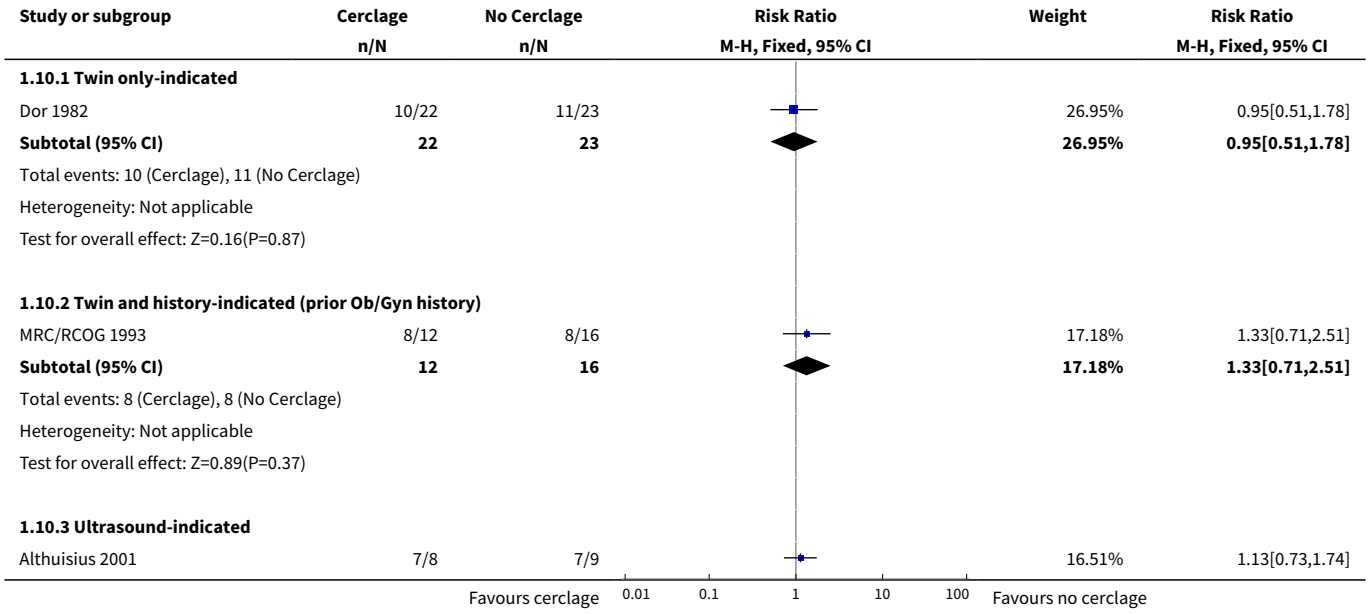


Analysis 1.9. Comparison 1 Cerclage versus no cerclage, Outcome 9 Preterm birth less than 35 weeks.

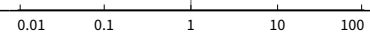




Analysis 1.10. Comparison 1 Cerclage versus no cerclage, Outcome 10 Preterm birth less than 37 weeks.

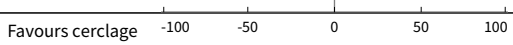


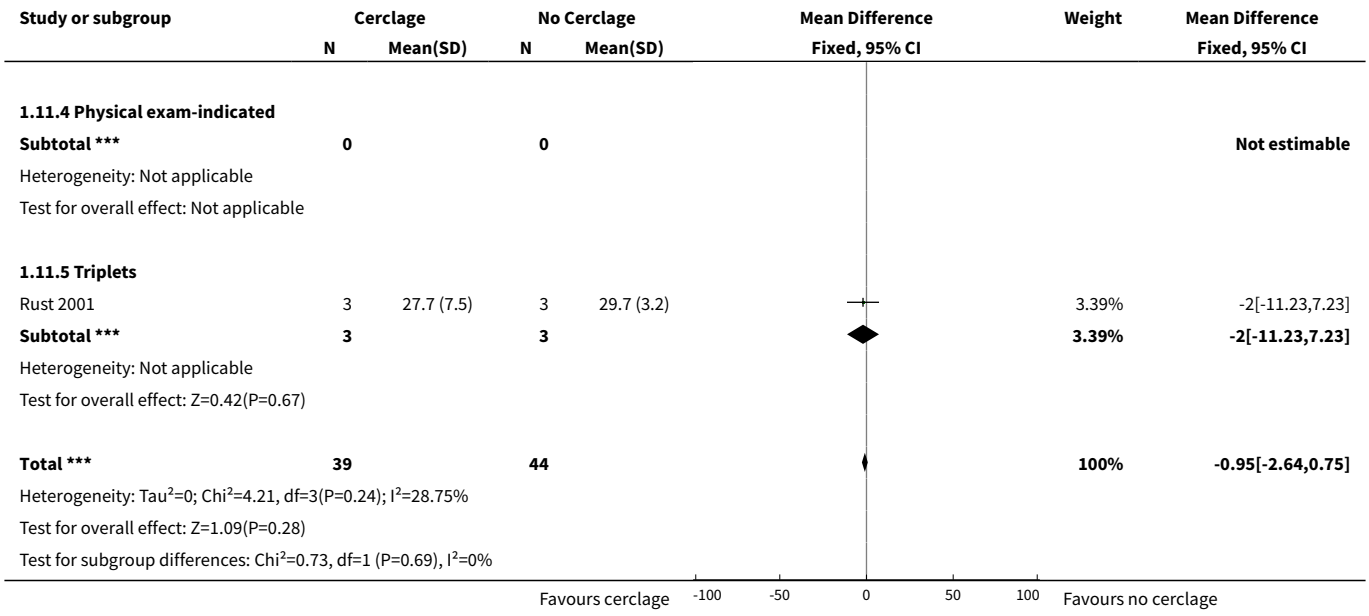
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Berghella 2004	3/3	1/1		5.01%	1[0.41,2.42]
Rust 2001	12/13	11/15		25.59%	1.26[0.89,1.77]
Subtotal (95% CI)	**24**	**25**		**47.11%**	**1.18[0.91,1.53]**
Total events: 22 (Cerclage), 19 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=1.28(P=0.2)					
1.10.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.10.5 Triplets					
Rust 2001	3/3	3/3		8.77%	1[0.59,1.69]
Subtotal (95% CI)	**3**	**3**		**8.77%**	**1[0.59,1.69]**
Total events: 3 (Cerclage), 3 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**61**	**67**		**100%**	**1.13[0.89,1.43]**
Total events: 43 (Cerclage), 41 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=1.22, df=5(P=0.94); I^2=0%					
Test for overall effect: Z=1.03(P=0.3)					
Test for subgroup differences: Chi^2=0.88, df=1 (P=0.83), I^2=0%					



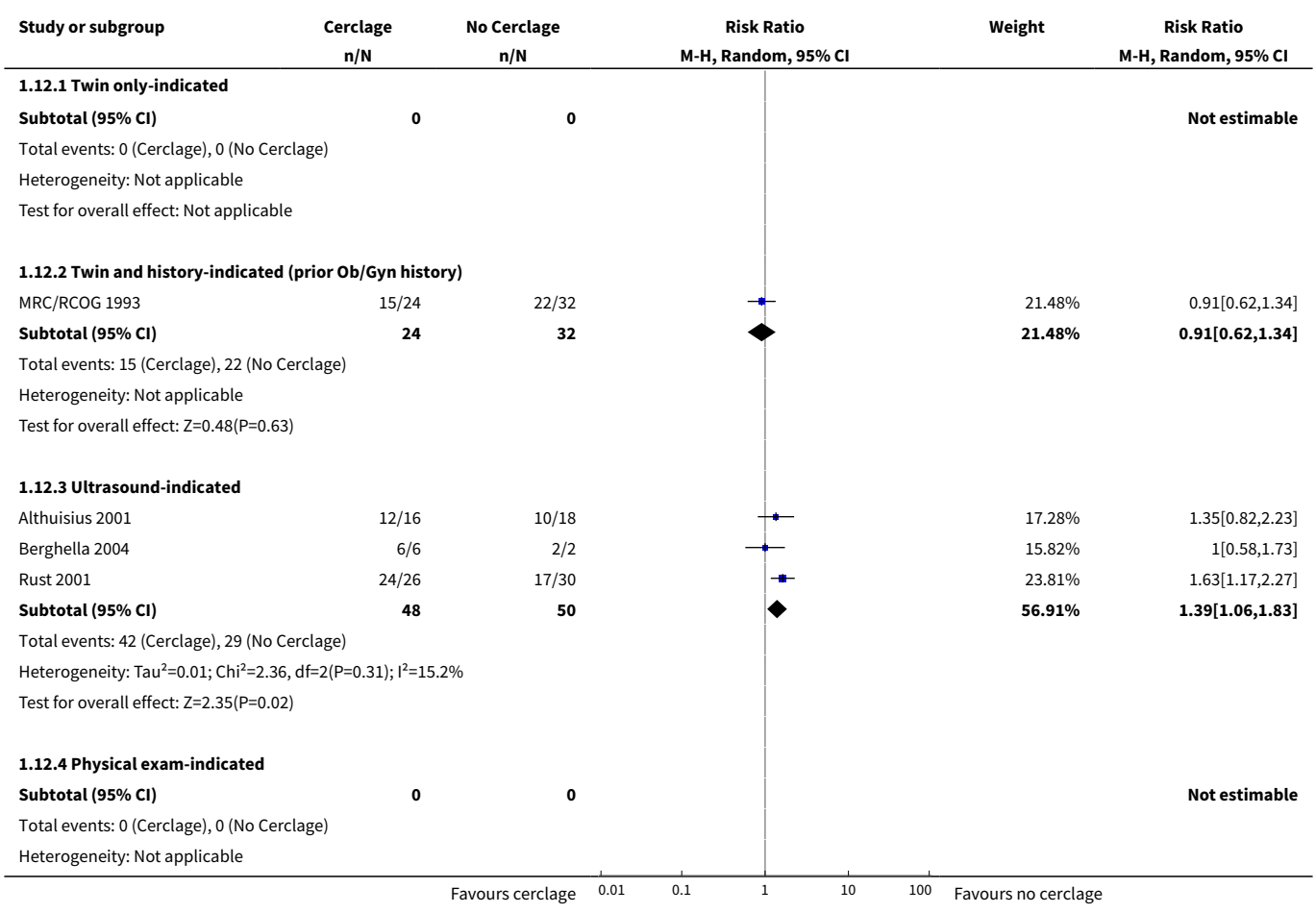
Analysis 1.11. Comparison 1 Cerclage versus no cerclage, Outcome 11 Mean gestational age at delivery.

Study or subgroup	Cerclage N	Cerclage Mean(SD)	No Cerclage N	No Cerclage Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.11.1 Twin only-indicated							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.11.2 Twin and history-indicated (prior Ob/Gyn history)							
MRC/RCOG 1993	12	34.9 (6.2)	16	34.2 (4.7)		16.38%	0.7[-3.5,4.9]
Subtotal ***	**12**		**16**			**16.38%**	**0.7[-3.5,4.9]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.33(P=0.74)							
1.11.3 Ultrasound-indicated							
Althuisius 2001	8	34.8 (2.4)	9	34.9 (2.3)		57.42%	-0.1[-2.34,2.14]
Berghella 2004	3	21 (1)	1	34 (0)			Not estimable
Rust 2001	13	29.8 (5.1)	15	33.9 (4.4)		22.81%	-4.1[-7.66,-0.54]
Subtotal ***	**24**		**25**			**80.23%**	**-1.24[-3.13,0.66]**
Heterogeneity: Tau^2=0; Chi^2=3.48, df=1(P=0.06); I^2=71.25%							
Test for overall effect: Z=1.28(P=0.2)							





Analysis 1.12. Comparison 1 Cerclage versus no cerclage, Outcome 12 Low birthweight defined as less than 2500 grams.



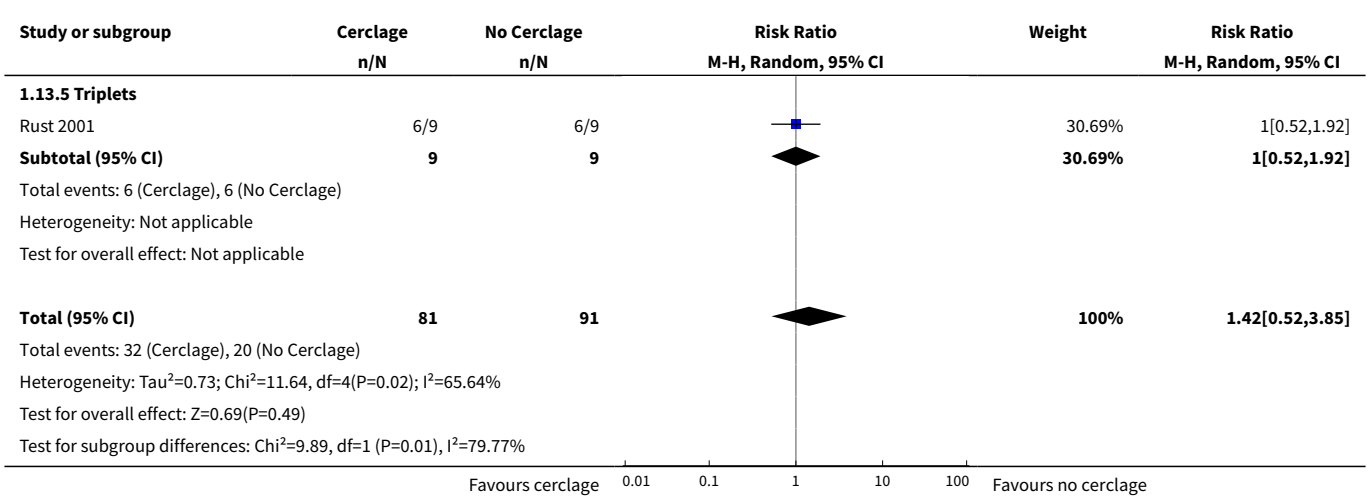
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Not applicable					
1.12.5 Triplets					
Rust 2001	7/9	9/9		21.6%	0.79[0.54,1.16]
Subtotal (95% CI)	**9**	**9**		**21.6%**	**0.79[0.54,1.16]**
Total events: 7 (Cerclage), 9 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
Total (95% CI)	**81**	**91**		**100%**	**1.1[0.82,1.48]**
Total events: 64 (Cerclage), 60 (No Cerclage)					
Heterogeneity: Tau^2=0.07; Chi^2=10.05, df=4(P=0.04); I^2=60.21%					
Test for overall effect: Z=0.64(P=0.53)					
Test for subgroup differences: Chi^2=6.53, df=1 (P=0.04), I^2=69.39%					

Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

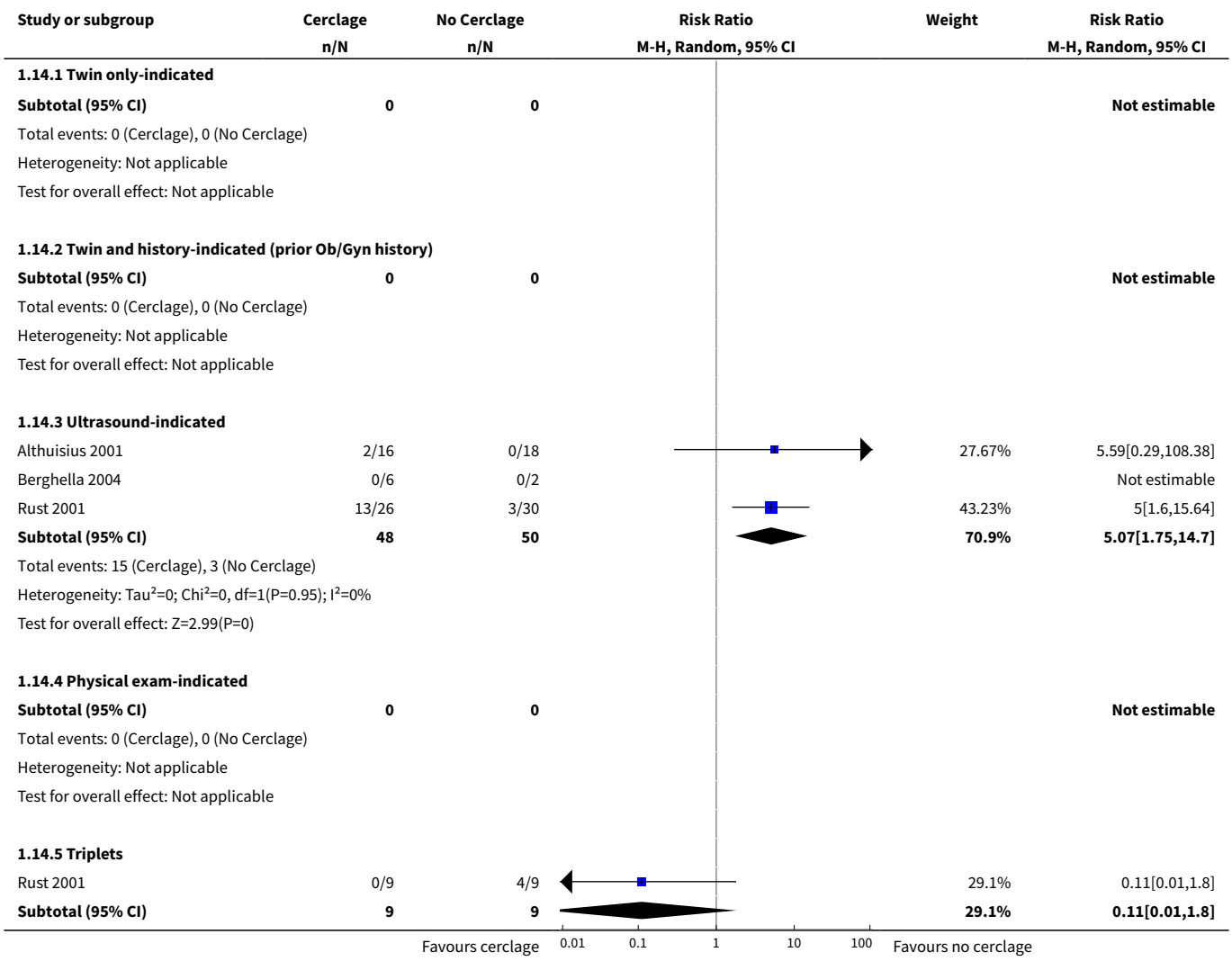
Analysis 1.13. Comparison 1 Cerclage versus no cerclage, Outcome 13 Very low birthweight defined as less than 1500 grams.

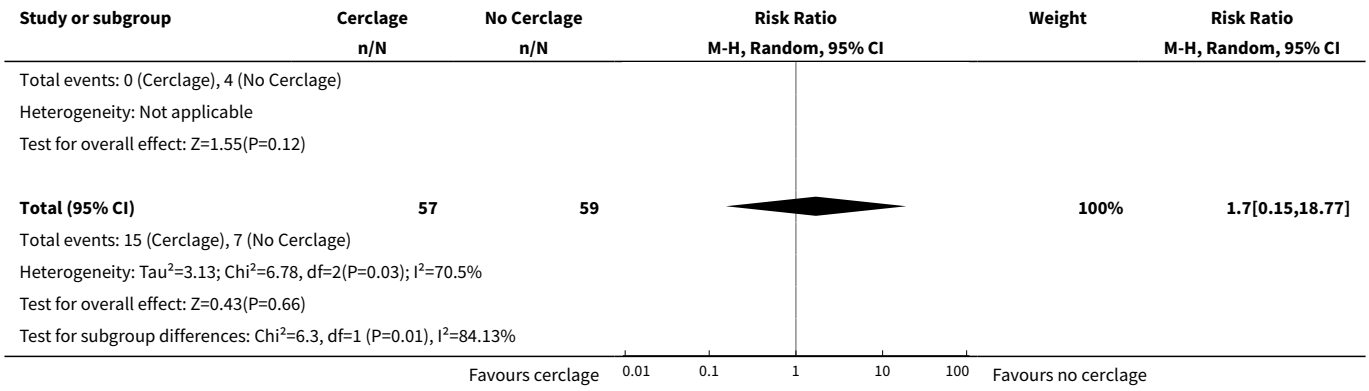
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Twin only-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.13.2 Twin and history-indicated (prior Ob/Gyn history)					
MRC/RCOG 1993	1/24	7/32		14.37%	0.19[0.03,1.45]
Subtotal (95% CI)	**24**	**32**		**14.37%**	**0.19[0.03,1.45]**
Total events: 1 (Cerclage), 7 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.6(P=0.11)					
1.13.3 Ultrasound-indicated					
Althuisius 2001	2/16	2/18		16.04%	1.13[0.18,7.09]
Berghella 2004	6/6	0/2		10.75%	5.57[0.44,70.55]
Rust 2001	17/26	5/30		28.16%	3.92[1.68,9.16]
Subtotal (95% CI)	**48**	**50**		**54.94%**	**3.31[1.58,6.91]**
Total events: 25 (Cerclage), 7 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=3.18(P=0)					
1.13.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

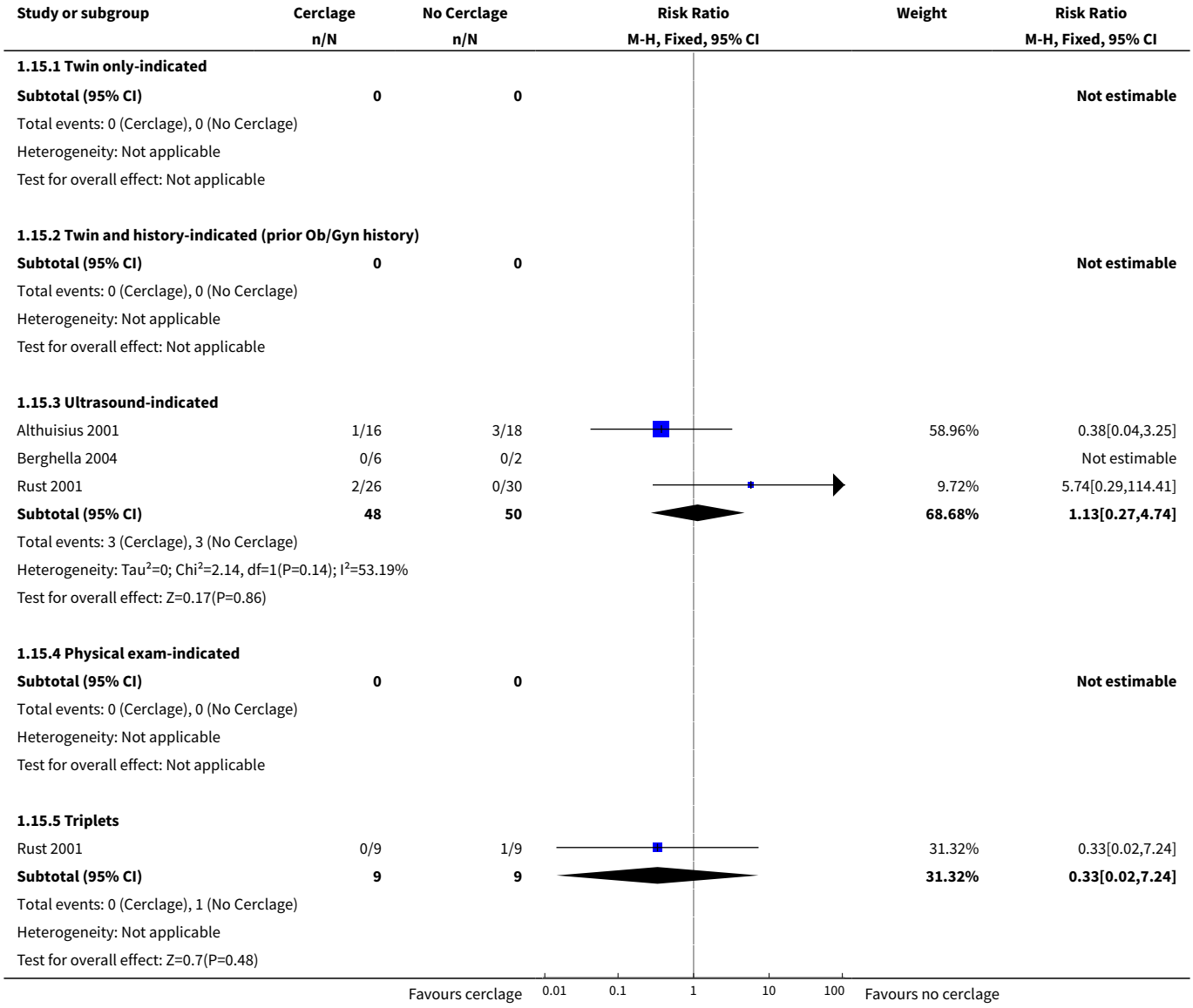


Analysis 1.14. Comparison 1 Cerclage versus no cerclage, Outcome 14 Respiratory distress syndrome (defined by trialists).





Analysis 1.15. Comparison 1 Cerclage versus no cerclage, Outcome 15 Intraventricular hemorrhage (defined by trialists).



Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**57**	**59**		**100%**	**0.88[0.25,3.12]**
Total events: 3 (Cerclage), 4 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=2.49, df=2(P=0.29); I^2=19.75%					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi^2=0.5, df=1 (P=0.48), I^2=0%					

Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Analysis 1.16. Comparison 1 Cerclage versus no cerclage, Outcome 16 Necrotising enterocolitis (defined by trialists).

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Twin only-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.2 Twin and history-indicated (prior Ob/Gyn history)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.3 Ultrasound-indicated					
Althuisius 2001	0/16	0/18			Not estimable
Berghella 2004	0/6	0/2			Not estimable
Rust 2001	0/26	0/30			Not estimable
Subtotal (95% CI)	**48**	**50**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.5 Triplets					
Rust 2001	0/9	0/9			Not estimable
Subtotal (95% CI)	**9**	**9**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**57**	**59**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					

Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

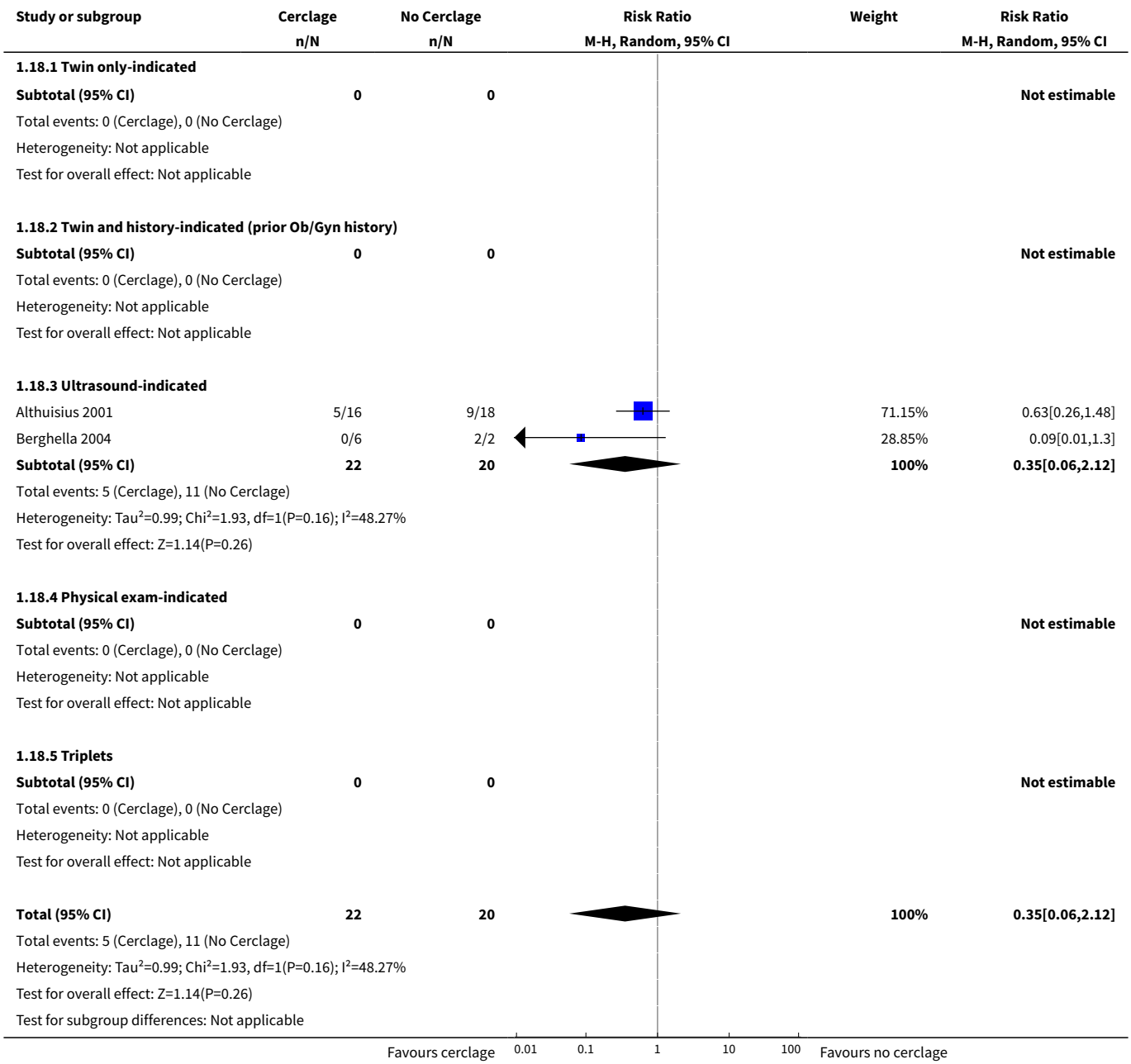
Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Analysis 1.17. Comparison 1 Cerclage versus no cerclage, Outcome 17 Sepsis (defined by trialists).

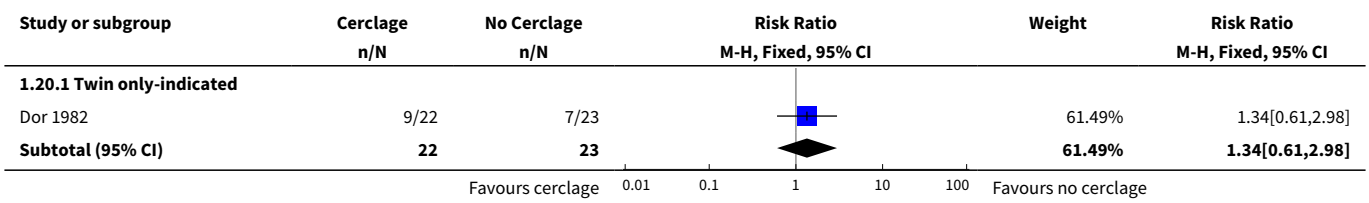
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Twin only-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.2 Twin and history-indicated (prior Ob/Gyn history)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.3 Ultrasound-indicated					
Althuisius 2001	0/16	0/18			Not estimable
Berghella 2004	0/6	0/2			Not estimable
Rust 2001	0/26	2/30		60.81%	0.23[0.01,4.58]
Subtotal (95% CI)	**48**	**50**		**60.81%**	**0.23[0.01,4.58]**
Total events: 0 (Cerclage), 2 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
1.17.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.5 Triplets					
Rust 2001	0/9	1/9		39.19%	0.33[0.02,7.24]
Subtotal (95% CI)	**9**	**9**		**39.19%**	**0.33[0.02,7.24]**
Total events: 0 (Cerclage), 1 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					
Total (95% CI)	**57**	**59**		**100%**	**0.27[0.03,2.31]**
Total events: 0 (Cerclage), 3 (No Cerclage)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.86), I^2=0%					

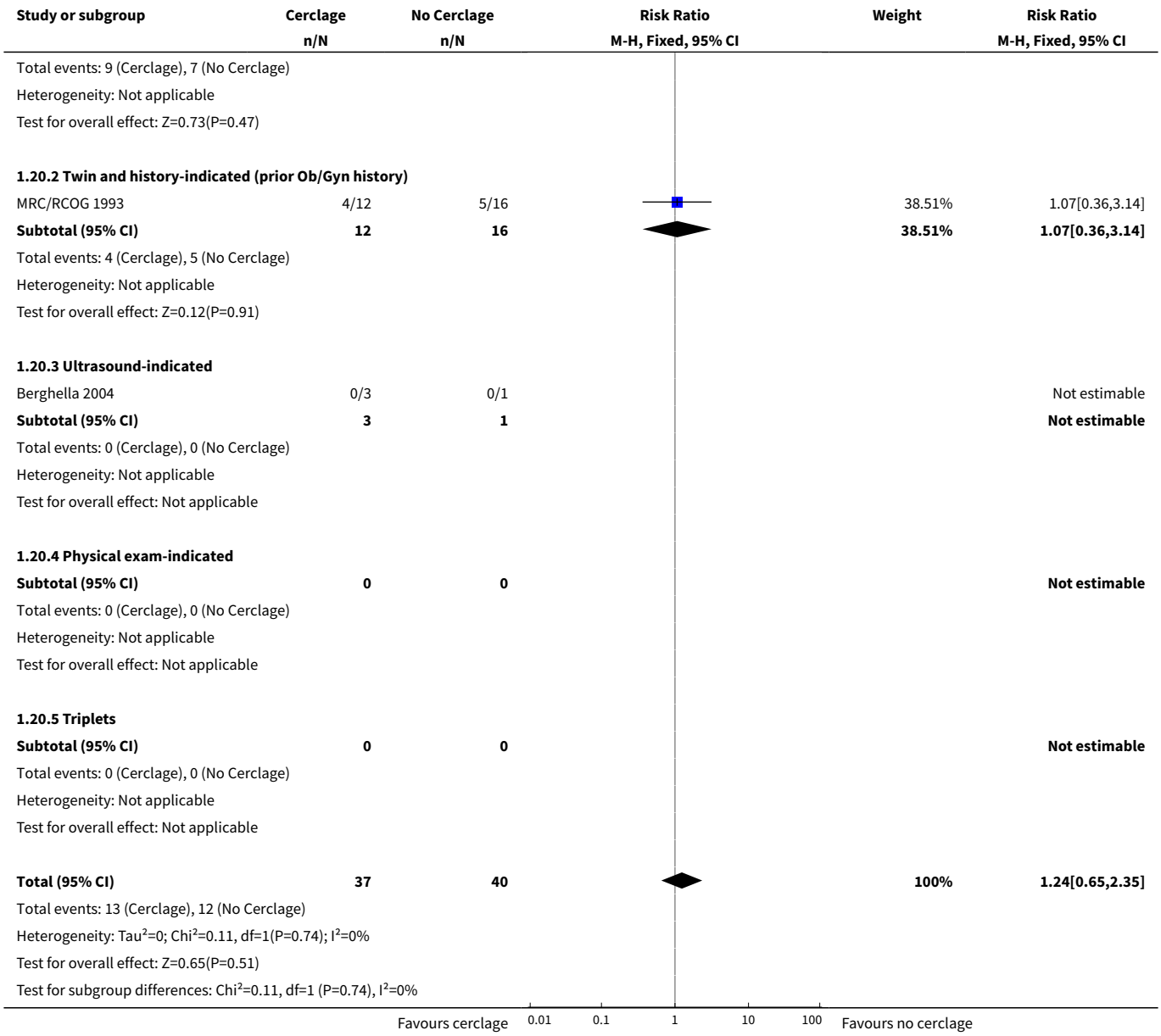
Favours cerclage 0.01 0.1 1 10 100 Favours no cerclage

Analysis 1.18. Comparison 1 Cerclage versus no cerclage, Outcome 18 Neonatal intensive care unit admission.

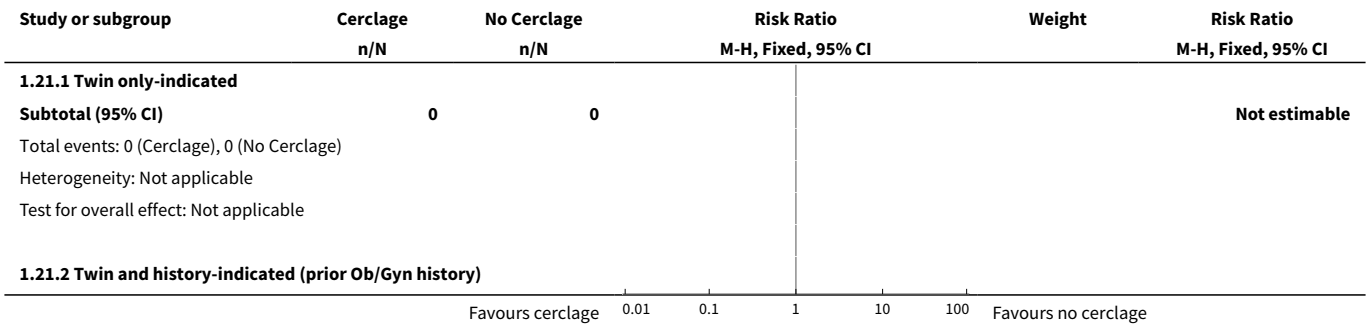


Analysis 1.20. Comparison 1 Cerclage versus no cerclage, Outcome 20 Caesarean section (elective and emergency).

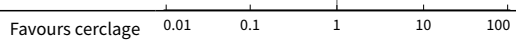




Analysis 1.21. Comparison 1 Cerclage versus no cerclage, Outcome 21 Maternal infection requiring intervention, e.g. antibiotics or delivery (including chorioamnionitis and endometritis).

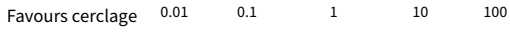


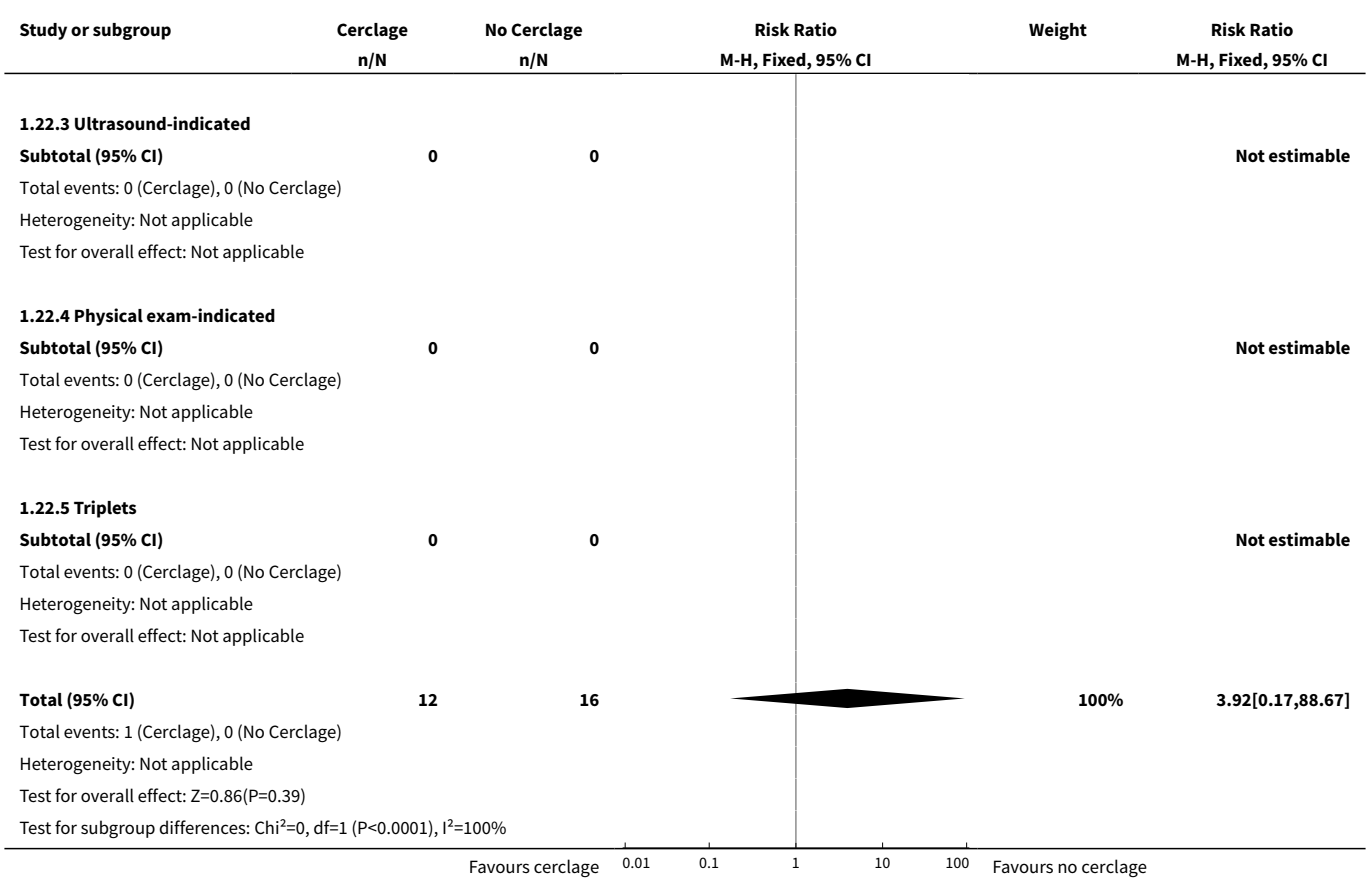
Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
MRC/RCOG 1993	0/12	0/16			Not estimable
Subtotal (95% CI)	**12**	**16**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.21.3 Ultrasound-indicated					
Althuisius 2001	0/8	0/9			Not estimable
Subtotal (95% CI)	**8**	**9**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.21.4 Physical exam-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.21.5 Triplets					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**20**	**25**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



Analysis 1.22. Comparison 1 Cerclage versus no cerclage, Outcome 22 Maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics).

Study or subgroup	Cerclage n/N	No Cerclage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Twin only-indicated					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.22.2 Twin and history-indicated (prior Ob/Gyn history)					
MRC/RCOG 1993	1/12	0/16		100%	3.92[0.17,88.67]
Subtotal (95% CI)	**12**	**16**		**100%**	**3.92[0.17,88.67]**
Total events: 1 (Cerclage), 0 (No Cerclage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					





CONTRIBUTIONS OF AUTHORS

Vincenzo Berghella (VB), the contact person, is the guarantor of the review. The protocol was devised by Zarko Alfirevic (ZA). Design was accomplished by Timothy Rafael (TR), VB, and ZA. All three authors provided co-ordination, methodological prospective, clinical prospective and policy prospective. All three authors contributed to writing the protocol. While all the authors contributed to the review, given that VB is the author of one of the included studies, ZA and TR alone were responsible for assessing studies for inclusion, performing data extraction, data entry and analysis, and assessing risk of biases for this study. All three authors contributed to writing the review.

DECLARATIONS OF INTEREST

While the above authors contributed to the review as stated above, given that VB is the author of one of the included studies, ZA and TR alone were responsible for assessing studies for inclusion, performing data extraction, data entry and analysis, and assessing risk of biases. All three authors contributed to writing the review. No conflict of interest that might be perceived by others as being capable of influencing their judgements, including personal, political, academic and other possible conflicts, as well as financial conflict exist. There are no additional sources of support.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was a modification from the original published protocol, specifically involving comparisons of different cerclage protocols and subgroup analyses, comparing different cerclage protocols, and secondary outcomes.

The original protocol specified subgroup analyses on:

1) high risk for preterm labour (previous history, cervical surgery)
,

2) low risk
, and

3) mixed, or unspecified (general population).

In an attempt to better delineate the various subgroups, and to illustrate clinical applicability by comparing different types of cerclage indications, each group was specified according to the original intent of the cerclage (e.g. twin only-indicated, twin and history-indicated, ultrasound-indicated, physical exam-indicated, and triplets). Along those lines, certain secondary outcomes were also used in subgroup analysis: preterm birth less than 32 and 35 weeks, low and very low birthweight, neonatal intensive care unit admission, and long-term infant neurodevelopmental outcomes. Whilst subgroup analyses are typically restricted to a review's primary outcomes, many of the secondary outcomes were in areas where there had been potential harm demonstrated in other trials, it was therefore felt beneficial to expand the subgroup analyses to these outcomes as well.

INDEX TERMS

Medical Subject Headings (MeSH)

Cerclage, Cervical [*methods]; Pregnancy, Triplet [*statistics & numerical data]; Pregnancy, Twin [*statistics & numerical data]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy