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Alfirevic Z, Stampalija T, Medley N

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[Intervention Review]

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

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ABSTRACT

Background

Cervical cerclage is a well-known surgical procedure carried out during pregnancy. It involves positioning of a suture (stitch) around the neck of the womb (cervix), aiming to give mechanical support to the cervix and thereby reduce risk of preterm birth. The effectiveness and safety of this procedure remains controversial. This is an update of a review last published in 2012.

Objectives

To assess whether the use of cervical stitch in singleton pregnancy at high risk of pregnancy loss based on woman's history and/or ultrasound finding of 'short cervix' and/or physical exam improves subsequent obstetric care and fetal outcome.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (30 June 2016) and reference lists of identified studies.

Selection criteria

We included all randomised trials of cervical suturing in singleton pregnancies. Cervical stitch was carried out when the pregnancy was considered to be of sufficiently high risk due to a woman's history, a finding of short cervix on ultrasound or other indication determined by physical exam. We included any study that compared cerclage with either no treatment or any alternative intervention. We planned to include cluster-randomised studies but not cross-over trials. We excluded quasi-randomised studies. We included studies reported in abstract form only.

Data collection and analysis

Three review authors independently assessed trials for inclusion. Two review authors independently assessed risk of bias and extracted data. We resolved discrepancies by discussion. Data were checked for accuracy. The quality of the evidence was assessed using the GRADE approach.

Main results

This updated review includes a total of 15 trials (3490 women); three trials were added for this update (152 women).

Cerclage versus no cerclage

Overall, cerclage probably leads to a reduced risk of perinatal death when compared with no cerclage, although the confidence interval (CI) crosses the line of no effect (RR 0.82, 95% CI 0.65 to 1.04; 10 studies, 2927 women; *moderate quality evidence*). Considering stillbirths and neonatal deaths separately reduced the numbers of events and sample size. Although the relative effect of cerclage is similar, estimates were less reliable with fewer data and assessed as of low quality (stillbirths RR 0.89, 95% CI 0.45 to 1.75; 5 studies, 1803 women; *low quality evidence*; neonatal deaths before discharge RR 0.85, 95% CI 0.53 to 1.39; 6 studies, 1714 women; *low quality evidence*). Serious neonatal morbidity was similar with and without cerclage (RR 0.80, 95% CI 0.55 to 1.18; 6 studies, 883 women; *low-quality evidence*). Pregnant women with and without cerclage were equally likely to have a baby discharged home healthy (RR 1.02, 95% CI 0.97 to 1.06; 4 studies, 657 women; *moderate quality evidence*).

Pregnant women with cerclage were less likely to have preterm births compared to controls before 37, 34 (average RR 0.77, 95% CI 0.66 to 0.89; 9 studies, 2415 women; *high quality evidence*) and 28 completed weeks of gestation.

Five subgroups based on clinical indication provided data for analysis (history-indicated; short cervix based on one-off ultrasound in high risk women; short cervix found by serial scans in high risk women; physical exam-indicated; and short cervix found on scan in low risk or mixed populations). There were too few trials in these clinical subgroups to make meaningful conclusions and no evidence of differential effects.

Cerclage versus progesterone

Two trials (129 women) compared cerclage to prevention with vaginal progesterone in high risk women with short cervix on ultrasound; these trials were too small to detect reliable, clinically important differences for any review outcome. One included trial compared cerclage with intramuscular progesterone (75 women) which lacked power to detect group differences.

History indicated cerclage versus ultrasound indicated cerclage

Evidence from two trials (344 women) was too limited to establish differences for clinically important outcomes.

Authors' conclusions

Cervical cerclage reduces the risk of preterm birth in women at high-risk of preterm birth and probably reduces risk of perinatal deaths. There was no evidence of any differential effect of cerclage based on previous obstetric history or short cervix indications, but data were limited for all clinical groups. The question of whether cerclage is more or less effective than other preventative treatments, particularly vaginal progesterone, remains unanswered.

PLAIN LANGUAGE SUMMARY

Can inserting a cervical stitch prevent early births of single babies?

What is the issue?

Cervical cerclage is a surgical procedure performed during pregnancy to place a stitch around the neck of the womb (cervix). The stitch is aimed to support the cervix and reduce risk of an early birth.

Why is this important?

The cervix stays tightly closed until towards the end of normal pregnancies, before starting to shorten and gradually soften to prepare for labour and delivery. However, sometimes the cervix starts to shorten and widen too early, causing either late miscarriage or an early birth. Inserting a cervical stitch may reduce the chance of late miscarriage or early birth.

What evidence did we find?

We searched for evidence up to 30 June 2016. This review includes 15 studies involving 3490 women (3 studies involving 152 women were added for this update).

Women with a stitch are less likely to have a baby who is born too early. Babies whose mothers had a stitch are also less likely to die during the first week of life. It is not clear whether a cervical stitch can prevent stillbirth or improve the baby's health once born.

What does this mean?

Inserting a stitch helps pregnant women who are at high risk avoid early births compared to no stitch. Inserting a stitch may also improve a baby's chance for survival. We found too few clinical trials to understand whether cervical stitch is more effective than other treatments for preventing early births, such as progesterone (a hormone drug used to prevent early birth). We found too few data to understand if it is better to have a stitch inserted early in pregnancy (based on the mother's previous history) or to wait to perform an ultrasound scan later in pregnancy to see if the cervix has become shortened.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Cerclage versus no cerclage

Patient or population: preventing preterm birth in women with singleton pregnancy
Setting: Belgium, Brazil, Canada, Chile, France, Greece, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, South Africa, Slovenia, UK, USA, Zimbabwe
Intervention: cerclage
Comparison: no cerclage

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no cerclage (SoF outcomes)	Risk with cerclage				
All perinatal losses	Study population		RR 0.82 (0.65 to 1.04)	2927 (10 RCTs)	⊕⊕⊕◯ MODERATE[1]	
	92 per 1000	75 per 1000 (60 to 96)				
Serious neonatal morbidity	Study population		RR 0.80 (0.55 to 1.18)	883 (6 RCTs)	⊕⊕◯◯ LOW [2]	
	116 per 1000	93 per 1000 (64 to 136)				
Baby discharged home healthy	Study population		RR 1.02 (0.97 to 1.06)	657 (4 RCTs)	⊕⊕⊕◯ MODERATE[3]	
	912 per 1000	930 per 1000 (885 to 967)				
Stillbirths	Study population		RR 0.89 (0.45 to 1.75)	1803 (5 RCTs)	⊕⊕◯◯ LOW [2]	
	19 per 1000	17 per 1000 (9 to 33)				
Neonatal deaths before discharge	Study population		RR 0.85 (0.53 to 1.39)	1714 (6 RCTs)	⊕⊕◯◯ LOW [2]	

	35 per 1000	30 per 1000 (19 to 49)			
Preterm birth before 34 completed weeks	**Study population**		average RR 0.77 (0.66 to 0.89)	2415 (9 RCTs)	⊕⊕⊕⊕ HIGH[4]
	238 per 1000	183 per 1000 (157 to 212)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Wide confidence interval crossing the line of no effect (-1).
[2] Wide confidence interval crossing the line of no effect and small sample size (-2)
[3] Estimate based on small sample size (-1).
4 Random effects model retained from primary analysis; there is no substantive difference in the risk estimate or the confidence intervals with fixed or random effects.

BACKGROUND

Description of the condition

During normal pregnancy the neck of the womb (cervix) stays tightly closed, allowing the pregnancy to reach full term. Towards the end of pregnancy, the cervix starts to shorten and progressively becomes softer (more favourable) - these changes are physiological preparations for normal labour and delivery.

Sometimes, the cervix starts to shorten and dilates too early, causing either late miscarriage or preterm birth. In the absence of uterine contractions, the cause of this pathological condition is considered to be cervical insufficiency (sometimes also called incompetence). The condition has been described as early as the 17th century (Riverius 1658). It has been suggested that cervical insufficiency complicates about 1% of an obstetric population (McDonald 1980) and 8% of a recurrent miscarriage population who have experienced mid-trimester pregnancy losses (Drakeley 1998). There is however, no consistent definition of cervical insufficiency (Berry 1995) which hampers any attempt to establish the true incidence.

Some researchers have defined cervical insufficiency as "the history of painless dilatation of the cervix resulting in second or early third trimester delivery and the passage, without resistance, of size nine Hegar dilator (an instrument which is used to measure the size of cervical dilatation in millimetres)" (Berry 1995). Other descriptions include: recurrent second trimester or early third trimester loss of pregnancy caused by the inability of the uterine cervix to retain a pregnancy until term (Althuisius 2001) and a physical defect in the strength of the cervical tissue that is either congenital (inherited) or acquired, i.e. caused by previous damage (Rust 2000).

Description of the intervention

Cervical cerclage is one of the best known surgical procedures in obstetrics. It involves the positioning of a suture (stitch) around the neck of the womb (cervix), aimed to provide mechanical support to the cervix and keep the cervix closed during the pregnancy.

There are a number of proposed surgical methods designed to keep the cervix closed until the expected time of birth. All interventions require at least regional anaesthesia in the form of a spinal or epidural block. Shirodkar 1955 reported the insertion of a cervical stitch (suture) at around 14 weeks of pregnancy. The anterior vaginal wall is cut and the bladder reflected (pushed) back and upwards allowing an access close to the level of the internal cervical os by the vaginal route. A stitch, usually silk, tape, or other non-absorbable material, is inserted around the cervix, enclosing it. McDonald 1957 described a simpler purse string stitch technique, whereby the stitch is inserted around the body of the cervix visible in the vagina in three or four bites. Athough the internal os is often not reached, the procedure is easier to perform with less bleeding. These techniques were described as elective (planned) procedures.

Total cervical occlusion is another proposed variation where, in addition to the standard cerclage, the external cervical os is closed with continuous nylon (Saling 1984; Secher 2007). The rationale for this technique is based on the observation that the mucous plug has a double role in preventing preterm labour. The plug is a mechanical barrier between the vagina and uterus, but its intrinsic richness in immune components also makes it a very important element in defending the fetal compartment from ascending infections. Intuitively, protective nylon could keep the plug in situ, thereby increasing the innate defence of the cervical canal.

There has been some suggestion recently that suture material may have an important influence on the outcome of pregnancy. However, the surgical methods for cerclage, including the choice of material, are beyond the scope of this review.

Stitches are normally inserted via the vaginal route, but transabdominal cerclage has also been proposed. This approach is used for women when vaginal stitches have failed, or when a woman has a short, scarred cervix making vaginal stitch insertion technically difficult (Anthony 1997; Gibb 1995). Initally, cerclage procedures have been carried out in early pregnancy around 12 weeks of gestation, but are increasingly being scheduled before pregnancy. Either way, during laparotomy, the bladder is reflected downwards away from the uterus and the cervical stitch is placed at the level of the internal cervical os. Vaginally inserted cervical stitches are either taken out at 37 weeks' gestation, or when the woman presents in labour, usually without an anaesthetic. Abdominal cervical stitches are left in place and the baby is delivered by caesarean section.

Cervical cerclage, by whichever technique employed, carries risks for the pregnancy. Surgical manipulation of the cervix can cause uterine contractions, bleeding or infection which may lead to miscarriage or preterm labour. These risks must be carefully balanced against the benefit from mechanical support of the cervix.

Cervical cerclage can either be inserted as a planned procedure based on previous history (history-indicated), because of a short cervical length detected on transvaginal ultrasound (ultrasound-indicated), or as an emergency procedure when women with threatened miscarriage present at the hospital (physical exam-indicated) (Chanrachakul 1998; Wong 1993). Ultrasound- and physical exam-indicated cerclages tend to be performed later in pregnancy; history-indicated procedures are usually planned around 14 weeks.

How the intervention might work

Intuitively, in the presence of a short cervix at ultrasound, or history of recurrent spontaneous mid-trimester losses, reinforcing the cervix by positioning a mechanical support should prolong pregnancy and reduce the risk of preterm birth and its sequelae.

Why it is important to do this review

Controversies concerning cervical cerclage include effectiveness, safety and risk/benefit to both mother and unborn baby. The avoidance of surgical trauma to the cervix may be as effective as intervention. Grant 1989 reviewed the evidence for the benefits and hazards of treatment by cervical cerclage to prolong pregnancy and suggested that cervical cerclage in women with a previous mid-trimester loss (or preterm delivery) may help to prevent one delivery before 33 weeks for every 20 stitches inserted (Grant 1989). Since 1989 there have been a number of randomised and non-randomised studies published, however, the issues surrounding effectiveness in preventing neonatal sequelae of prematurity, timing of cerclage and optimal techniques have not been addressed adequately. The evidence on which to base practice for physical exam-indicated cerclage is even less robust. A meta-analysis estimated the effectiveness of physical examination-indicated cerclage versus expectant management in the setting of second-trimester cervical dilatation (14 to 27 gestational weeks) (Ehsanipoor 2015). The physical examination-indicated cerclage was associated with a significant increase in neonatal survival and prolongation of pregnancy. However, as well as including randomised controlled trials, Ehsanipoor 2015 also included retrospective and prospective cohort studies in the meta-analysis. A previous Cochrane Review on this topic did not find clear benefit, although heterogeneity was high for some important obstetric outcomes. In their meta-analysis of individual patient data, Berghella 2005 concluded that cerclage could be beneficial in women with singleton pregnancies, short cervix and experience of prior preterm birth. In a similar meta-analysis, no statistical significance was found for singleton pregnancies (Jorgensen 2007). Both meta-analyses showed no benefit for multiple gestation pregnancies. In an indirect comparison meta-analysis of randomised controlled trials, Conde-Agudelo 2013 et al found that either cerclage or vaginal progesterone are equally efficacious in the prevention of preterm birth in women with sonographic short cervix in the mid trimester, singleton gestation and previous preterm birth.

A Cochrane Review investigating cervical cerclage for preventing preterm birth in multiple gestation pregnancies has been published (Rafael 2014).

OBJECTIVES

To assess whether the use of cervical stitch in singleton pregnancy at high risk of pregnancy loss based on woman's history and/or ultrasound finding of 'short cervix' and/or physical exam improves subsequent obstetric care and fetal outcome.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing cervical stitch in singleton pregnancies of women considered to be at high risk of pregnancy loss. We planned to include cluster-randomised studies but not cross-over trials. We excluded quasi-randomised studies. We included studies reported in abstract form only.

Types of participants

Women with singleton pregnancies considered to be at high risk for pregnancy loss based any of the following: woman's history (e.g. previous preterm birth); prior cervical surgery (loop excision, cone biopsy, surgical termination of pregnancy); short cervix on ultrasound scanning; or physical exam-detected cervical changes (including emergency or rescue cerclage). Cervical cerclage for multiple pregnancies was investigated in another Cochrane Review (Rafael 2014).

Types of interventions

Cervical stitch in singleton pregnancies considered for women to be at high risk for pregnancy loss.

Comparisons

1. Cervical stitch (cerclage) versus no stitch according to clinical subgroups (history- versus ultrasound- versus physical exam-indicated cerclage).
2. Cervical stitch (cerclage) versus any alternative preventative treatment (e.g. progesterone or pessary).
3. Any comparison of different cerclage protocols (history- versus ultrasound- versus physical exam-indicated cerclage).

Types of outcome measures

We selected outcome domains based on consensus work undertaken to define core outcome measures for clinical research and evidence synthesis for pregnancy and childbirth generally (Devane 2007) and for preterm birth prevention specifically (van 't Hooft 2016).

Primary outcomes

- Perinatal loss: all losses including miscarriages, stillbirth and neonatal deaths.
- Serious neonatal morbidity (as defined by trialists).
- Baby discharged home healthy (without obvious pathology - as defined by trialists).

It may seem unusual to not include preterm birth rates as the primary outcome. In the context of this review, preterm births

should be regarded as 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, an early birth in a setting with adequate neonatal care resources may be better for the infant.

Secondary outcomes

Neonatal

- Stillbirth: intra-uterine death at 24 weeks or more weeks; or greater than 500 g fetal weight or reaching viability as defined by trialist.
- Neonatal death before discharge.
- Miscarriages: perinatal loss before 24 weeks.
- Preterm birth (birth before 28, 34 and 37 completed weeks of pregnancy).
- Serious intracranial pathology, e.g. intraventricular haemorrhage or periventricular leukomalacia (as defined by trialists).
- Serious respiratory morbidity, e.g. respiratory distress syndrome or oxygen dependency after 28 days of life.
- Necrotising enterocolitis requiring surgery.
- Retinopathy of prematurity.
- Apgar less than seven at five minutes.

Maternal

- Caesarean section (elective and emergency).
- Maternal infection requiring intervention, e.g. antibiotics or delivery.
- Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics).

We also planned to report non-prespecified outcomes if they were reported by more than one included trial.

Not prespecified outcomes

- Any intravenous, oral or combined tocolysis.
- Preterm premature rupture of the membranes (PPROM).
- Chorioamnionitis.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (30 June 2016).

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '*Specialized Register*' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

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

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

Searching other resources

We searched the reference lists of the studies identified. We did not apply any language or date restrictions.

Data collection and analysis

Methods used in the previous version of this review are presented in Alfirevic 2012. The following methods were used for this update to assess records identified as a result of the 2016 search.

Selection of studies

Two review authors independently assessed all potential studies identified as a result of the search for inclusion. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a data extraction form. Two review authors extracted data from eligible studies using the form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

When information was unclear, we planned to contact authors of the original reports to provide further details.

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). Any disagreement was resolved 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 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 planned to re-include 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.

(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 is 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 fails 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.

(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 planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, we assessed evidence quality using the GRADE approach as outlined in the GRADE handbook relating to the following outcomes:

1. perinatal loss: all losses including miscarriages, stillbirth and neonatal deaths;
2. serious neonatal morbidity (as defined by trialists);
3. baby discharged home healthy (without obvious morbidity, as defined by trialists);
4. Stillbirth: intra-uterine death at 24 or more weeks or more than 500 g fetal weight or reaching viability as defined by trialists;
5. neonatal death before discharge; and
6. preterm birth before 34 completed weeks of pregnancy.

GRADEpro GDT was used to import data from Review Manager 5.3 (RevMan 2014) to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

We presented results as summary risk ratio with 95% confidence intervals for dichotomous data.

Continuous data

No continuous data were analysed in this review. In future updates, if applicable, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

For this update, we did not include any cluster-randomised trials. If in future updates of the review we find cluster-randomised trials, we will include these trials in the analyses along with individually randomised trials. We will adjust their sample sizes or standard errors using the methods described in the *Handbook* (Section 16.3.4 or 16.3.6) (Higgins 2011) 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. 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 a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not feasible for the population of interest or for interventions relevant to this systematic review.

Other unit of analysis issues

Multiple pregnancy was not eligible for inclusion in this review. Where trials reported both singleton and multiple pregnancy, we used data for women with singleton pregnancies.

Dealing with missing data

Levels of attrition were noted for included studies. In future updates, if more studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored in sensitivity analyses.
Analyses for all outcomes were carried out, 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. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau², I² and Chi² statistics. We regarded heterogeneity as substantial if I² was greater than 30% and either Tau² was greater than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity. If we identified substantial heterogeneity (above 30%), we explained in the text possibly sources of clinical heterogeneity between trials. See also Data synthesis.

Assessment of reporting biases

In future updates, 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.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2014). We used 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 substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects. We also discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau² and I².

Within each comparison, analyses for all outcomes are displayed according to clinical groups (history-indicated, physical-exam indicated, etc). Subgroup analysis was conducted only for comparison of cerclage versus no cerclage.

Subgroup analysis and investigation of heterogeneity

If we found substantial heterogeneity (I² > 30%) for our primary outcomes, and had adequate numbers of included trials in each relevant subgroup, we planned to investigate sources using subgroup analyses to consider whether an overall summary was meaningful, and if so, to use random-effects analysis to investigate.

We planned to carry out the following subgroup analyses for the main comparison (cerclage versus no cerclage). Five potential subgroups were examined: history-indicated cerclage; one-off ultrasound-indicated cerclage in high-risk women, serial ultrasound-indicated cerclage, physical exam-indicated cerclage (rescue cerclage) and one-off ultrasound-indicated cerclage in low or unspecified risk women. There were too few trials in each subgroup to make meaningful conclusions regarding differences in effect in subgroups. Forest plots show trials within the appropriate subgroup for display only.

If in future updates, if we have adequate numbers of trials, we will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). If evidence of subgroup differences are identified, we plan to report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² value.

Sensitivity analysis

For primary outcomes only, we carried out sensitivity analyses to explore the impact of trial quality, assessed as high quality if the trial reported adequate methods for sequence generation and allocation concealment and had no other clear markers of poor trial quality (unacceptable attrition, for example). We reported whether or not the exclusion of studies with substantial risks of bias changed the overall effect estimate or its interpretation.

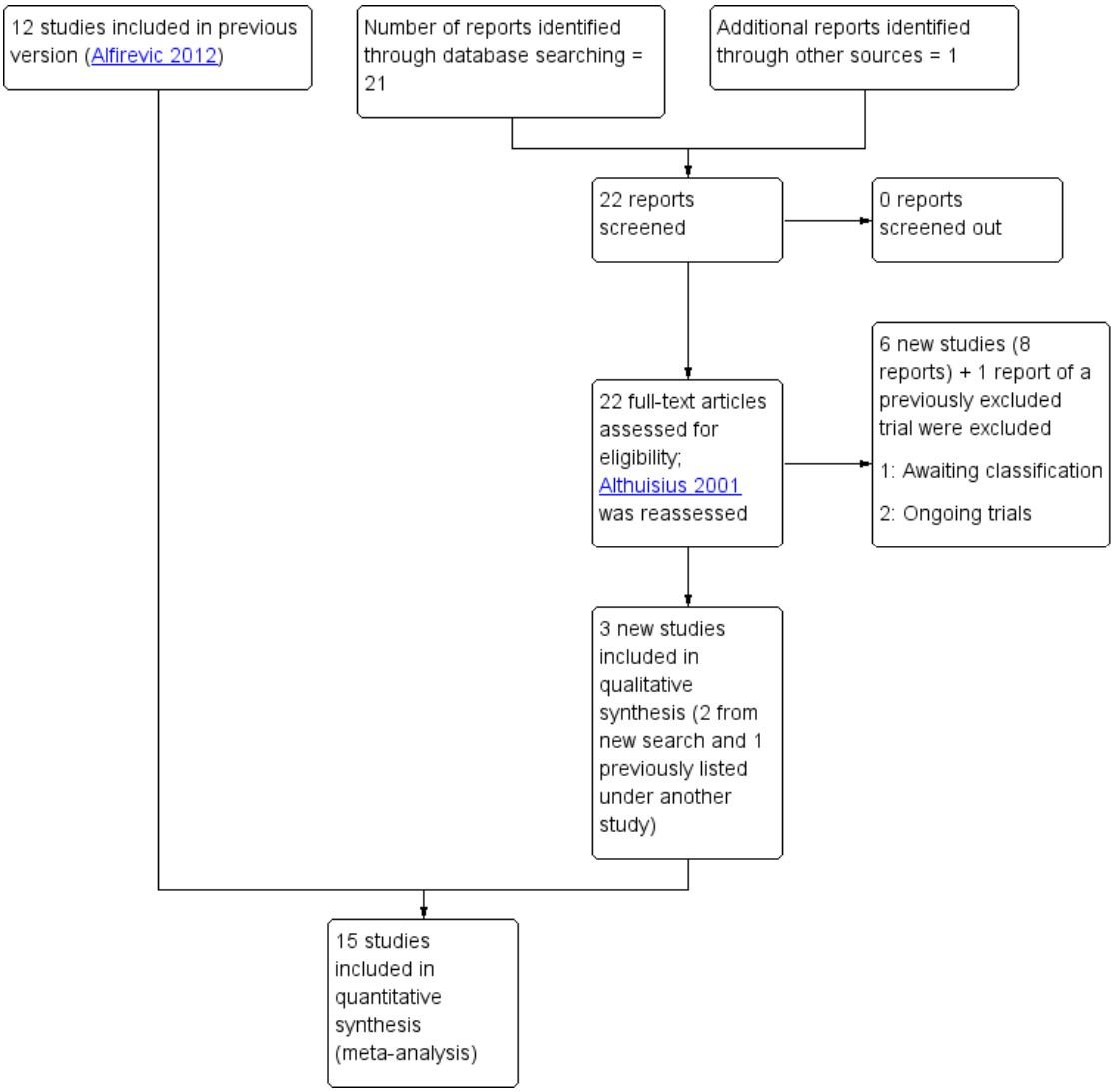
RESULTS

Description of studies

Results of the search

An updated search (June 2016) identified 22 new reports. We also re-assessed Althuisius 2001, and included Althuisius 2003, which had previously been listed as a report of this study. We also included two new studies (five reports) from the 2016 search (Chandiramani 2010; Ionescu 2012), added five additional reports of two already included studies (MRC/RCOG 1993 (1 report); Owen 2009 (4 reports)). We also identified and excluded another report of a previously excluded study (Secher 2007). We excluded six new studies (Hui 2013; Israfil-Bayli 2014 (two reports); Ismail 2014; Üçyiğit 2013 (two reports); Zakhera 2015; Zolghadri 2014). There are two ongoing studies (Hezelgrave 2015; Koulalli 2014) and one study (Ragab 2015) awaiting classification. See Figure 1.

Figure 1. Study flow diagram



Included studies

Interventions

Most included studies (n = 10) compared cerclage versus no cerclage (Althuisius 2001; Althuisius 2003; Berghella 2004; Ezechi 2004; Lazar 1984; MRC/RCOG 1993; Owen 2009; Rush 1984; Rust 2000; To 2004). Of these, two studies required women in both the intervention (cerclage) and control (no cerclage) groups to undertake bed rest (Althuisius 2001; Berghella 2004). Three studies incorporated a rescue arm for women randomised to the control group based on physical exam (Owen 2009) or ultrasound-detected changes of the cervix (Althuisius 2001; Rust 2000).

Two studies compared cerclage versus progesterone for pregnant women with a history of preterm birth undergoing serial ultrasound who developed short cervix (< 25 mm) (Chandiramani 2010; Ionescu 2012). One study compared cervical cerclage versus weekly intramuscular injections of 17 OHP-C (Keeler 2009).

Two studies compared different management protocols for cervical cerclage: elective cerclage based on previous obstetrical history versus cerclage based on cervical changes on serial transvaginal ultrasound scans (Beigi 2005; Simcox 2009).

Setting

Studies took place in many countries including: USA (4), UK (2), France (2), Netherlands (3), South Africa (2), Brazil, Slovenia, Greece, Chile, Iran, Nigeria, Romania, Hungary, Norway, Italy, Belgium, Zimbabwe, Iceland, Ireland, Belgium and Canada. Two trials took place in multiple countries (MRC/RCOG 1993; To 2004).

Population

Only women at high risk of preterm labour were included in 11 studies. Risk of preterm labour was assessed based on previous obstetrical history (n = 5; Beigi 2005; Ezechi 2004; MRC/RCOG 1993; Rush 1984; Simcox 2009) and serial ultrasound scans (Owen 2009). Lazar 1984 used a mixed scoring system based on obstetrical history, serial ultrasound scans of the cervix and physical exam. Althuisius 2001 assessed risk of preterm labour based on previous obstetrical history in half the population and serial ultrasound scans of the cervix in the other half. Althuisius 2003 assessed women with ultrasound and physical exam. Ionescu 2012 and Chandiramani 2010 included pregnant women with both history of preterm birth and short cervix < 25 mm on serial ultrasound.

To 2004 included an unselected general obstetric population with the need for cerclage assessed using a one-off ultrasound scan. Three studies included a mixed population, with indication for cerclage based either on serial ultrasound scans of the cervix in women at high risk of preterm birth, or a one-off ultrasound scan in women at low risk (Berghella 2004; Keeler 2009; Rust 2000).

Nine studies involved singleton pregnancies only (Althuisius 2001; Beigi 2005; Chandiramani 2010; Keeler 2009; Lazar 1984; Owen 2009; Rush 1984; Simcox 2009; To 2004) and four assessed both singleton and multiple pregnancies (Althuisius 2003; Berghella 2004; MRC/RCOG 1993; Rust 2000). Two trials did not state if only singleton pregnancies were included (Ezechi 2004; Ionescu 2012); however, Ezechi 2004 reported individual patient data for singletons only.

We classified trials according to clinical groups for display purposes only: pregnant women with a history of preterm birth (Beigi 2005; Ezechi 2004; Lazar 1984; MRC/RCOG 1993; Rush 1984; Simcox 2009); pregnant women with one-off ultrasound (To 2004); serial ultrasound (Althuisius 2001; Owen 2009) or using both ultrasound protocols (Berghella 2004; Rust 2000). We included Althuisius 2003 in the physical exam-indicated subgroup. Three trials compared cerclage with natural progesterone (Chandiramani 2010; Ionescu 2012) or 17 OHP-C (Keeler 2009).

See Characteristics of included studies.

Excluded studies

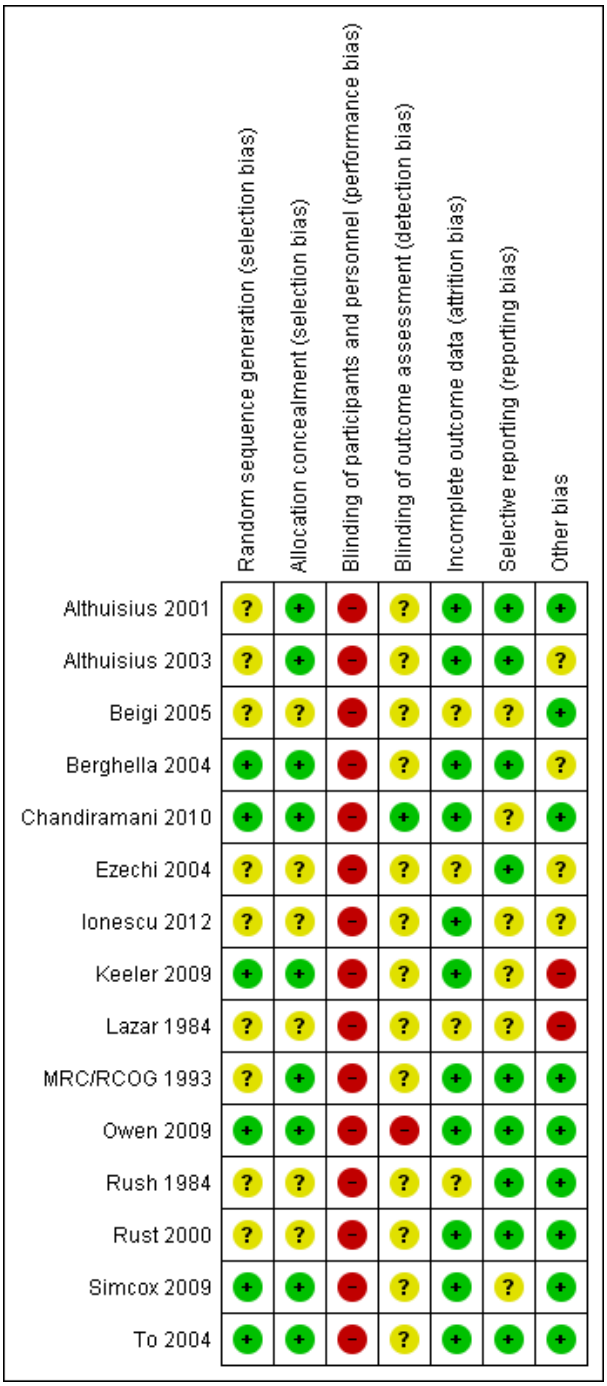
We excluded a total of 17 studies; of these, six were excluded based on assessments for the 2016 search. Three studies included only twin pregnancies (Dor 1982; Nicolaides 2001; Rust 2001); six compared different types of cervical cerclage (Broumand 2011; Caspi 1990; Secher 2007; Tsai 2009; Üçyiğit 2013; Zolghadri 2014). We excluded two studies that did not use adequate randomisation procedures (Kassanos 2001; Von Forster 1986). Blair 2002 compared outpatient cerclage with inpatient cerclage. Hui 2013 compared Arabin pessary with no treatment for women with sort cervix at 20 to 24 weeks' gestation. Three trials compared suture materials (Israfil-Bayli 2014; Ismail 2014). Zakhera 2015 included women for cerclage on the basis of recurrent early bleeding in pregnancy; women did not have a short cervix or history of preterm birth. Varma 1986 is a study protocol, and we doubt that this trial was carried out.

See Characteristics of excluded studies.

Risk of bias in included studies

The overall quality of most studies was good, with adequate reporting of sequence generation, allocation concealment and outcome data. However, several trials had insufficient information in published reports to inform assessment of these key domains. It is not feasible to blind cerclage treatment, and therefore, all trials were assessed at high risk of performance bias due to lack of blinding. We feel that the impact of lack of blinding in trials will vary by outcomes, and we took this into consideration for our GRADE assessments (Characteristics of included studies; Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Six studies reported adequate methods for random sequence generation and concealment allocation (Berghella 2004; Chandiramani 2010; Keeler 2009; Owen 2009; Simcox 2009; To 2004). Allocation concealment was judged as low risk of bias, but sequence generation was unclear in three studies (Althuisius 2001; Althuisius 2003; MRC/RCOG 1993). Six studies had both unclear sequence generation and concealment allocation (Beigi 2005; Ezechi 2004; Ionescu 2012; Lazar 1984; Rush 1984; Rust 2000).

Blinding

Blinding of participants and personnel was not feasible due to the nature of the intervention. Nevertheless, information on attempts to protect against biased assessment of the outcomes (detection bias) was available in one study (Owen 2009). Chandiramani 2010 had adequate blinding for laboratory staff assessing the primary aim of the study (cytokine concentrations).

Incomplete outcome data

Eleven studies adequately addressed the issue of incomplete outcome data assessment (attrition bias) (Althuisius 2001; Althuisius 2003; Berghella 2004; Chandiramani 2010; Ionescu 2012; Keeler 2009; MRC/RCOG 1993; Owen 2009; Rust 2000; Simcox 2009; To 2004). In four studies, the quality of outcome data assessment was judged as unclear (Beigi 2005; Ezechi 2004; Lazar 1984; Rush 1984). Only a few studies provided information on the number of women approached to take part in the study, the number eligible for inclusion, and the overall refusal rate. Although not sources of bias, high exclusion and refusal rates may affect the generalisability of findings and interpretation of results.

Selective reporting

With one exception(To 2004), trial protocols were not available to inform assessment of prespecified primary and secondary outcomes. Despite this, we judged nine studies to be free of selective reporting on the basis that prespecified data extraction forms were provided by the authors (Althuisius 2001; Althuisius 2003; Berghella 2004; Ezechi 2004; MRC/RCOG 1993; Owen 2009; Rush 1984; Rust 2000; To 2004). Selective reporting was judged as unclear in the remaining included studies (Beigi 2005; Chandiramani 2010; Ionescu 2012; Keeler 2009; Lazar 1984; Simcox 2009).

Other potential sources of bias

We assessed 10 studies to be free of other sources of bias (Althuisius 2001; Althuisius 2003; Beigi 2005; Chandiramani 2010; MRC/RCOG 1993; Owen 2009; Rush 1984; Rust 2000; Simcox 2009; To 2004); three studies were judged as unclear (Berghella 2004; Ezechi 2004; Ionescu 2012). Two studies were stopped early and considered to be of high risk of bias (Keeler 2009; Lazar 1984).

Sensitivity analyses

To determine which studies to exclude in sensitivity analyses based on their quality, we referred to both adequate (low risk of bias) labelled sequence generation and adequate (low risk of bias) allocation concealment as essential criteria for adequate quality. If there were obvious additional sources of risk of bias, such as unacceptable attrition or the was trial stopped early, we also considered these factors. We assessed five studies (Berghella 2004; Chandiramani 2010; Owen 2009; Simcox 2009; To 2004) to be at overall low risk of bias (Figure 2).

Effects of interventions

See: **Summary of findings for the main comparison** Cerclage versus no cerclage

Some trial data included in the analyses for all perinatal losses and baby discharged home healthy outcomes were based on individual patient data meta-analyses published in Jorgensen 2007. Data for some trials may not match the published reports because we obtained data sets from trial authors (see Characteristics of included studies).

The denominator used for the outcomes of neonatal death, baby discharged home healthy and Apgar less than seven at five minutes, was as far as possible, live births (where reported, we subtracted the number of stillbirths and miscarriages from the total number randomised to calculate live births). The denominator for all other outcomes was the total number of participants randomised. The all perinatal losses outcome includes miscarriage, stillbirth and neonatal death events.

Trial effect estimates are reported according to clinical groups based on indication for cerclage (history- or physical-exam indicated) and trial protocol (one-off or serial ultrasound) for Comparison 1. We pooled effect estimates for all analyses where heterogeneity was not substantial and did not formally discuss subgroup interaction tests. The small number of trials in clinical groups means these interaction tests are not valid. Plausible explanations for sources of substantial heterogeneity are provided.

GRADEpro GDT software is unable to analyse data split into clinical groups. Therefore, we collapsed the clinical groups for summary of findings outcomes from Comparison 1 and assessed these in Comparison 5 (Cerclage versus no cerclage (Summary of findings outcomes)).

Comparison 1. Cerclage versus no cerclage

Several trials in this comparison were split according to clinical groups as shown in the forest plots.

Primary outcomes

1.1 All perinatal losses

Cerclage may lead to reduced risk of perinatal death when compared with no cerclage, although the confidence interval (CI) just crosses the line of no effect (RR 0.82, 95% CI 0.65 to 1.04; 10 studies, 2927 participants; moderate-quality evidence; Analysis 1.1).

1.2 Serious neonatal morbidity

Treatment groups had similar rates of serious neonatal morbidity (RR 0.80, 95% CI 0.55 to 1.18; 6 studies, 883 participants; low-quality evidence; Analysis 1.2).

1.3 Baby discharged home healthy

In four trials similar numbers of women with and without cerclage had healthy babies discharged home (RR 1.02, 95% CI 0.97 to 1.06; 4 studies, 657 participants; moderate-quality evidence; Analysis 1.3).

Secondary outcomes

1.4 Stillbirth and 1.6 Miscarriage

There was no evidence that cerclage had an impact on rates of stillbirth (RR 0.89, 95% CI 0.45 to 1.75; 5 studies, 1803 participants; low-quality evidence; Analysis 1.4) or miscarriage (RR 0.84, 95% CI 0.58 to 1.22; 7 studies, 2091 participants; Analysis 1.6).

1.5 Neonatal deaths before discharge

There was no clear evidence that cerclage prevented neonatal deaths before discharge (RR 0.85, 95% CI 0.53 to 1.39; 6 studies, 1714 participants; low-quality evidence; Analysis 1.5).

1.7 Preterm birth < 37 weeks, 1.8 Preterm birth < 34 weeks, 1.9 Preterm birth < 28 weeks

Cerclage was associated with reduced risk of preterm births before 37 weeks, with some heterogeneity noted (average RR 0.80, 95% CI 0.69 to 0.95; 9 studies, 2898 participants; I^2 = 39%; Analysis 1.7). Pregnant women who underwent cerclage were also less likely to give birth before 34 weeks' gestation (average RR 0.77, 95% CI 0.66 to 0.89; 9 studies, 2415 participants; high-quality evidence; Analysis 1.8) and also probably less likely to give birth before 28 weeks, although this result was marginal, with the CI meeting the line of no effect (RR 0.80, 95% CI 0.64 to 1.00; 8 studies, 2392 participants; Analysis 1.9).

Reporting of various aspects of neonatal morbidity was inconsistent and meta-analyses showed no clear evidence of an effect from cerclage. There was marginally more respiratory morbidity in the cerclage group (Analysis 1.11), but less intracranial pathology (Analysis 1.10), less necrotising enterocolitis (Analysis 1.12) and less retinopathy of prematurity (Analysis 1.13) with cerclage. None of these differences reached statistical significance.

One small trial reported similar numbers of babies with Apgar score less than seven at five minutes in both treatment arms (RR 0.68, 95% CI 0.40 to 1.15; 301 participants; Analysis 1.14).

1.15 Caesarean section (emergency and elective)

Women with cerclage were more likely to have caesarean sections, although the CI for this result was marginal (RR 1.19, 95% CI 1.01 to 1.40; 8 studies, 2817 participants; Analysis 1.15).

1.16 Maternal side effects

Cervical cerclage was associated with a higher rate of maternal side effects (vaginal discharge and bleeding and pyrexia) although this result did not reach statistical significance and had substantial heterogeneity (average RR 2.25, 95% CI 0.89 to 5.69; 3 studies, 953 participants; I^2 = 66%; Analysis 1.16). An increased risk of pyrexia appears to be a particular problem, with three trials reporting significantly higher rates in cerclage groups (6% versus 2.4%) (RR 2.39, 95% CI 1.35 to 4.23; 1245 participants; Analysis 1.17).

Two small trials reported similar numbers of women receiving any intravenous, oral or combined tocolysis in both arms (RR 1.28, 95% CI 0.80 to 2.05; 2 studies, 217 participants; Analysis 1.18).

1.19 Preterm premature rupture of membranes (PPROM) (not prespecified)

There was no evidence of a difference in the rates of PPROM, although this analysis had substantial heterogeneity (average RR 0.96, 95% CI 0.62 to 1.48; 6 studies, 2010 participants; I^2 = 33%; Analysis 1.19).

1.20 Chorioamnionitis (not prespecified)

There were similar group rates of chorioamnionitis showing no evidence of benefit of cerclage, with the exception of Althuisius 2001. However, Althuisius 2001 contributed to substantial heterogeneity in the analysis (average RR 0.84, 95% CI 0.26 to 2.72; 3 studies, 1506 participants; I^2 = 58%; Analysis 1.20).

Subgroup analysis

Where possible, five potential subgroups were examined: history-indicated cerclage; one-off ultrasound-indicated cerclage in high risk women, serial ultrasound-indicated cerclage, physical exam-indicated cerclage (rescue cerclage) and one-off ultrasound-indicated cerclage in low or unspecified risk women. There were too few trials in each subgroup to make meaningful conclusions.

Sensitivity analysis

Three studies were assessed as high quality (Berghella 2004; Owen 2009; To 2004) based on adequate reported methods of sequence generation and allocation concealment. Confidence intervals overlapped for estimates of primary outcomes, and conclusions regarding effect estimates for our primary outcomes did not change when trials of worse quality were removed from analyses (data not shown).

Comparison 2. Cerclage versus vaginal progesterone

Chandiramani 2010 compared cerclage and natural progesterone (Cyclogest) in a small randomised study nested in a larger prospective observational study. All pregnant women underwent serial ultrasound, but only those with a history of preterm birth who developed a short cervix (< 25 mm) at less than 24 weeks' gestation were randomised to receive treatment. Ionescu 2012 randomised pregnant women with short cervix (< 25 mm) at 19 to 24 weeks' gestation; this trial was reported as an abstract only, but received additional information and unpublished data through correspondence with the author. Few data per outcome limit the conclusions that can be made for this comparison.

There was considerable heterogeneity for several outcomes in this comparison. Differences in relative effects may be due to the different trial objectives (the primary outcome in Chandiramani 2010 was cervical cytokines); the dose of progesterone also differed (400 mg/day Chandiramani 2010 and 200 mg/day Ionescu 2012).

There were no group differences detected for any review outcome, apart from greater incidence of PPROM in the cerclage arm in a single small trial (N = 92)(Ionescu 2012).

Primary outcomes

2.1 All perinatal losses

Cerclage and progesterone had similar efficacy to prevent perinatal deaths (RR 0.94, 95% CI 0.36 to 2.48; 2 studies, 108 participants; Analysis 2.1).

2.2 Serious neonatal morbidity

Two small trials reached different conclusions regarding the relative effect of progesterone on serious morbidity (average RR 0.49, 95% CI 0.05 to 4.52; 2 studies, 120 participants; I^2 = 84%; Analysis 2.2).

2.3 Baby discharged home healthy

There were no clear differences in the number of babies who went home healthy (RR 0.97, 95% CI 0.88 to 1.07; 2 studies, 119 participants; Analysis 2.3).

Secondary outcomes

2.4 Stillbirth

There were no treatment group differences detected in rates of stillbirth (RR 2.70, 95% CI 0.12 to 62.17; 2 studies, 128 participants; Analysis 2.4).

2.5 Neonatal deaths before discharge

There were no treatment group differences detected for rates of neonatal death (RR 2.18, 95% CI 0.34 to 13.86; 2 studies, 120 participants; Analysis 2.5).

2.6 Miscarriages

Similar numbers of pregnant women miscarried in each treatment group (RR 0.58, 95% CI 0.17 to 2.01; 2 studies, 128 participants; Analysis 2.6).

2.7 Preterm birth < 37 weeks, 2.8 Preterm birth < 34 weeks, 2.9 Preterm birth < 28 weeks

Data were sparse, and results for preterm birth at all time points showed no evidence of a difference between treatments: preterm birth < 37 weeks (RR 1.16, 95% CI 0.64 to 2.08; 2 studies, 128 participants; Analysis 2.7); preterm birth < 34 weeks (RR 1.01, 95% CI 0.51 to 2.01; 2 studies, 128 participants; Analysis 2.8); preterm birth < 28 weeks (RR 0.92, 95% CI 0.37 to 2.27; 2 studies, 128 participants; Analysis 2.9).

There was no evidence of group differences for the following review outcomes: serious intracranial pathology (intraventricular haemorrhage or periventricular leukomalacia: RR 0.96, 95% CI 0.17 to 5.28; 2 studies, 128 participants; Analysis 2.10); serious respiratory morbidity (respiratory distress syndrome or oxygen dependency after 28 days of life (average RR 0.48, 95% CI 0.04 to 6.41; 2 studies, 128 participants; I^2 = 64%; Analysis 2.11); Apgar less than seven at five minutes (RR 1.90, 95% CI 0.37 to 9.80; 2 studies, 120 participants; Analysis 2.14); caesarean section (average RR 0.67, 95% CI 0.18 to 2.47; 2 studies, 128 participants;

I^2 = 70%; Analysis 2.15); and chorioamnionitis (RR 1.53, 95% CI 0.10 to 23.61; 2 studies, 128 participants; I^2 = 54%; Analysis 2.21).

Ionescu 2012 reported very few events and no group differences for necrotising enterocolitis (RR 3.00, 95% CI 0.13 to 71.78; 92 participants; Analysis 2.12) and retinopathy of prematurity (RR 1.00, 95% CI 0.06 to 15.51; 92 participants; Analysis 2.13).

Ionescu 2012 reported very few maternal side effects (vaginal discharge, bleeding or pyrexia not requiring antibiotics) (RR 3.00, 95% CI 0.32 to 27.79; 92 participants; Analysis 2.17) and no instances of maternal pyrexia in either treatment arm (RR not calculated due to zero events in both arms; 92 participants).

No trials reported maternal infection requiring intervention (antibiotics or delivery).

Progesterone led to fewer women with preterm premature rupture of membranes, although this result was based on a single trial (Ionescu 2012) with few events and small sample size (RR 8.00, 95% CI 1.04 to 61.42; 92 participants; Analysis 2.20).

Sensitivity analysis

There were too few studies in this comparison to conduct sensitivity analysis.

Comparison 3. Cerclage versus intramuscular progesterone

Keeler 2009 (79 participants) compared cerclage with weekly intramuscular injections of 17 α-hydroxyprogesterone caproate in women with a short cervix detected by transvaginal ultrasound scan. The study was interrupted after three years of recruitment because interim analysis did not reveal any obvious differences in obstetric and neonatal outcomes. Therefore the results of this trial must be interpreted with caution (Keeler 2009).

Primary outcomes

3.1 All perinatal losses

There was no evidence of a difference in prevention of perinatal death (RR 1.12, 95% CI 0.58 to 2.16; Analysis 3.1).

3.2 Serious neonatal morbidity

There were similar rates of neonatal morbidity in treatment groups (RR 1.13, 95% CI 0.47 to 2.74; Analysis 3.2).

3.3 Baby discharged home healthy

Similar numbers of healthy infants were reported in both treatment arms (RR 1.17, 95% CI 0.82 to 1.67; Analysis 3.3).

Secondary outcomes

No trials reported the following secondary outcomes: stillbirth, neonatal death before discharge, preterm birth less than 34 weeks, serious intracranial pathology, serious respiratory morbidity, necrotising enterocolitis, retinopathy of prematurity, Apgar less than seven at five minutes, caesarean section, maternal infection, maternal side effects or maternal pyrexia. Keeler 2009 (79 participants) provided data for the following analyses.

3.6 Miscarriages

There was no clear evidence of an impact on the risk of miscarriage (RR 1.47, 95% CI 0.38 to 5.73; Analysis 3.6).

Data were sparse, and results for preterm birth at all time points showed no evidence of a difference between treatments.

3.7 Preterm birth < 37 weeks

Cerclage and intramuscular progesterone were associated with similar risks of preterm birth (RR 0.88, 95% CI 0.60 to 1.30; Analysis 3.7).

3.9 Preterm birth < 28 weeks

There was no clear evidence of group differences for preterm birth less than 28 weeks, although data were few (RR 1.26, 95% CI 0.53 to 2.97; Analysis 3.9).

3.19 Preterm premature rupture of membranes

Pregnant women with cerclage and intramuscular progesterone experienced similar rates of preterm premature rupture of membranes (RR 0.88, 95% CI 0.47 to 1.65; Analysis 3.19).

3.20 Chorioamnionitis

Pregnant women in both treatment groups had similar rates of chorioamnionitis (RR 1.32, 95% CI 0.61 to 2.88; Analysis 3.20).

Sensitivity analysis

There were too few studies in this comparison to conduct sensitivity analysis.

Comparison 4. Cerclage versus pessary

There were no included trials eligible for this comparison and therefore no data for any review outcome.

Comparison 5. Comparisons of different cerclage protocols

Simcox 2009 and Beigi 2005 compared the benefits of two cerclage protocols in women at high risk of preterm birth. In one group, the indication to perform cerclage was based on previous history, in the other women had cerclage only if the cervix was found to be short on transvaginal ultrasound (≤ 20 mm). The trials were not entirely comparable because only 20% of high risk women in Simcox 2009 received cerclage when assigned to elective management (80% were left untreated). Beigi 2005 treated all women; one arm were treated with elective cerclage and the other arm with serial transvaginal sonography followed by ultrasound-indicated cerclage. Of the women randomised to this second arm, 54% received cerclage.

There was no significant difference in any of the primary and secondary outcomes in either of these trials. Miscarriage rate was the only prespecified outcome reported by both trials (Analysis 5.6).

Sensitivity analysis

Simcox 2009 was assessed as a high-quality study, but with only two studies included in this comparison, formal sensitivity analysis based on quality was not appropriate.

Comparison 6. Summary of findings outcomes

We include GRADE assessments in our reporting of Comparison 1; the outcomes reported under this comparison are identical to those above in Comparison 1.

DISCUSSION

Summary of main results

The evidence from 15 included randomised trials demonstrated that, compared with expectant management, the placement of cervical cerclage in women at risk of preterm birth reduced risk of preterm birth.

The key issue is whether such prolongation of pregnancy improves the outcome for the baby; there is a distinct possibility that a baby may be better off after an early birth in a setting with adequate neonatal care resources. The difference in all perinatal losses was not established because the upper limit for the 95% confidence interval (CI) for the pooled effect estimate crossed the line of no effect (RR 0.82, 95% CI 0.65 to 1.04; 10 studies, 2927 participants). Women with cerclage and expectant management had a similar rate of serious neonatal morbidity and a similar chance of having a healthy baby at discharge.

The key question regarding long-term development in terms of neurological and respiratory outcomes was not addressed; most trials did not follow-up mother and baby after discharge from hospital. Data for short-term neonatal morbidity are also sparse because of inconsistencies between trials in terms of how this outcome was defined and reported.

In terms of safety, it is clear that cerclage is associated with a higher rate of maternal side effects, especially pyrexia. However, side effects tend to be self-limiting (vaginal discharge and bleeding) or treatable (pyrexia) and do not appear to put maternal health at risk. The higher rates of caesarean section after cervical cerclage have not been reported previously. This is unsurprising given few participants in primary studies and relatively modest increase in absolute terms (3% absolute risk increase; 95% CI 0.06% to 5.5% increase). The exact mechanism is difficult to establish, but we were mindful that none of the trials was double-blind. The decision to perform caesarean section is very subjective, and therefore, the knowledge of allocated treatment may have been a significant source of bias. It is possible that cervical cerclage causes damage to the cervix that increases the need for caesarean section. However, we also speculate that increased caesarean section is due to biased (more frequent) diagnosis of failed induction or failure to progress in labour when clinicians know that a woman had cervical cerclage earlier in pregnancy.

We prespecified three clinical scenarios based on the indications for cervical cerclage in current clinical practice:

1. history-indicated cerclage - usually because of previous preterm births and sometimes referred to as elective cerclage;
2. cerclage performed because a short cervix is found on transvaginal sonography (one-off ultrasound indicated cerclage and serial ultrasound-indicated cerclage); and
3. physical exam-indicated cerclage, also called emergency or rescue cerclage, when symptomatic women are found to have either significant cervical shortening or cervical dilatation detected on vaginal examination (performed digitally or with speculum).

We found four trials of history-indicated cerclage, five trials of ultrasound-indicated cerclage and one small trial of physical exam-indicated cerclage.

Women with previous preterm birth are often extremely anxious in subsequent pregnancies and there are an increasing number of specialist clinics for these women. The issue of prevention is clearly a hot topic, particularly when a cervix is found to be short on transvaginal sonography. Treatment options include daily vaginal pessaries of natural progesterone (Fonseca 2007; Hassan 2011), weekly intramuscular injections of 17 α-hydroxyprogesterone (Meis 2003), or Arabin pessary (Arabin 2003).

No robust conclusions could be made about cerclage versus alternative interventions such as vaginal and intramuscular progesterone or pessary. Two studies compared cerclage to vaginal progesterone (Chandiramani 2010; Ionescu 2012). These two trials had different objectives (the primary outcome of the Chandiramani

2010 trial was cervical cytokines) and used different dose of progesterone - differences which likely contributed to the significant heterogeneity noted in meta-analyses.

Only Keeler 2009 attempted to compare ultrasound-indicated cerclage with 17 α-hydroxyprogesterone, but this trial was halted prematurely and was too small for any meaningful conclusions to be made. No included trials assessed cerclage versus pessary. These findings underline the necessity of high quality data.

There is also the question of whether it is better to perform a prophylactic procedure electively in early pregnancy, or wait and see if the cervix gets shorter before performing cerclage. Simcox 2009 and Beigi 2005 attempted to answer this question but both studies were quite small and important clinical outcomes were reported inconsistently, precluding meaningful comparisons and conclusions from pooled data. Interestingly, in the Simcox 2009 study only 20% of the women managed without ultrasound scans had cerclage, despite being identified as of high risk. An improved design may have been for women to be randomised only if clinicians were in equipoise whether to perform prophylactic cerclage or wait for ultrasound shortening of the cervix, as was the case in Beigi 2005.

Overall completeness and applicability of evidence

The consistency in the size and direction of effects across all clinical scenarios is reassuring. However, the lack of robust neonatal morbidity data and lack of long-term follow-up studies, in particular, are considerable weaknesses. As the data are emerging that natural vaginal progesterone has a more pronounced protective effect for women with a short cervix (Fonseca 2007; Hassan 2011), the role of cervical cerclage in the prevention of preterm birth remains unclear.

There is often a lot of pressure to perform cervical cerclage in early pregnancy as a prophylaxis for women who have experienced late miscarriage in a previous pregnancy. Unfortunately, the results from Simcox 2009 and Beigi 2005 are inconclusive and further similar studies are urgently needed with strict inclusion criteria and firm management protocols.

We were unable to provide what would be considered as definitive evidence regarding benefits, or harms, associated with rescue cerclage, i.e. cerclage performed when women are found to have a dilated cervix in the second trimester of pregnancy. Published observational data are likely to be biased (Pereira 2007), but consenting and randomising this group of patients is very difficult.

Quality of the evidence

Overall, most included trials were at low risk of bias. Selective reporting of the results is always a concern when trial protocols are unavailable for review. We significantly minimised this risk by asking study authors to provide outcome data for prespecified outcomes, including individual patient data if available. It was particularly gratifying that the response was excellent and additional information was provided by Althuisius 2001; Chandiramani 2010; MRC/RCOG 1993; Owen 2009; Rush 1984; Rust 2000 and To 2004.

Performance bias (blinding of personnel and participants) will always be an issue in cerclage trials; it is not practical to blind participants to the type of treatment. However, several key outcomes (perinatal mortality, serious neonatal morbidity) and gestational age at birth are objective and therefore, unlikely to be influenced by lack of blinding.

For the comparison of cerclage versus no cerclage we assessed six primary and secondary outcomes using GRADE methods. Perinatal deaths evidence was assessed as moderate quality (good quality trials and adequate sample size); we downgraded the evidence one level because the confidence interval just crossed 1. We assessed evidence for preterm birth before 34 weeks' gestation to be of high quality. Evidence for baby discharged home healthy was assessed as moderate quality, downgraded one level due to small sample size. Serious neonatal morbidity, neonatal death and stillbirth were all assessed as low quality due to small sample size and wide confidence intervals crossing the line of no effect.

Potential biases in the review process

We followed the proscribed Cochrane methods for reducing bias in the process of writing a systematic review. We conducted a comprehensive search of the literature and have no reason to believe any relevant trials were left out. We completed study selection, appraisal and data extraction in duplicate.

Agreements and disagreements with other studies or reviews

Systematic reviews

An indirect meta-analysis compared progesterone and cerclage for women with ultrasound-detected short cervix (< 25 mm), singleton pregnancy and history of preterm birth. Treatments were estimated to be of similar efficacy for preventing preterm birth. Compared with placebo or no cerclage, both interventions reduced the risk of preterm birth before 32 weeks and composite perinatal morbidity and mortality (Conde-Agudelo 2013).

A recent network meta-analysis compared use of cerclage, progesterone and pessary. The review included 40 trials and 11,637 women and found pessary ranked best for preterm birth before 37 weeks, followed by progesterone with cerclage not more effective than control. For births before 34 weeks, no single treatment (cerclage, pessary or progesterone) was significantly better than control (Jarde 2016).

An individual patient data meta-analysis comparing cerclage versus no cerclage in patients at high risk of preterm labour did not demonstrate a statistically significant reduction of perinatal loss in the cerclage group (Jorgensen 2007). Furthermore, the main indication for cerclage (obstetric history versus short cervical length) did not influence the effect estimate for pregnancy loss.

A meta-analysis by Berghella 2011a compared cerclage versus no cerclage in a subgroup of women with short cervix and previous preterm delivery. Berghella 2011a reported a significant decrease in preterm births in the cerclage group, together with a significant decrease in composite perinatal mortality and morbidity. When considered individually, perinatal mortality and composite morbidity decreased in the cerclage group (perinatal mortality 8.8% versus 13.8% and composite neonatal morbidity 8.2% versus 14.3% respectively), although statistical significance was not achieved. These data were broadly in accordance with our results. Berghella and colleagues published a separate meta-analysis comparing history-indicated cerclage with ultrasound-indicated cerclage in women at high risk for preterm labour (Berghella 2011b). Berghella 2011b did not identify any differences in terms of preterm birth or perinatal outcomes between management strategies and concluded that women with prior preterm birth may be monitored safely with ultrasound-indicated cerclage. Berghella 2011b suggested that history-indicated cerclage should be reserved for women with three prior early preterm births or second-trimester losses.

Our analysis did not find significant differences in key primary and secondary outcomes; however, we urge caution in interpreting data. Unlike Berghella 2011b, we excluded Kassanos 2001 from our analysis, because this was likely to be a quasi-randomised study. Data from Althuisius 2001 were not included because primary randomisation was to prophylactic cerclage or no treatment. Two included studies comparing history-indicated with ultrasound-indicated cerclage (Beigi 2005; Simcox 2009) are not entirely comparable because in Simcox 2009 only 20% of women randomised to the elective cerclage group received the intervention. For this reason, we feel that it is too premature to conclude that both management strategies are equally safe.

Emergency cerclage

A recent meta-analysis pooled data on the use of emergency cerclage in pregnant women with singleton pregnancy and cervical dilation of at least 0.5 cm. Evidence comparing cerclage with no cerclage from 10 studies (1 randomised controlled trial and 9 cohort studies) and 757 women showed an association between emergency cerclage and improved neonatal survival as well as prolongation of pregnancy for approximately one month (Ehsanipoor 2015).

A retrospective study of 158 pregnant women receiving emergency cerclage for cervical dilation and bulging membranes (mean gestation 21.45 weeks; SD 2.23) reported that cerclage placement led to live birth for 130/158 women. The study authors compared women with dilation > 3 cm and women with dilation < 3 cm; survival, birthweight and suture-to-delivery interval were all greater for women with cervical dilation < 3 cm (Zhu 2015).

Observational evidence

A retrospective, multicentre cohort study examined a specific subset of pregnant women with singleton pregnancy. All included women had a preterm birth before 37 weeks for their first pregnancy. All women had ultrasound-indicated cerclage for short cervix (< 25 mm) during their second pregnancy. At the third singleton pregnancy, women received either history-indicated cerclage or transvaginal ultrasound screening. The cohort study compared outcomes from the third pregnancy; 38 women received cervical length screening and 64 women underwent cerclage. Pregnancy outcomes were similar for women managed with either cerclage or ultrasound, but just under half of women receiving ultrasound screening developed short cervix < 25 mm and required cerclage (Suhag 2015).

Khalifeh 2016 argued for a cervical length screening programme for all pregnant women, with cut-off of < 25 mm as standard; the study authors proposed that such a test is acceptable to women, effective in preventing the prevalent condition of preterm birth, and cost-effective.

AUTHORS' CONCLUSIONS

Implications for practice

Cervical cerclage prevents preterm births, but so does the natural progesterone given vaginally to women with a short cervix, without an increased risk of caesarean section (Romero 2012). However, transvaginal sonography and prolonged treatment with progesterone may not be affordable for all. Also, the progesterone option may be unacceptable to women who have already had a successful pregnancy with cervical cerclage. Therefore, the decision on how best to minimise the risk of recurrent preterm birth in women at risk, either because of poor history or a short or dilated cervix, has to be personalised and based on the clinical circumstances, the skill and expertise of the clinical team and, most importantly, the woman's informed choice.

Implications for research

- Women with a short cervix on transvaginal sonography should be randomised to either cervical cerclage, natural progesterone, neither, or both. It would be important to report separately results for women who had routine transvaginal sonography screening (low risk) and for those who had serial ultrasound scans because of previous preterm birth or other risk factors.

- Further randomised data that includes women with a dilated cervix found on physical examination (digital/speculum) would be welcome.

- We need definitive studies to ascertain whether it is better for women at particularly high risk of preterm birth to have cervical cerclage early (as prophylaxis), or to have serial transvaginal scanning.

All future studies should have neonatal morbidity as the primary outcome on which sample size calculations should be based. Such studies will have more than adequate power to address the impact on preterm births and most safety aspects. Studies that use gestational age as the primary outcome do so primarily to justify the smaller (more feasible) sample size. It is unlikely that these will have adequate power to answer the key question of whether there is a benefit for mother and baby.

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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 - block randomisation. July 1995 to July 2000. University Hospital Vrije Universiteit and Olze Lieve Vrouwe Gastus, Amsterdam
Participants	Eligible participants from 3 populations: • **Group I:** "Women with a previous PTL before 34 weeks of gestation who met clinical criteria for the diagnosis of cervical incompetence or previous PPROM before 32 weeks were allocated to receive a prophylactic cerclage or not in a proportion of 1:2" "TV US follow-up examination of the cervix was performed in both groups. When a patient of the group without prophylactic cerclage had a cervical length of < 25 mm before 27 weeks, a secondary randomisation was performed that allocated women for treatment with therapeutic cerclage with bed rest vs bed rest only". • **Group II:** "Women with a gynaecological history with one or more accepted risk factors for cervical incompetence, such as cold knife conization, exposure to diethylstilbestrol in utero, and uterine anomaly, were followed by TV US of the cervix; and when a cervical length of < 25 mm was found before 27 weeks of gestation, randomisation allocated women to therapeutic cerclage and bed rest vs bed rest only". In both the first and second groups, women were included before a GA of 15 weeks. • **Group III:** "Women who met the inclusion criteria of I and II 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, such as the feeling of pressure low in the abdomen and mucous vaginal discharge and a cervical length of < 25 mm before 27 weeks, were randomised to receive therapeutic cerclage and bed rest vs bed rest only". Women randomised and included in this review came from groups I (N = 18), II (N = 8) and III (N = I0) **Inclusion criteria:** "high risk of PTL as diagnosed by cervical length of < 25 mm before gestational age of 27 weeks." "…cervical length was measured by TV US in women with risk factors or symptoms of cervical incompetence" "only patients with singleton pregnancies were included" **Exclusion criteria:** women with pregnancies complicated by fetal congenital/chromosomal anomalies, PROM, membranes bulging into the vagina, or intrauterine infection in the current pregnancy were not eligible for trial entry
Interventions	Therapeutic cerclage (N = 20) with bed rest compared to **bed rest** only (N = 16). One woman was excluded due to bulging membranes, leaving 19 women in the cerclage group
Outcomes	**Primary:** PTL < 34 weeks, neonatal morbidity defined as admission to NICU and/or neonatal death and neonatal survival **Secondary:** not stated
Notes	Additional information and the database for cross-checking of the published results provided by the first author

Althuisius 2001 (*Continued*)

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 was the random sequence generated
Allocation concealment (selection bias)	Low risk	Telephone randomisation
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 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 patient was excluded because the membrane was bulging into the vagina. Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Full study protocol not available, but prespecified data extraction form provided by authors. Secondary outcome not prespecified in the article
Other bias	Low risk	Study was not stopped early. No baseline imbalance

Althuisius 2003

Methods	RCT - block randomisation. July 1995 to July 2000. University Hospital Vrije Universiteit and Olze Lieve Vrouwe Gastus, Amsterdam This trial recruited women alongside Althuisius 2001 and reported identical methodology

Althuisius 2003 (*Continued*)

Participants	Women were recruited at the same time as for Althuisius 2001. For Althuisius 2003, all women were < 27 weeks' gestation and had imminent preterm birth due to cervical incompetence with membranes bulging at or beyond the cervical os Women were evaluated for trial entry with transvaginal ultrasound and an additional speculum examination when cervical length < 25 mm **Exclusion criteria**: signs of infection including fever, uterine tenderness, fetal tachycardia, leukocytosis, and/or elevated C-reactive protein
Interventions	**Emergency cerclage** (N = 13, 10 singleton and 3 twins): Emergency cerclage (MacDonald) and indomethacin 100 mg suppository 2 hours before and 6 hours after the operation **Bed rest** (N = 10, 6 singleton and 4 twins) Women in both arms received amoxicillin/clavulanic acid 1 g intravenously every 6 hours and metronidazole 500 mg intravenously every 8 hours for 1 week. All women remained hospitalised and on bed rest until 30 weeks' gestation. Cerclage removed on indication or at 37 weeks' gestation One woman had membranes rupture during cerclage placement and the intervention was abandoned
Outcomes	Preterm delivery at < 34 weeks of gestation, compound neonatal morbidity (defined as admission to the neonatal intensive care unit and/or neonatal death), and neonatal survival We did not include deaths in the review outcome of 'neonatal morbidity'
Notes	Data from this trial were not included in previous versions of this review. We included women reported here in the 'physical-exam indicated' subgroup

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Telephone allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. No losses to follow-up
Selective reporting (reporting bias)	Low risk	Stated outcomes are reported

Althuisius 2003 (*Continued*)

Other bias	Unclear risk	Demographics at baseline comparable

Beigi 2005

Methods	RCT. January 2001 to September 2003. Arash Maternity Hospital, Tehran University of Medical Sciences
Participants	**N = 97** **Inclusion criteria:** "singleton pregnancies with an obstetric history of spontaneous midtrimester loss or early preterm delivery (between 15 and 32 weeks) accompanied by painless and progressive dilatation of cervix and/or PROM without preceding contractions, in the absence of other possible causes of midtrimester loss or early PTD were included" **Exclusion criteria:** multiple pregnancies, major fetal defect and intra-uterine fetal death
Interventions	Elective cerclage - cerclage placement at 12 to 15 weeks' gestation versus serial transvaginal sonography of the cervix and cerclage only if indicated by cervical changes. Serial TV sonography of the cervix performed every 2 weeks, beginning at 14 weeks' gestation, and were offered an emergency cerclage placement only if the endocervical canal length shortened to 20 mm or less
Outcomes	**Primary:** GA at delivery. **Secondary:** not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random assignment was performed immediately after inclusion in the trial and women were allocated to receive either an elective cerclage or serial transvaginal sonography of the cervix."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded

Beigi 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Any loss of participants to follow-up at each data collection point: • not stated. Any exclusion of participants after randomisation: • not stated. Was the analysis intention-to-treat? • Not stated
Selective reporting (reporting bias)	Unclear risk	Study protocol not available. Secondary outcome not prespecified in the article
Other bias	Low risk	Study was not stopped early There seemed to be no baseline imbalance

Berghella 2004

Methods	RCT Thomas Jefferson University Hospital from February 1998 until June 2003 and University of Pennsylvania Hospital from February 2002 until June 2003
Participants	**Participants (N = 61)** • "Asymptomatic pregnant women who were identified… To have high risk factors for PTB were screened by TVU of the cervix every 2 weeks between 14 + 0 weeks of gestation and 23 + 6 weeks of gestation". • "twin pregnancies also were screened prospectively". **Inclusion criteria** • Singletons and twins. • High risk for PTD. • Screened twin pregnancies and non screened low-risk women (who were identified incidentally, first on routine trans-abdominal anatomy ultrasound scanning) with trans-vaginal ultrasound criteria for a short cervix were also offered enrolment, with twin pregnancies randomly assigned separately. • Advanced cervical dilatation or membrane 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 multiple gestations. • Previous inclusion in another trial. • Current drug abuse. • Regular contractions that led to PTL after identification of abnormal cervix by US scanning
Interventions	Cerclage with bed rest

Outcomes	**Primary:** • PTB < 35 weeks. **Secondary:** • GA at delivery, PTL, PPROM, interval from enrolment to delivery. • Neonatal outcomes: death; for the survivors, neonatal intensive care nursery admission, days in the NICU, and composite morbidity (any of respiratory distress syndrome, intraventricular haemorrhage (III or IV), NEC, or sepsis
Notes	Additional information and the data base for cross-checking published results provided by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization 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 to participants and personnel
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	No losses of participants. Describe any exclusion of participants after randomisation: • 1 woman was excluded from low-risk group because of current illicit drug abuse; • 14/333 women in the high-risk group were excluded (9 included in another study, 3 with persistent contractions, 2 current illicit drug abuse); • 1/92 woman in twin group was excluded because of current illicit drug abuse. Although not stated, from numbers, study seems to be intention-to-treat
Selective reporting (reporting bias)	Low risk	Full study protocol not available, but pre-specified data extraction form provided by authors

Berghella 2004 (*Continued*)

Other bias	Unclear risk	Study was not stopped early. • 15/26 women in low-risk group declined participation; • 46/333 women in high-risk group declined participation; • 6/92 women in twin group declined participation

Chandiramani 2010

Methods	• Prospective observational study that randomised women to treatment to ensure equal groups. • Aim was to prospectively investigate cervico-vaginal fluid inflammatory markers longitudinally in tandem with cervical length and to examine the influence of cervical cerclage and progesterone treatment. The prospective study investigated cervico-vaginal fluid inflammatory markers and cervical length. Women were randomised to cerclage or progesterone. • June 2006 to November 2008. • Teaching hospitals, London, UK
Participants	1223 women assessed for eligibility; 112 women enrolled for study. 101 allocated to treatment arms **Inclusion criteria**: pregnant women (14 to 24 weeks' gestation) with at least 1 previous preterm delivery and short cervix (< 25 mm) at < 24 weeks' gestation were randomised. Women who did not develop a short cervix served as an additional third arm of controls. We have only included data for randomised women in this review **Exclusion criteria**: multiple pregnancy, previous iatrogenic preterm birth, unable to consent
Interventions	Cerclage versus progesterone; N = 37 • Cerclage arm: 20. • Vaginal progesterone (Cyclogest 400 mg once daily): 17. • "Recruits were initially assessed every 2 weeks by transvaginal cervical length assessment as well as cervico-vaginal fluid and blood sampling between 16 and 28 weeks' gestation." The study then randomly allocated women who developed short cervix < 25 mm before 24 weeks' gestation to either cerclage or progesterone. Women who did not develop short cervix served as controls; we have not used data for controls
Outcomes	Cytokine concentrations in the cervico-vaginal fluid prior to cervical shortening, and before and after the treatment; many obstetric/delivery outcomes were also recorded and not reported in published reports. We obtained data directly from study authors
Notes	Authors: "The study was not designed or powered to directly compare the two treatment groups (e.g. for cytokine concentrations, cervical length or preterm birth), although some exploratory comparisons have been included" Funding: Action Medical Research and Tommy's Charity. Results from this study formed the rationale for the NIHR funded SUPPORT trial comparing progesterone, cerclage and pessary

Chandiramani 2010 (*Continued*)

	4 women in the progesterone group received cerclage for bulging membranes We obtained unpublished individual patient data from the authors for this review from Rachel Tribe, MD. Where events are discrepant between reports, we used data from the data set

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Low risk	Personal communication from authors: allocation concealed in password-protected database. Investigator performing allocations blind to assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind these interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory staff were blind to allocation for the principal aims of the study (cytokine concentrations). It is unclear if those collecting delivery data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman excluded from cerclage arm due to incomplete sample collection
Selective reporting (reporting bias)	Unclear risk	We obtained unpublished outcome data relevant to this review directly from authors
Other bias	Low risk	Personal communication from authors clarified methods and data in published reports

Ezechi 2004

Methods	July 2000 to June 2002. Havana Specialist Hospital Lagos, Nigeria
Participants	• N = 81. • "Women with previous preterm delivery." • Exclusion criteria: not stated
Interventions	Cerclage at 14 weeks of gestation versus no cerclage

Ezechi 2004 (*Continued*)

Outcomes	GA at delivery, birthweight, neonatal admission and outcome, hospital stay and cumulative hospital bill
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The women were randomised into cerclage (cases) and non cerclage (controls) after their consent had been obtained."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description available
Selective reporting (reporting bias)	Low risk	Full study protocol not available, but prespecified data extraction form provided by authors Primary outcome only described in the article
Other bias	Unclear risk	No description available

Ionescu 2012

Methods	RCT (abstract only); unpublished data and additional information obtained from authors Tertiary care obstetrics and gynaecology department at a University Hospital, Romania
Participants	Women were recruited between 19 and 24 weeks' gestation. Pregnant women had a history of 1 or more previous preterm birth (N = 92 randomised); all women also had short cervix detected with serial TVU (< 25 cm) at 19 to 24 weeks' gestation and were randomised to treatment with cerclage or vaginal progesterone Singleton pregnancy only. Exclusion criteria: not stated

Ionescu 2012 (*Continued*)

Interventions	All women: cerclage (N = 46) and progesterone (N = 46). All women with short cervix: Cerclage (N = 46) treatment Shrodikar cerclage. Progesterone (N = 46) 200 mg/day intravaginal capsule of progesterone
Outcomes	Mean GA at delivery; preterm birth < 34 weeks; several other unpublished data obtained directly from author
Notes	Study reported in abstract form only. Data reported as percentages only. Mean GA reported without standard deviations in published abstract. All data used in meta-analyses for this review came directly from trial author This trial followed 92 women with serial TVU. Of these 92, 90% had 1 previous preterm birth; the remaining had more than 1 previous preterm birth

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; no further details
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described but not possible to blind these interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up described. Unpublished data for all 92 women randomised
Selective reporting (reporting bias)	Unclear risk	Not apparent, but study reported in abstract form only. We have obtained unpublished outcome data from authors
Other bias	Unclear risk	Baseline characteristics not described; regimen and dose of progesterone not described in abstract but obtained from authors

Keeler 2009

Methods	RCT. November 2003 to December 2006. Lehigh Valley Hospital Perinatal Testing Center. Pennsylvania, USA
Participants	Participants (N = 79) • "…women …with risk factors for spontaneous PTB were screened with serial transvaginal US beginning at 16 weeks' gestation". "Risk factors for PTB included history of spontaneous PTB, second-trimester pregnancy loss, previous cervical surgery (conization or loop excision), or documented uterine anomaly." • "Also low-risk, asymptomatic singleton pregnancies between 16 and 24 weeks' gestation were screened for evidence of cervical shortening with transabdominal ultrasound as part of routine anatomical survey." • "Patients with ultrasonographic evidence of short cervix, defined as transvaginal CL ≤ 25 mm, were offered enrolment into study". **Exclusion criteria** • "…any known fetal chromosomal or structural anomaly, multiple gestation, known allergy to progesterone, ruptured membranes, vaginal bleeding, evidence of an active intra-amniotic infection (diagnosed clinically or by amniocentesis), prolapse of endocervical membranes beyond the external cervical os, persistent uterine activity accompanied by cervical change, or an obstetrically indicated delivery."
Interventions	McDonald cerclage versus weekly intramuscular injections of 17 OHP-C
Outcomes	**Primary:** spontaneous preterm birth prior to 35 weeks' gestation. **Secondary:** obstetrical complications and neonatal morbidity and mortality • Obstetrical complications: included chorioamnionitis, abruption placentae, PPROM, need for a rescue procedure, days from study enrolment to delivery, and GA at delivery. • Neonatal morbidity was stratified as follows: no morbidity was defined as no NICU admission and routine newborn care; mild morbidity was defined as NICU admission without severe morbidity; severe morbidity was defined as life threatening morbidity including respiratory distress syndrome requiring mechanical ventilation > 24 h, intraventricular haemorrhage, neonatal sepsis, or NEC. • Perinatal death included any stillbirth or neonatal death during the study period
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was accomplished by computer generated assignment…" "The randomisation sequence was secured by administrative stuff until enrolment was terminated."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in sequentially numbered opaque envelopes by a co-

Keeler 2009 (*Continued*)

		ordinator not involved in screening, enrolment, or randomisation." "Randomisation was accomplished by handing out the sequentially numbered opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Due to the intrinsic nature of the study design, there was no masking in this trial."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	• 8/91 participants declined randomisation; • no participants lost to follow-up; • 4/91 patients were excluded (2 PPROM, 2 positive amniocentesis); • Analysis was intention-to-treat
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	High risk	Study was stopped early: "We anticipated randomising 160 patients to allow for attrition during the study. However, the trial was stopped early by the authors because 3 years of recruitment, an interim analysis showed no difference in outcome between treatment groups" No known baseline imbalance

Lazar 1984

Methods	RCT Dates of data collection: not stated. Setting: • 4 obstetric teams used cervical cerclage for "obvious cervical incompetence"; • an initial partial score was established at the first visit, and then recalculated at each visit between 10 and 28 weeks' gestation; • hospitals in France
Participants	N = 506 (268 cerclage, 238 no cerclage) **Inclusion criteria** "The eligibility of the rest was assessed using a scoring system." The scores were established by points given to two kinds of risk factors: "permanent" (factors present before the index pregnancy) and "evolving" (factors that appeared or changed during the pregnancy)."

	"Patients with score ≥ 20 points at the first visit were deemed to be ineligible for the trial. Similarly, low risk patients with scores < 9 at the first or subsequent visits were also deemed to be ineligible. Women became eligible for the entry into the trial as soon as a score of ≥ 9 had been reached, and they remained in the trial whether or not the score subsequently rose to ≥ 20. The target trial population were pregnant women who had a risk of cervical incompetence that was lower than the pregnant women excluded for the following" **Exclusion criteria** • Previous late spontaneous abortion of a living fetus at 14 to 28 weeks. • State of the cervix (cervix torn up to the lateral cul de sac; cervix open including inner os (1 finger width). • Enlargement of uterine isthmus ≥ 1 cm in width demonstrated at hysterogram. • Twin pregnancies
Interventions	Cerclage versus no cerclage
Outcomes	Not specified
Notes	242/268 women in cerclage arm received cerclage; 26 women in no cerclage arm had cerclage

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"…eligible patients were randomly allocated (using prepared envelopes) into…"
Allocation concealment (selection bias)	Unclear risk	"…eligible patients were randomly allocated (using prepared envelopes) into…"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel
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	Losses to follow up not reported. Exclusion of participants after randomisation not reported. Analysis appears to be intention-to-treat "Of the women entered into the trial, 90% received the management to which they had been allocated."
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

Lazar 1984 (*Continued*)

Other bias	High risk	Study stopped early: "It was decided to conduct a first analysis of the data after about 500 patients had been recruited, and to decide in the light of the results whether or not to pursue the trial. The results reported here are those of the first analysis." Baseline imbalance: "Women allocated to the cerclage policy, however, were more likely to have had previous abortions. This difference is largely a reflection of a difference between the experimental and control groups in one of the four centres. Although selection bias may have been operating in this centre we have included data derived from cases and controls managed there because analyses conducted after excluding these patients did not make any difference to the conclusions we have reached after analysing data derived from all four centres."

MRC/RCOG 1993

Methods	RCT - block randomisation. 1981 to 1988. Multicentre - the trial involved more than 200 obstetricians in the UK and 11 other countries: UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, Netherlands, Canada
Participants	Participants (N = 1292): twins and singletons. **Inclusion criteria:** "Women whose obstetricians were uncertain whether to recommend cervical cerclage, most of whom had a history of early delivery or cervical surgery" **Exclusion criteria:** not specified
Interventions	Recommendation to insert suture as soon as possible versus recommendation to avoid the suture
Outcomes	**Primary:** length of pregnancy (deliveries < 33 and < 37 weeks); vital status of the baby at the time of completion of the form **Secondary:** postpartum pyrexia; causes of fetal/neonatal death; indications for CS; usual technique of cervical cerclage
Notes	Additional information and the data base for cross-checking of the published results provided by the authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

MRC/RCOG 1993 (*Continued*)

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 organized in balanced blocks, but no prognostic stratification was used."
Allocation concealment (selection bias)	Low 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 participants and personnel
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	2% participants lost to follow-up. Not stated if participants were excluded of after randomisation Analysis intention-to-treat analysis: 598/647 in cerclage group received cerclage; 49/645 in no cerclage group received cerclage
Selective reporting (reporting bias)	Low risk	Study protocol not available, but the authors provided individual data for independent data extraction
Other bias	Low risk	Study was not stopped early. No baseline imbalance

Owen 2009

Methods	RCT January 2003 to November 2007. 15 ultrasound clinical centres
Participants	Participants (N = 302) "Healthy multiparous women carrying a singleton gestation who enrolled for prenatal care were screened to identify those with at least 1 prior spontaneous preterm birth

	between 17 + 0 and 33 + 6 weeks' gestation." **Inclusion criteria** • "Eligible women consented to serial TV US examinations to measure their cervical length." • "If on any evaluation the cervical length was less than 25 mm, the woman became eligible for randomisation." **Exclusion criteria** • "fetal anomaly, planned history indicated cerclage for a clinical diagnosis of cervical insufficiency, and clinically significant maternal-fetal complications (e.g. fetal red cell iso-immunisation, treated chronic hypertension, insulin-dependent diabetes) that would increase the risk of an indicated preterm birth and potentially confound the primary study outcome." • Uterine anomalies
Interventions	Cerclage versus "Women in the no-cerclage group could receive a physical examination indicated cerclage for acute cervical insufficiency diagnosed on clinical examination"
Outcomes	**Primary** • **"**birth at < 35 weeks' project gestational age." **Secondary** • Rates of birth less than 7 days from randomisation. • Perinatal death defined as either a stillbirth or a postnatal death prior to hospital discharge. • Preterm birth before 37 weeks
Notes	Additional information and data provided by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Centralized random assignment." "Randomization in predetermined blocks was stratified by each centre and qualifying cervical length less than 20 mm vs 20-24 mm." Stratified randomisation sequence was generated by SAS, permuted in blocks of size 2, 4, and 6. There was a 1:1 cerclage to no-cerclage allocation ratio throughout. Early in the study the intent to use progesterone stratification was added
Allocation concealment (selection bias)	Low risk	Centralised randomisation - via the cerclage web site
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Because the cerclage intervention was not masked, managing physicians might infer that the cervical length was less than 25

		mm, but they were otherwise masked to the results of the sonographic evaluations except in cases of complete placenta previa, oligohydramnios, or fetal death." Impossible to blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	At delivery, randomisation assignment may or may not have been known. There was no attempt to blind at delivery
Incomplete outcome data (attrition bias) All outcomes	Low risk	• 1 participant lost to follow-up from cerclage group after randomisation. • 30/1044 exclusions - 16 ineligible on further review and 14 withdrew from trial. • 673/1014 cervical length ≥ 25 mm (23 exclusions: 16 lost or unable to contact; 4 withdrew from trial; 3 became ineligible). • 318/1014 cervical length < 25 mm (16 exclusions: 13 declined randomisation; 2 ineligible at randomisation visit; 1 withdrew from trial). • 302 randomised. • 149 cerclage group: 138/149 received assigned treatment (3 cerclage contraindication; 8 declined to undergo surgery; 1 emergent cerclage revision). • 153 no cerclage group: 139/153 received no cerclage (10 received emergent cerclage; 4 received off-protocol cerclage). • 673/1014 cervical length ≥ 25 mm (23 exclusions: 16 lost or unable to contact; 4 withdrew from trial; 3 became ineligible). • 318/1014 cervical length < 25 mm (16 exclusions: 13 declined randomisation; 2 ineligible at randomisation visit; 1 withdrew from trial). • 302 randomised. • 149 cerclage group: 138/149 received assigned treatment (3 cerclage contraindication; 8 declined to undergo surgery; 1 emergent cerclage revision). • 153 no cerclage group: 139/153 received no cerclage (10 received emergent cerclage; 4 received off-protocol cerclage).

Owen 2009 (*Continued*)

		• 149 cerclage group: 138/149 received assigned treatment (3 cerclage contraindication; 8 declined to undergo surgery; 1 emergent cerclage revision). • 153 no cerclage group: 139/153 received no cerclage (10 received emergent cerclage; 4 received off-protocol cerclage). Analysis was intention-to-treat
Selective reporting (reporting bias)	Low risk	Study protocol not available, but Cochrane data extraction sheet completed by the authors, so any selective reporting unlikely
Other bias	Low risk	Study was not stopped early. Baseline imbalance: 691 participants declined participation; 1044 met initial criteria and consented

Rush 1984

Methods	RCT. 20 January 1979 to 19 April 1982. Reproductive failure clinic at the Groote Schuur Maternity Centre, Peninsula Maternity and Neonatal Service, Capetown, South Africa Women entered the study at 15 to 21 weeks' gestation.
Participants	Participants (N = 194): high-risk women for PTL or late abortion **Inclusion criteria:** 1. 2, 3 or 4 previous pregnancies which has ended spontaneously before 37 completed weeks' gestation; and 2. at least 1 previous pregnancy which ended spontaneously between 14 and 36 completed weeks' gestation. **Exclusion criteria:** age > 35 years; smoking > 5 cigarettes/day; medical disorders (cardiac disease, hypertension, diabetes, thyroid disease); obstetric/gynaecological conditions (recurrent 1st trimester abortions, multiple gestation in present pregnancy, congenital uterine abnormality, uterine fibromyomata, previous cervical surgery - cone biopsy, trachelorrhaphy, cervical cerclage); cervix < 2.0 cm long or dilated at entry
Interventions	Cervical suture versus no suture
Outcomes	Not stated
Notes	Additional information and the data base for cross-checking of the published results provided by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rush 1984 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"…patients were allocated at random either to have a cervical suture (96 patients) or to be managed without a suture (98 patients) by reference to a series of sealed envelopes. "
Allocation concealment (selection bias)	Unclear risk	"…reference to a series of sealed envelopes. "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss of participants not stated. Exclusion of participants after randomisation not stated. Intention-to-treat analysis: "All but two of 194 women entered into the trial received the management to which they were allocated."
Selective reporting (reporting bias)	Low risk	Study protocol not available. The full database was provided by the authors, so any selective reporting unlikely
Other bias	Low risk	Study was not stopped early. Baseline imbalance: "Although the frequency of two or more previous second trimester abortions or preterm deliveries was somewhat greater in women allocated to cerclage, this difference was not statistically significant."

Rust 2000

Methods	RCT. May 1998 to August 2000. Lehigh Valley Hospital Outpatient Perinatal Testing Center. USA
Participants	**Participants (N = 61):** "Any patients between the gestational ages of 16 and 24 weeks with transvaginal ultrasound demonstration of (1) dilatation of the internal os, (2) prolapse 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

Rust 2000 (*Continued*)

	transfundal pressure was considered a candidate for enrolment" **Inclusion criteria:** "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 cm". "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:** "Exclusion criteria included membrane prolapse 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 diagnose of preterm labour), or any other contraindication for a cerclage procedure."
Interventions	McDonald cerclage (N = 31) versus no cerclage (N = 30) All prospective participants had indomethacin and clindamycin before randomisation. Women in the cerclage group had indomethacin and clindamycin for 24 h after the cerclage procedure, while women in the no cerclage group had indomethacin and clindamycin stopped at 24 h after randomisation Women were send home after 24 h and monitored weekly by ultrasound
Outcomes	Perinatal death, neonatal morbidity according to 4 categories: none (routine neonatal care), minimal (intensive care admission with no mechanical ventilation or serious morbidity), serious (mechanical ventilation, respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, sepsis, or other life-threatening morbidity), and perinatal death (stillborn fetus or death during the first 28 days after birth)
Notes	Additional information and the data base for cross-checking of the published results provided by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"If the patients continued to meet inclusion criteria, they were randomly assigned to receive a McDonald cerclage under regional anaesthesia or not cerclage therapy. "
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel

Rust 2000 (*Continued*)

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	Loss of participants: • 135 patients met the inclusion criteria; • 20/135 declined randomisation. Exclusion of participants after randomisation: • 2/135 were excluded because of chorioamnionitis that was diagnosed by amniocentesis. Intention-to-treat analysis: "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	Study protocol not available. The full database was provided by the authors, so any selective reporting unlikely
Other bias	Low risk	Study was not stopped early. No apparent baseline imbalance

Simcox 2009

Methods	RCT. November 2003 to March 2006. 9 UK hospitals
Participants	Participants (N = 248): pregnant women < 24 weeks of gestation **Inclusion criteria:** singleton pregnancy with at least 1 previous spontaneous delivery between 16 + 0 and 34 + 0 weeks **Exclusion criteria:** unable to give informed consent
Interventions	Cerclage based on history "For those women allocated to the history-indicated arm of the trial, a history-indicated suture was offered if the treating clinicians considered that the obstetric history justified a cerclage. There were no prescribed minimum criteria for history-indicated suture insertion. The decision to insert a cerclage or not, based on history, was made in every case before randomisation by the attending clinician, and then carried out if the patient was randomised to history arm" versus

	Cerclage based on serial US scanning "Women allocated to the scanning arm of the trial underwent cervical length assessment by transvaginal US every 2 weeks from entry into the trial until 24 + 0 weeks of gestation. If the cervix shortened to ≤ 20 mm, a cervical cerclage was inserted."
Outcomes	**Primary:** PTD before 34 weeks. **Secondary:** frequency of suture insertion, incidence of histological chorioamnionitis, incidence of maternal pyrexia, hospital admissions, bed rest, use of steroids, tocolysis and progesterone Neonatal outcomes: need for oxygen therapy at 28 days and US evidence of brain abnormality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomisation sequence was computer generated in balanced block multiples. Stratification was performed to control for gestation of last delivery before 24 weeks."
Allocation concealment (selection bias)	Low risk	"Allocation was made by telephone to the central trials office in London, UK."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind to participants and personnel
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	Loss of participants to follow-up: "primary outcome data were available on 247/248 women (99.6%)". Exclusion of participants after randomisation: 5 women were excluded "three were subsequently identified as not fitting eligibility criteria and a further two were excluded from analysis as they elected to terminate the pregnancy after a diagnosis of fetal anomaly" Intention-to-treat analysis: "There were 9 patients who did not receive the randomisation intervention. Eight women in the history arm were scanned" "All analysis was

Simcox 2009 (*Continued*)

		conducted according to the original allocation, following the intention to treat principle."
Selective reporting (reporting bias)	Unclear risk	Study protocol not available. All outcomes prespecified in the article were reported
Other bias	Low risk	Study was not stopped early Baseline imbalance: "One women in each arm declined a suture."

To 2004

Methods	RCT - block randomisation. January 1998 to May 2002. "Women with singleton pregnancies undergoing routine antenatal care in 12 hospitals in UK, Brazil, South Africa, Slovenia, Greece and Chile."
Participants	**N = 253** "Women with singleton pregnancies", "women attending for the 22-24 week scan were offered a transvaginal scan to measure cervical length, as a screening test for spontaneous preterm delivery." **Inclusion criteria:** "women with a cervical length of 15 mm or less were invited to participate in the randomised study of cervical cerclage" **Exclusion criteria: "**women with major fetal abnormalities, painful regular uterine contractions, or history of ruptured membranes and cervical cerclage in situ were excluded from screening, and women with dilatated cervix during screening were excluded from the randomised study."
Interventions	Shirodkar cerclage (N = 127) versus no cerclage (N = 126).
Outcomes	**Primary:** delivery before 33 completed weeks (231 days) of gestation. **Secondary:** centile-adjusted birthweight, stillbirth, and neonatal death or major adverse outcome before discharge from hospital (bronchopulmonary dysplasia, intraventricular or periventricular haemorrhage grade 3 or 4, retinopathy of prematurity, or positive fetal blood culture), maternal morbidity during antenatal hospital stay (fever of 38°C or more on 2 occasions), or symptomatic vaginal discharge."
Notes	Additional information and the data base for cross-checking of the published results provided by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"the randomisation sequence was computer generated for individual centres in balanced block multiples of ten. These codes were

		held at a central trials office in London, UK."
Allocation concealment (selection bias)	Low risk	"…allocation was made by telephone."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Because of the invasive nature of the cervical cerclage, masking of treatment allocation to participants and investigators was not practical in this study."
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	Loss of participants to follow-up: 1 neonate lost to follow-up in cerclage group. Exclusion of participants after randomisation: 2 in cerclage group ruptured the membranes Intention-to-treat analysis: 4/127 in cerclage group did not have cerclage; 2/126 in no cerclage group had cerclage
Selective reporting (reporting bias)	Low risk	Study protocol available, but primary outcome only specified. The full database was provided by the authors, so any selective reporting unlikely
Other bias	Low risk	Baseline imbalance: 470 eligible patients, 217 (54%) declined participation. Women who declined participation did not differ from the study group in their main demographic characteristics and preterm delivery rate (data not shown)

CS: caesarean section
GA: gestational age
h: hour
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
PROM: premature rupture of membranes
PPROM: preterm premature rupture of membranes
PTB: preterm birth
PTD: preterm delivery
PTL: preterm labour
RCT: randomised controlled trial
TA: transabdominal

TVU: transvaginal ultrasound
US: ultrasound

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

Study	Reason for exclusion
Blair 2002	Outpatient cerclage versus inpatient cerclage
Broumand 2011	Double cerclage versus traditional cerclage
Caspi 1990	Cervical internal os cerclage versus Shirodkar cerclage
Dor 1982	Twin pregnancies
Hui 2013	This trial compared use of Arabin pessary with no treatment for pregnant women with short cervix < 25 mm at 20 to 24 weeks' gestation
Ismail 2014	This protocol described a trial to compare suture types for cervical cerclage
Israfil-Bayli 2014	This was a feasibility RCT to compare 2 types of suture materials for cervical cerclage
Kassanos 2001	Likely to be quasi-randomised study: "the patients were randomised to be treated either by elective cerclage or by weekly serial vaginal US (every second patient) with the possibility of an emergency cerclage and were divided into 2 groups."
Nicolaides 2001	Twin pregnancies
Rust 2001	Multiple gestation
Secher 2007	Protocol for a randomised study comparing double cerclage compared with a single cerclage
Tsai 2009	Double cervical cerclage versus traditional single cervical cerclage
Varma 1986	We have been unable to find any published report to suggest that this proposed study of cerclage was ever carried out. Therefore, we have moved this report from awaiting assessment to excluded studies
Von Forster 1986	Quasi-randomised study: "patients were divided into 3 groups on the basis of initial letter of their surname."
Zakhera 2015	The inclusion criteria for this trial was recurrent bleeding in early pregnancy. Women did not have short cervix on US or physical exam or previous history of preterm birth
Zolghadri 2014	This report describes and RCT to compare McDonald cerclage vs a double cerclage method
Üçyiğit 2013	RCT, Compared low vaginal, high vaginal and abdominal cerclage

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ragab 2015

Methods	• Prospective randomised trial. • Mansoura University Hospitals, Egypt. • June 2013 to October 2014
Participants	• Inclusion criteria: singleton pregnancy (24 to 28 weeks' gestation) with regular labour pains, cervical dilation < 5 cm, effacement < 50%, intact membranes bulging inside cervical canal but not outside the external os. • Exclusoin criteria: preterm premature rupture of membranes, intact membranes bulging outside the external os, multiple pregnancy, infection (as known by pyrexia, discharge, positive swab or high white cell count), antepartum haemorrhage, placenta previa. Women < 24 weeks' gestation were also excluded due to poor postnatal infant survival and unfeasibility of intensive care in trial setting
Interventions	**Cerclage + progesterone versus progesterone alone (N = 100)** • Intervention: Group A: emergency cervical cerclage stitch McDonald procedure. Natural progesterone 100 mg/2 mL intramuscular injection daily dose for 48 h maintenance by single vaginal pessary 200 mg daily to delivery or 37 weeks. Women were observed for 48 h after cerclage placement in the emergency department and then kept inpatient for the remainder of pregnancy. Total number randomised: 50. • Control/comparison intervention: progesterone as per protocol above. Women were kept inpatient for the duration of the pregnancy. Total number randomised: 50. • All randomised women in both arms had prophylactic antibiotics 1 g amoxicillin in admission followed by 500 mg/8 h for 48 h and single course dexamethasone 12 mg/12 h intramuscular in 2 doses (the preferred betamethasone was unavailable). All women were inpatients in hospital from treatment to delivery
Outcomes	Primary outcome: duration of prolongation of pregnancy, live birth, neonatal morbidity and mortality
Notes	Authors contacted to clarify preterm birth outcome data (reported only in the discussion of the paper) and the high number of neonatal deaths in published report (emailed May 2016). We are still awaiting the response - it should be noted that these data, as published, significantly change the result of meta-analysis for the outcome of neonatal death

h: hour

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

Hezelgrave 2015

Trial name or title	SuPPoRT: Stitch, Progesterone or Pessary: a randomised controlled trial The prevention of pre-term birth in women who develop a short cervix. A multi-centre randomised controlled trial to compare 3 treatments; cervical cerclage, cervical pessary and vaginal progesterone
Methods	3-arm randomised controlled trial. Main objective of the trial: for asymptomatic women at risk of preterm birth who develop a short cervix on transvaginal ultrasound scan, which is the optimal preventative strategy; cervical cerclage, arabin pessary or vaginal progesterone? Secondary objectives of the trial: does the success of the intervention depend on early pregnancy biomarker

Hezelgrave 2015 (*Continued*)

	expression?
Participants	**Planned number of subjects: 540** **Principal inclusion criteria:** women with singleton pregnancies who are found to have cervical length < 25 mm on transvaginal ultrasound between 14 + 0 weeks' gestation (dated by ultrasound or LMP and adjusted for ultrasound estimated date of delivery once ultrasound performed if no miscarriage prior to dating ultrasound) until 23 + 6 weeks' gestation and 1 or more of the following risk factors • Written informed consent to participate • History of previous preterm premature rupture of the fetal membranes (≤ 37 weeks') • History of previous PTB/second trimester loss (≥ 16 weeks' or ≤ 37 weeks' gestation). • Any cervical procedure to treat abnormal smears, i.e. large loop excision, laser conisation, cold knife conisation or radical diathermy. • Incidental finding of a short cervix on ultrasound scan (e.g. at the time of anomaly scan). **Principal exclusion criteria:** • Women with persistent fresh vaginal bleeding evident on speculum examination. • Women with visible membranes evident on speculum examination or open cervix on ultrasound scan. • Women with severe abdominal pain/evidence of sepsis (as judged by attending clinician). • Known significant congenital or structural or chromosomal fetal abnormality. • Suspected or proven rupture of the fetal membranes at the time of recruitment. • Women currently using progesterone pessaries or who have taken progesterone beyond 18 weeks' gestation. • Women who have a cervical suture in situ. • Women who already have a cervical pessary in situ. • Insufficiuent understanding of the trial in the opinion of the Investigator. Any contra-indications or cautions to the investigational medicinal product including: • known allergy or hypersensitivity to progesterone. • hepatic dysfunction; • undiagnosed vaginal bleeding; • mammary or genital tract carcinoma; • thrombophlebitis; • thromboembolic disorders; • cerebral haemorrhage; and • porphyria.
Interventions	Cervical cerclage versus progesterone (Cyclogest 200 mg) versus arabin pessary
Outcomes	**Primary end point:** delivery < 37 completed weeks' gestation (powered). Timepoint of evaluation of this end point: date of delivery. **Secondary end point(s):** 1. Adverse perinatal outcome, defined as a composite outcome of death (antepartum/intrapartum stillbirths plus neonatal deaths prior to discharge from neonatal services) or 1 (or more) of intraventricular haemorrhage, periventricular leukomalacia, hypoxic ischaemic encephalopathy, necrotising enterocolitis, bronchopulmonary dysplasia and sepsis. 2. Delivery < 30 and 34 completed weeks' gestation. 3. Gestation at delivery. 4. Time between intervention and delivery. 5. Requirement for rescue cerclage (bulging fetal membranes). 6. Other maternal and fetal outcomes: clinical course, therapies administered, maternal and fetal morbidity and mortality data.

Hezelgrave 2015 (*Continued*)

	7. Participant and clinician's perceptions of treatment: questionnaires with a selection of participants at 0 to 2 weeks post procedure. Questionnaires at 1 year are planned if funding is obtained participant and clinician adherence to protocol. • Health costs at 28 days postnatal. • Biochemical end-points (if performed): endocervical swabs will be taken to determine the presence of cervico-vaginal infection and concentrations of biomarkers of preterm birth, infection and inflammation. Saliva samples will be collected for salivary hormone levels, and blood samples taken for inflammatory markers and genetic analysis. Results will be correlated with maternal and fetal outcomes.
Starting date	Ethical approval May 2015
Contact information	Dr Natahsa Hezelgrave, natasha.hezelgrave@gstt.nhs.uk
Notes	EudraCT Number: 2015-000456-15 Funding: NIHR (UK), Tommy's Charity, Guys and St Thomas' NHS Foundation Trust

Koulalli 2014

Trial name or title	PC-study. Pessary or Cerclage to Prevent Preterm birth in women with short cervical length and a history preterm birth
Methods	Parallel randomised controlled trial
Participants	**Target number of participants: 440** **Inclusion criteria:** 1. singleton pregnancy 2. previous preterm birth < 34 weeks of gestation 3. cervical length < 25 mm or multiple preterm births. **Exclusion criteria:** 1. maternal age < 18 years 2. inability to give informed consent 3. placenta praevia 4. vasa praevia 5. preterm premature rupture of the membranes 6. uterine anomalies 7. cervical dilatation (the cut off is unclear in the published report) 8. cervical length < 5 mm 9. identified major congenital abnormalities 10. women with clinical signs of chorioamnionitis or signs of intra uterine infection 11. women whose child has signs of fetal distress defined as abnormal cardiotocograph or abnormal biophysical profile
Interventions	Pessary versus cervical cerclage
Outcomes	Primary outcome: preterm birth < 32 weeks' gestation. Secondary outcomes: preterm rate birth before 24, 28, 34 and 37 weeks, time from intervention to delivery, (early) premature rupture of membranes, maternal infection, maternal side effects and composite bad neonatal outcome including both morbidity and mortality rate of children as well as costs

Koulalli 2014 (*Continued*)

Starting date	2014. End date 2018
Contact information	Dr B Koullali, pc@studies-obsgyn.nl and Dr E Pajkrt, d.pajkrt@amc.uva.nl
Notes	**NTR4415** Sponsor: Academic Medical Center, Amsterdam Funding: ZON-MW, The Netherlands Organization for Health Research and Development

DATA AND ANALYSES

Comparison 1. Cerclage versus no cerclage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	10	2927	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.04]
1.1 History-indicated cerclage vs no cerclage	4	2045	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.12]
1.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.14, 4.25]
1.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	509	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.41, 1.06]
1.4 Physical exam indicated cerclage vs no cerclage	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.77, 5.01]
1.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
2 Serious neonatal morbidity	6	883	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.25]
2.1 History-indicated cerclage vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.14, 4.25]
2.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	510	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.25]
2.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	1	30	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.73]
2.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.60, 3.17]
3 Baby discharged home healthy	4	657	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.06]
3.1 History-indicated cerclage vs no cerclage	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.07]
3.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	2	238	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.14]

3.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	236	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.08]
4 Stillbirths	5	1803	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.75]
4.1 History-indicated cerclage vs no cerclage	2	1458	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.45, 2.20]
4.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.58]
4.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	2	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	2	207	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.20, 4.59]
5 Neonatal deaths before discharge	6	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.53, 1.39]
5.1 History-indicated cerclage vs no cerclage	2	1350	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.29, 1.27]
5.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.21, 22.37]
5.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	2	73	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.12, 5.26]
5.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.77, 5.01]
5.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	2	207	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.18, 2.18]
6 Miscarriages	7	2091	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.22]
6.1 History-indicated cerclage vs no cerclage	3	1539	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]
6.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	3	209	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.25, 1.66]

6.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.16, 18.22]
7 Preterm birth before 37 completed weeks	9	2898	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.95]
7.1 History-indicated cerclage vs no cerclage	4	2045	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.27]
7.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.30, 0.99]
7.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	510	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.02]
7.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.16]
8 Preterm birth before 34 completed weeks	9	2415	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.89]
8.1 History-indicated cerclage vs no cerclage	3	1539	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.40, 1.46]
8.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.27, 1.46]
8.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	510	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.10]
8.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	1	23	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.34, 0.93]
8.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.55, 1.22]
9 Preterm birth before 28 completed weeks	8	2392	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.00]
9.1 History-indicated cerclage vs no cerclage	3	1539	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.59, 1.13]
9.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.18, 2.62]

9.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	510	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.04]
9.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.55, 1.83]
10 Serious intracranial pathology (IVH or periventricular leukomalacia)	5	839	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.23, 3.09]
10.1 History-indicated cerclage vs no cerclage	1	194	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.09]
10.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.02, 9.01]
10.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	3	382	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.05, 19.53]
10.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	2	207	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.98]
11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)	5	839	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.88]
11.1 History-indicated cerclage vs no cerclage	1	194	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.32, 28.93]
11.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.06, 6.00]
11.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	3	382	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.53, 1.81]
11.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	2	207	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.39, 6.86]
12 Necrotising enterocolitis	3	372	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.16, 4.12]

12.1 History-indicated cerclage vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	3	362	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.16, 4.12]
12.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy of prematurity	2	553	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.14, 1.48]
13.1 History-indicated cerclage vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.58]
13.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.53]
13.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
14 Apgar < 7 at 5 minutes	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.15]
14.1 History-indicated cerclage vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.15]
14.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

15 Caesarean section (elective and emergency)	8	2817	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.01, 1.40]
15.1 History-indicated cerclage vs no cerclage	3	1964	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.96, 1.52]
15.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.52, 3.50]
15.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	4	510	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.82, 1.46]
15.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.84, 2.04]
16 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	3	953	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.89, 5.69]
16.1 History-indicated cerclage vs no cerclage	2	700	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.76, 3.24]
16.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	253	Risk Ratio (M-H, Random, 95% CI)	5.95 [1.36, 26.06]
17 Pyrexia	3	1245	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.35, 4.23]
17.1 History-indicated vs. no cerclage	2	992	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.22, 4.01]
17.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.15, 81.09]
17.3 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	197	Risk Ratio (M-H, Fixed, 95% CI)	6.66 [0.35, 127.20]
18 Any intravenous, oral or combined tocolysis (not prespecified)	2	217	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.80, 2.05]

18.1 History-indicated vs. no cerclage	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.66, 3.58]
18.2 Physical exam-indicated cerclage in high risk for PTL versus no cerclage	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.72, 1.56]
19 PPROM (not prespecified)	6	2010	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.62, 1.48]
19.1 History-indicated vs. no cerclage	2	1458	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.71, 3.70]
19.2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage	1	56	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.14, 1.72]
19.3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	3	209	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.18, 1.45]
19.4 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	3	287	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.78, 2.23]
20 Chorioamnionitis (not prespecified)	3	1506	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.26, 2.72]
20.1 History-indicated vs. no cerclage	1	1264	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.81]
20.2 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage	2	162	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.03, 6.21]
20.3 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage	1	80	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.39, 4.23]

Comparison 2. Cerclage versus vaginal progesterone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	2	108	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.36, 2.48]
2 Serious neonatal morbidity	2	120	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.05, 4.52]
3 Baby discharged home healthy	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.88, 1.07]
4 Stillbirths	2	128	Risk Ratio (M-H, Fixed, 95% CI)	2.7 [0.12, 62.17]
5 Neonatal deaths before discharge	2	120	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.34, 13.86]
6 Miscarriages	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.17, 2.01]
7 Preterm birth before 37 completed weeks	2	128	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.64, 2.08]
8 Preterm birth before 34 completed weeks	2	128	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.51, 2.01]

9 Preterm birth before 28 completed weeks	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.37, 2.27]
10 Serious intracranial pathology (IVH or periventricular leucomalacia)	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.17, 5.28]
11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)	2	128	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.04, 6.41]
12 Necrotising enterocolitis	1	92	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.78]
13 Retinopathy of prematurity	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.51]
14 Apgar < 7 at 5 minutes	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.37, 9.80]
15 Caesarean section (elective and emergency)	2	128	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.47]
16 Maternal infection requiring intervention(antibiotics or delivery)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	1	92	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.79]
18 Pyrexia	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Any intravenous, oral or combined tocolysis (not prespecified)	1	92	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [1.93, 7.29]
20 PPROM (not prespecified)	1	92	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [1.04, 61.42]
21 Chorioamnionitis (not prespecified)	2	128	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.10, 23.61]

Comparison 3. Cerclage versus intramuscular progesterone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.58, 2.16]
2 Serious neonatal morbidity	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.47, 2.74]
3 Baby discharged home healthy	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.82, 1.67]
4 Stillbirths	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Neonatal deaths before discharge	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Miscarriages	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.38, 5.73]
7 Preterm birth before 37 completed weeks	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.60, 1.30]
8 Preterm birth before 34 completed weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Preterm birth before 28 completed weeks	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.53, 2.97]
10 Serious intracranial pathology (IVH or periventricular leucomalacia)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Necrotising enterocolitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy of prematurity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Apgar < 7 at 5 minutes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Caesarean section (elective and emergency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Maternal infection requiring intervention(antibiotics or delivery)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Pyrexia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 PPROM (not prespecified)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.47, 1.65]
20 Chorioamnionitis (not prespecified)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.61, 2.88]

Comparison 4. Cerclage versus pessary

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious neonatal morbidity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Baby discharged home healthy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Stillbirths	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Neonatal deaths before discharge	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Miscarriages	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Preterm birth before 37 completed weeks	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Preterm birth before 34 completed weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Preterm birth before 28 completed weeks	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Serious intracranial pathology (IVH or periventricular leucomalacia)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Necrotising enterocolitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy of prematurity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Apgar < 7 at 5 minutes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Caesarean section (elective and emergency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

16 Maternal infection requiring intervention(antibiotics or delivery)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Pyrexia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 PPROM (not prespecified)	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20 Chorioamnionitis	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 5. Any comparison of different cerclage protocols

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.96]
2 Serious neonatal morbidity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.51, 5.69]
3 Baby discharged home healthy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Stillbirths	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.31]
5 Neonatal deaths before discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.15]
5.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Miscarriages	2	344	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.55, 5.30]
6.1 History-indicated cerclage vs ultrasound-indicated cerclage	2	344	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.55, 5.30]
7 Preterm birth before 37 completed weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

7.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.25, 2.05]
8 Preterm birth before 34 completed weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.57, 1.87]
9 Preterm birth before 28 completed weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Serious intracranial pathology (IVH or periventricular leucomalacia)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.36, 10.46]
10.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.25, 8.61]
11.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Necrotising enterocolitis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Retinopathy of prematurity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Apgar < 7 at 5 minutes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

14.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Caesarean section (elective and emergency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 History-indicated cerclage vs ultrasound-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Maternal infection requiring intervention(antibiotics or delivery)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.91]
16.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	243	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.21, 1.42]
17.2 History-indicated cerclage vs physical exam-indicated cerclage	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Tocolysis (not prespecified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 History-indicated cerclage vs ultrasound-indicated cerclage	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.24]

Comparison 6. Cerclage versus no cerclage (Summary of findings outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All perinatal losses	10	2927	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.04]
2 Serious neonatal morbidity	6	883	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.18]
3 Baby discharged home healthy	4	657	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.06]
4 Stillbirths	5	1803	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.75]
5 Neonatal deaths before discharge	6	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.53, 1.39]
6 Preterm birth before 34 completed weeks	9	2415	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.89]

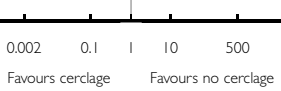
Analysis 1.1. Comparison 1 Cerclage versus no cerclage, Outcome 1 All perinatal losses.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 1 All perinatal losses

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 History-indicated cerclage vs no cerclage					
Lazar 1984	2/268	1/238		0.8 %	1.78 [0.16, 19.46]
Ezechi 2004	0/39	2/42		1.8 %	0.22 [0.01, 4.34]
Rush 1984	9/96	9/98		6.6 %	1.02 [0.42, 2.46]
MRC/RCOG 1993	53/635	66/629		49.3 %	0.80 [0.56, 1.12]
Subtotal (95% CI)	**1038**	**1007**		**58.4 %**	**0.82 [0.60, 1.12]**
Total events: 64 (Cerclage), 78 (No cerclage)					
Heterogeneity: Chi^2 = 1.43, df = 3 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.26 (P = 0.21)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	2/26	3/30		2.1 %	0.77 [0.14, 4.25]
Subtotal (95% CI)	**26**	**30**		**2.1 %**	**0.77 [0.14, 4.25]**
Total events: 2 (Cerclage), 3 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	0/19	3/16		2.8 %	0.12 [0.01, 2.19]
Berghella 2004	4/25	4/22		3.2 %	0.88 [0.25, 3.11]
Rust 2000	7/61	5/66		3.6 %	1.51 [0.51, 4.52]
Owen 2009	13/148	25/152		18.3 %	0.53 [0.28, 1.00]
Subtotal (95% CI)	**253**	**256**		**27.9 %**	**0.66 [0.41, 1.06]**
Total events: 24 (Cerclage), 37 (No cerclage)					
Heterogeneity: Chi^2 = 4.17, df = 3 (P = 0.24); I^2 =28%					
Test for overall effect: Z = 1.72 (P = 0.085)					
4 Physical exam indicated cerclage vs no cerclage					
Althuisius 2003	9/16	4/14		3.2 %	1.97 [0.77, 5.01]
Subtotal (95% CI)	**16**	**14**		**3.2 %**	**1.97 [0.77, 5.01]**
Total events: 9 (Cerclage), 4 (No cerclage)					
Heterogeneity: not applicable					



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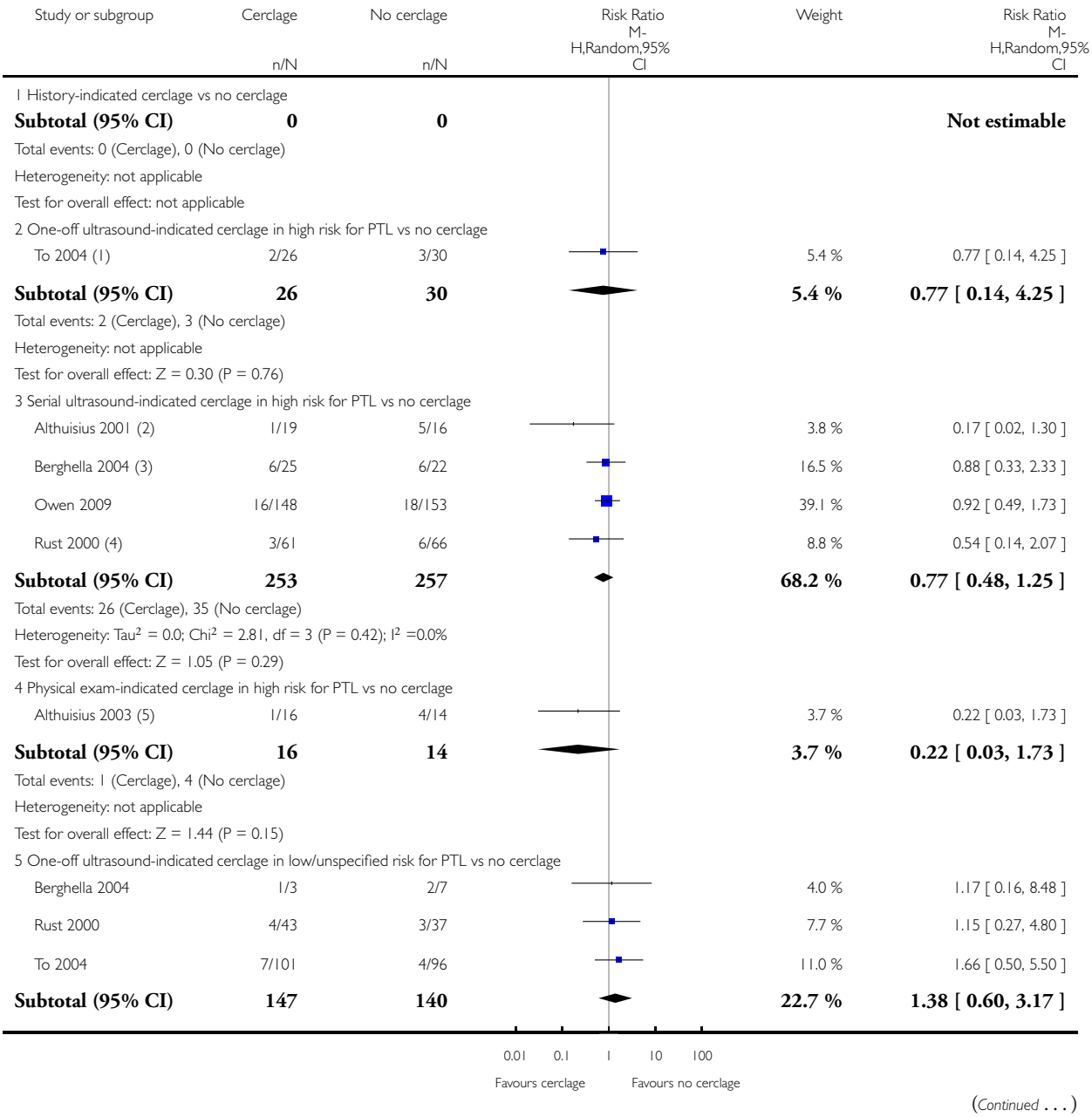
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.42 (P = 0.16)					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	0/3	0/7			Not estimable
Rust 2000	5/43	2/37		1.6 %	2.15 [0.44, 10.44]
To 2004	7/101	9/96		6.9 %	0.74 [0.29, 1.91]
Subtotal (95% CI)	**147**	**140**		**8.5 %**	**1.01 [0.46, 2.22]**
Total events: 12 (Cerclage), 11 (No cerclage)					
Heterogeneity: Chi^2 = 1.30, df = 1 (P = 0.26); I^2 =23%					
Test for overall effect: Z = 0.01 (P = 0.99)					
Total (95% CI)	**1480**	**1447**		**100.0 %**	**0.82 [0.65, 1.04]**
Total events: 111 (Cerclage), 133 (No cerclage)					
Heterogeneity: Chi^2 = 10.95, df = 11 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 1.60 (P = 0.11)					
Test for subgroup differences: Chi^2 = 4.44, df = 4 (P = 0.35), I^2 =10%					

Analysis 1.2. Comparison 1 Cerclage versus no cerclage, Outcome 2 Serious neonatal morbidity.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 2 Serious neonatal morbidity



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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
Total events: 12 (Cerclage), 9 (No cerclage)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 2 (P = 0.91); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
Total (95% CI)	**442**	**441**		**100.0 %**	**0.84 [0.57, 1.25]**
Total events: 41 (Cerclage), 51 (No cerclage)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.10$, df = 8 (P = 0.64); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.85 (P = 0.39)					
Test for subgroup differences: $Chi^2 = 3.10$, df = 3 (P = 0.38), $I^2 = 3\%$					

(1) Defined as bronchopulmonary dysplasia, IVH or PVH grade 3 or 4, retinopathy of prem, positive fetal blood culture.

(2) Serious morbidity defined as NICU admission.

(3) Defined as any of respiratory distress syndrome, intraventricular haemorrhage [III or IV], necrotizing enterocolitis, or sepsis.

(4) Defined as mechanical ventilation, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, or other life-threatening morbidity.

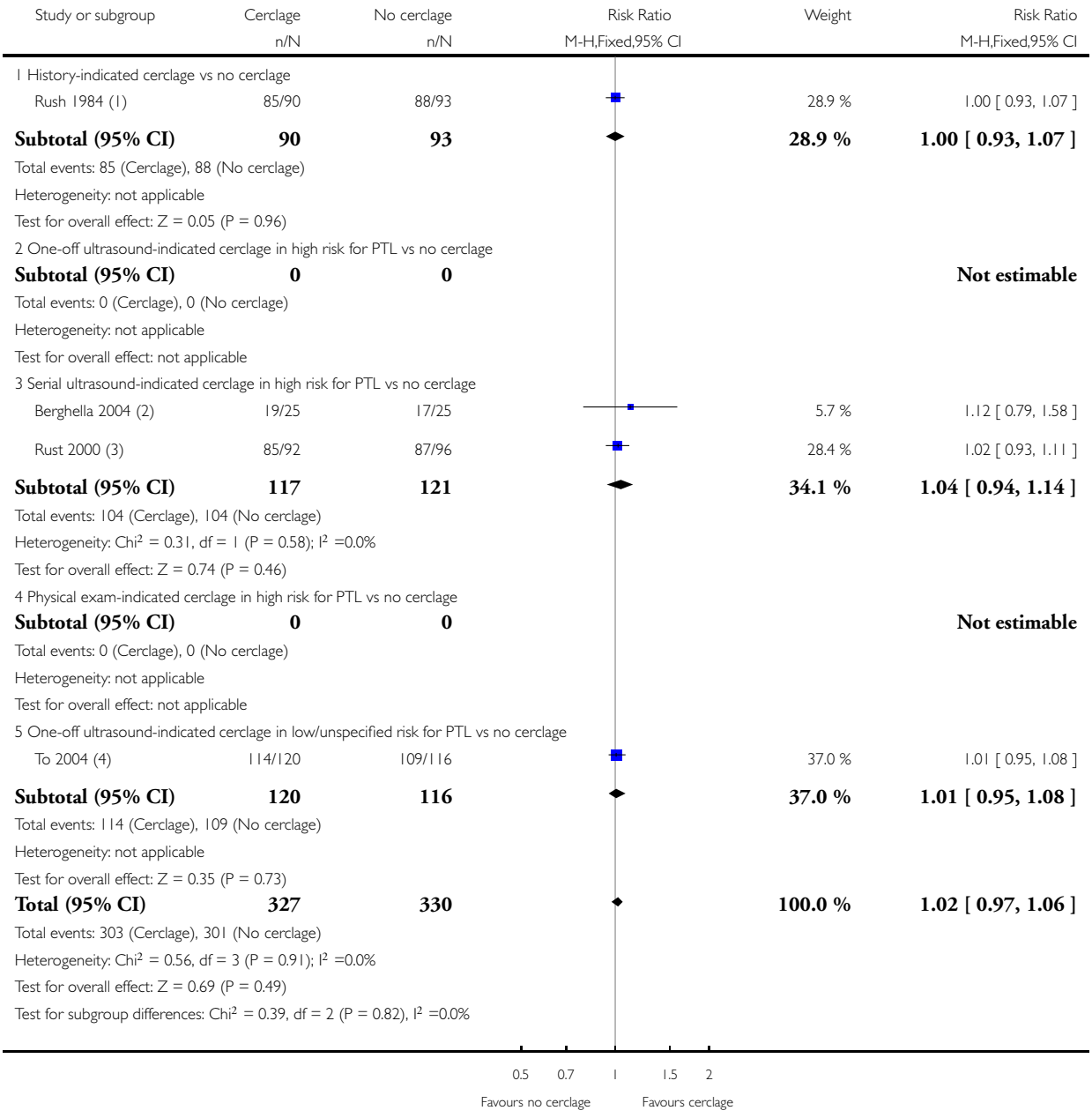
(5) Defined as admission to NICU.

Analysis 1.3. Comparison 1 Cerclage versus no cerclage, Outcome 3 Baby discharged home healthy.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 3 Baby discharged home healthy



(1) Included women had a history of at least one preterm delivery < 37 weeks; women with cervical dilation > 2mm were excluded.

(2) From Jorgenson 2007 (excluding deaths from denominator. One-off and serial ultrasound together).

(3) From Jorgenson 2007 (excluding deaths from denominator).

(4) From Jorgenson 2007 (excluding deaths; both risk groups together.)

Analysis 1.4. Comparison 1 Cerclage versus no cerclage, Outcome 4 Stillbirths.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 4 Stillbirths

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 History-indicated cerclage vs no cerclage					
MRC/RCOG 1993	8/635	10/629		57.6 %	0.79 [0.31, 1.99]
Rush 1984	4/96	2/98		11.4 %	2.04 [0.38, 10.89]
Subtotal (95% CI)	**731**	**727**		**69.0 %**	**1.00 [0.45, 2.20]**
Total events: 12 (Cerclage), 12 (No cerclage)					
Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² =0.0%					
Test for overall effect: Z = 0.00 (P = 1.0)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	0/26	2/30		13.4 %	0.23 [0.01, 4.58]
Subtotal (95% CI)	**26**	**30**		**13.4 %**	**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)					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	0/19	0/16			Not estimable
Berghella 2004	0/25	0/22			Not estimable
Subtotal (95% CI)	**44**	**38**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					

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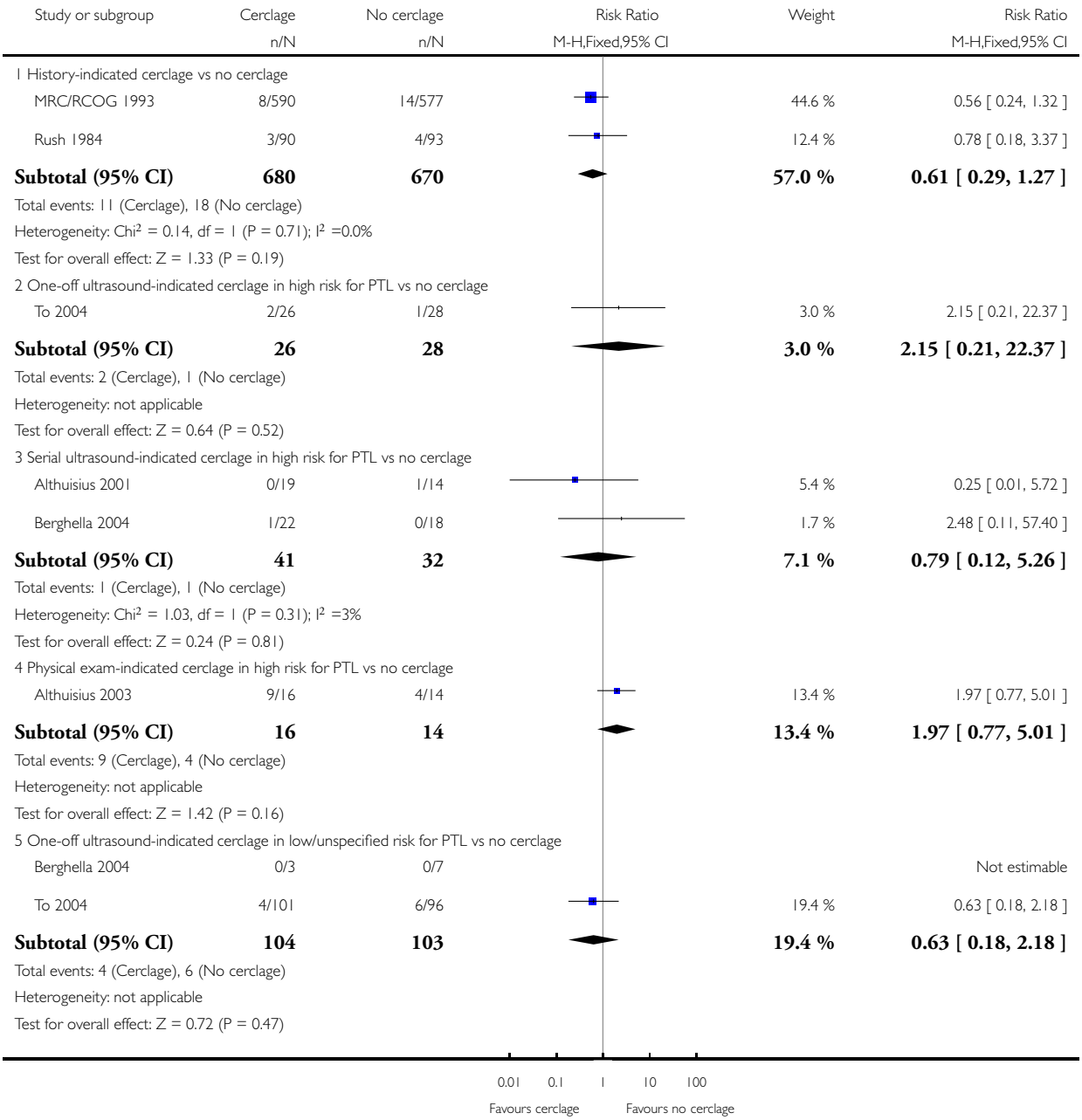
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	0/3	0/7			Not estimable
To 2004	3/101	3/96		17.6 %	0.95 [0.20, 4.59]
Subtotal (95% CI)	**104**	**103**		**17.6 %**	**0.95 [0.20, 4.59]**
Total events: 3 (Cerclage), 3 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
Total (95% CI)	**905**	**898**		**100.0 %**	**0.89 [0.45, 1.75]**
Total events: 15 (Cerclage), 17 (No cerclage)					
Heterogeneity: Chi^2 = 1.80, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.73)					
Test for subgroup differences: Chi^2 = 0.87, df = 2 (P = 0.65), I^2 =0.0%					

Analysis 1.5. Comparison 1 Cerclage versus no cerclage, Outcome 5 Neonatal deaths before discharge.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 5 Neonatal deaths before discharge



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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)	**867**	**847**		**100.0 %**	**0.85 [0.53, 1.39]**
Total events: 27 (Cerclage), 30 (No cerclage)					
Heterogeneity: Chi^2 = 5.88, df = 6 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.53)					
Test for subgroup differences: Chi^2 = 4.65, df = 4 (P = 0.33), I^2 =14%					

Analysis 1.6. Comparison 1 Cerclage versus no cerclage, Outcome 6 Miscarriages.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 6 Miscarriages

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 History-indicated cerclage vs no cerclage					
Ezechi 2004	0/39	0/42			Not estimable
MRC/RCOG 1993	37/635	42/629		75.2 %	0.87 [0.57, 1.34]
Rush 1984	2/96	3/98		5.3 %	0.68 [0.12, 3.98]
Subtotal (95% CI)	**770**	**769**		**80.5 %**	**0.86 [0.57, 1.30]**
Total events: 39 (Cerclage), 45 (No cerclage)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	0/26	0/30			Not estimable
Subtotal (95% CI)	**26**	**30**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	0/19	2/16		4.8 %	0.17 [0.01, 3.30]

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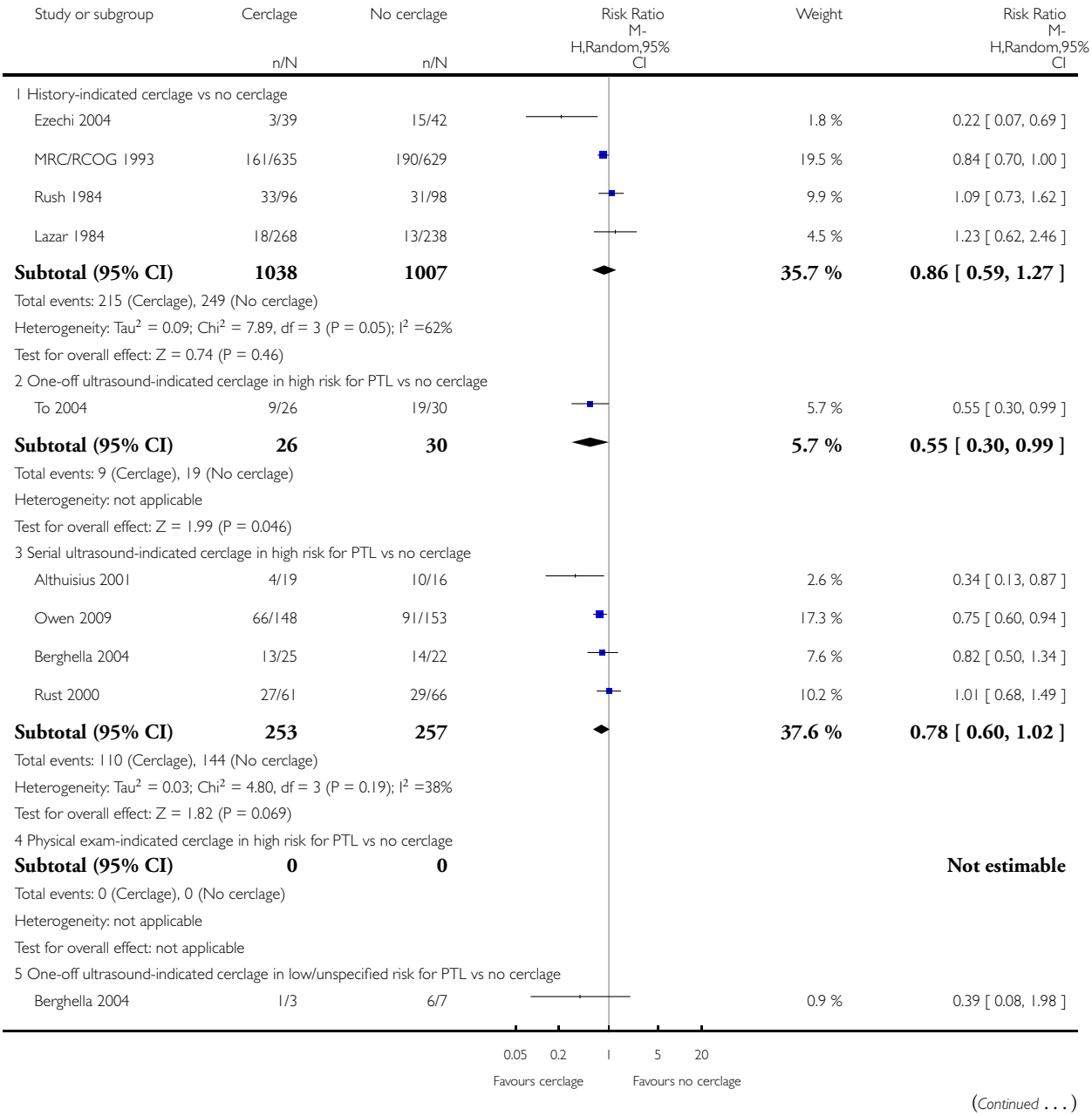
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berghella 2004	3/25	4/22		7.6 %	0.66 [0.17, 2.63]
Rust 2000	3/61	3/66		5.1 %	1.08 [0.23, 5.16]
Subtotal (95% CI)	**105**	**104**		**17.5 %**	**0.65 [0.25, 1.66]**
Total events: 6 (Cerclage), 9 (No cerclage)					
Heterogeneity: Chi^2 = 1.20, df = 2 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.90 (P = 0.37)					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	0/3	0/7			Not estimable
Rust 2000	2/43	1/37		1.9 %	1.72 [0.16, 18.22]
To 2004	0/101	0/96			Not estimable
Subtotal (95% CI)	**147**	**140**		**1.9 %**	**1.72 [0.16, 18.22]**
Total events: 2 (Cerclage), 1 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
Total (95% CI)	**1048**	**1043**		**100.0 %**	**0.84 [0.58, 1.22]**
Total events: 47 (Cerclage), 55 (No cerclage)					
Heterogeneity: Chi^2 = 1.77, df = 5 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.92 (P = 0.36)					
Test for subgroup differences: Chi^2 = 0.66, df = 2 (P = 0.72), I^2 =0.0%					

Analysis 1.7. Comparison 1 Cerclage versus no cerclage, Outcome 7 Preterm birth before 37 completed weeks.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 7 Preterm birth before 37 completed weeks



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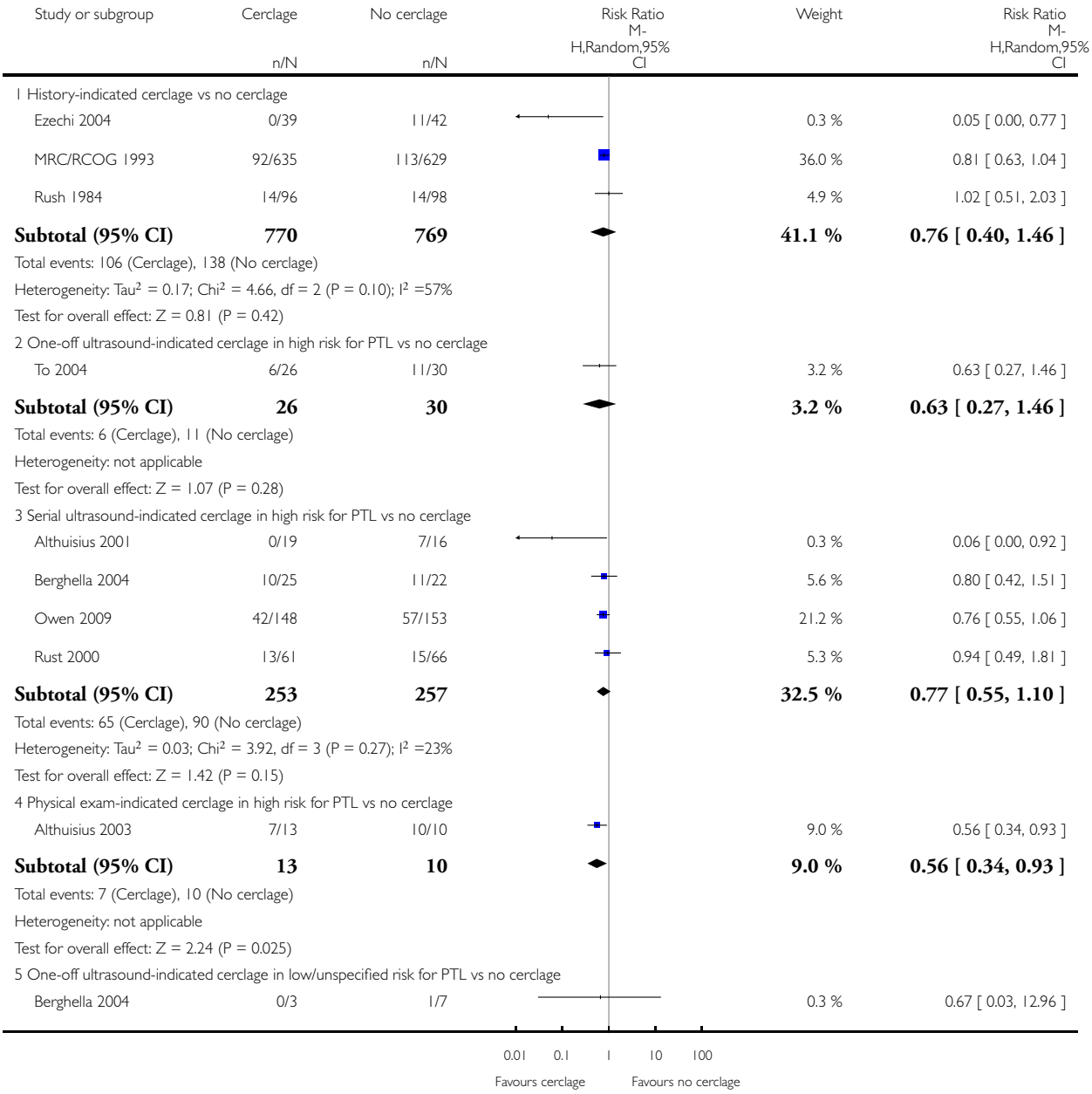
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
To 2004	32/101	44/96		11.3 %	0.69 [0.48, 0.99]
Rust 2000	22/43	18/37		8.8 %	1.05 [0.68, 1.64]
Subtotal (95% CI)	**147**	**140**		**21.0 %**	**0.80 [0.55, 1.16]**
Total events: 55 (Cerclage), 68 (No cerclage)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.90, df = 2 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Total (95% CI)	**1464**	**1434**		**100.0 %**	**0.80 [0.69, 0.95]**
Total events: 389 (Cerclage), 480 (No cerclage)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 18.11, df = 11 (P = 0.08); I^2 =39%					
Test for overall effect: Z = 2.64 (P = 0.0082)					
Test for subgroup differences: Chi^2 = 1.66, df = 3 (P = 0.65), I^2 =0.0%					

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

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 8 Preterm birth before 34 completed weeks



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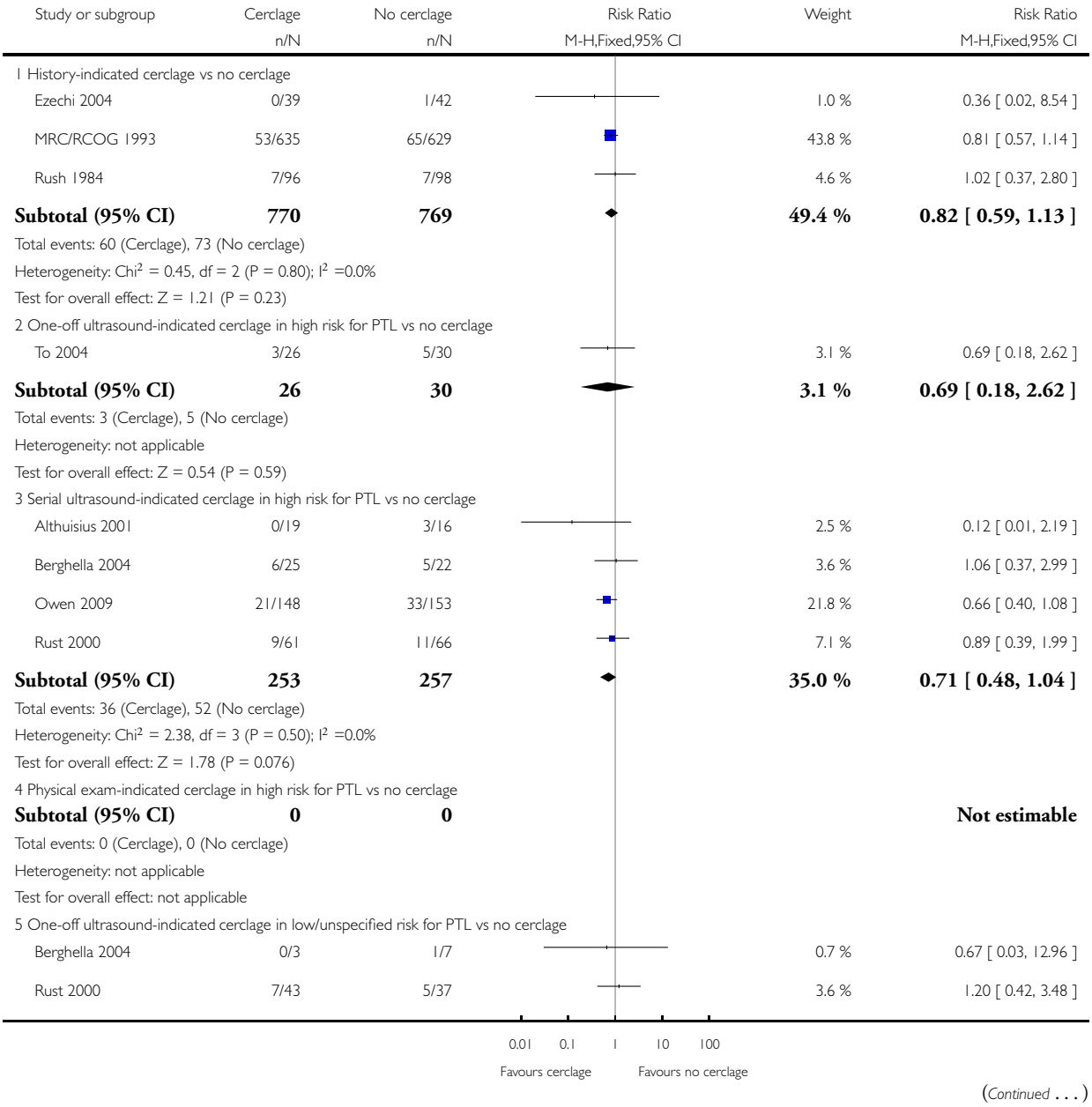
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rust 2000	11/43	12/37		4.8 %	0.79 [0.40, 1.57]
To 2004	22/101	25/96		9.1 %	0.84 [0.51, 1.38]
Subtotal (95% CI)	**147**	**140**		**14.2 %**	**0.82 [0.55, 1.22]**
Total events: 33 (Cerclage), 38 (No cerclage)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 2 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.99 (P = 0.32)					
Total (95% CI)	**1209**	**1206**		**100.0 %**	**0.77 [0.66, 0.89]**
Total events: 217 (Cerclage), 287 (No cerclage)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.31$, df = 11 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.41 (P = 0.00065)					
Test for subgroup differences: $Chi^2 = 1.59$, df = 4 (P = 0.81), $I^2 = 0.0\%$					

Analysis 1.9. Comparison 1 Cerclage versus no cerclage, Outcome 9 Preterm birth before 28 completed weeks.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 9 Preterm birth before 28 completed weeks



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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
To 2004	12/101	12/96		8.3 %	0.95 [0.45, 2.01]
Subtotal (95% CI)	**147**	**140**		**12.5 %**	**1.01 [0.55, 1.83]**
Total events: 19 (Cerclage), 18 (No cerclage)					
Heterogeneity: Chi^2 = 0.21, df = 2 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	**1196**	**1196**		**100.0 %**	**0.80 [0.64, 1.00]**
Total events: 118 (Cerclage), 148 (No cerclage)					
Heterogeneity: Chi^2 = 3.87, df = 10 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.051)					
Test for subgroup differences: Chi^2 = 1.05, df = 3 (P = 0.79), I^2 =0.0%					

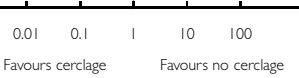
Analysis 1.10. Comparison 1 Cerclage versus no cerclage, Outcome 10 Serious intracranial pathology (IVH or periventricular leukomalacia).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 10 Serious intracranial pathology (IVH or periventricular leukomalacia)

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 History-indicated cerclage vs no cerclage					
Rush 1984	1/96	1/98		22.5 %	1.02 [0.06, 16.09]
Subtotal (95% CI)	**96**	**98**		**22.5 %**	**1.02 [0.06, 16.09]**
Total events: 1 (Cerclage), 1 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	0/26	1/30		17.1 %	0.38 [0.02, 9.01]
Subtotal (95% CI)	**26**	**30**		**17.1 %**	**0.38 [0.02, 9.01]**
Total events: 0 (Cerclage), 1 (No cerclage)					



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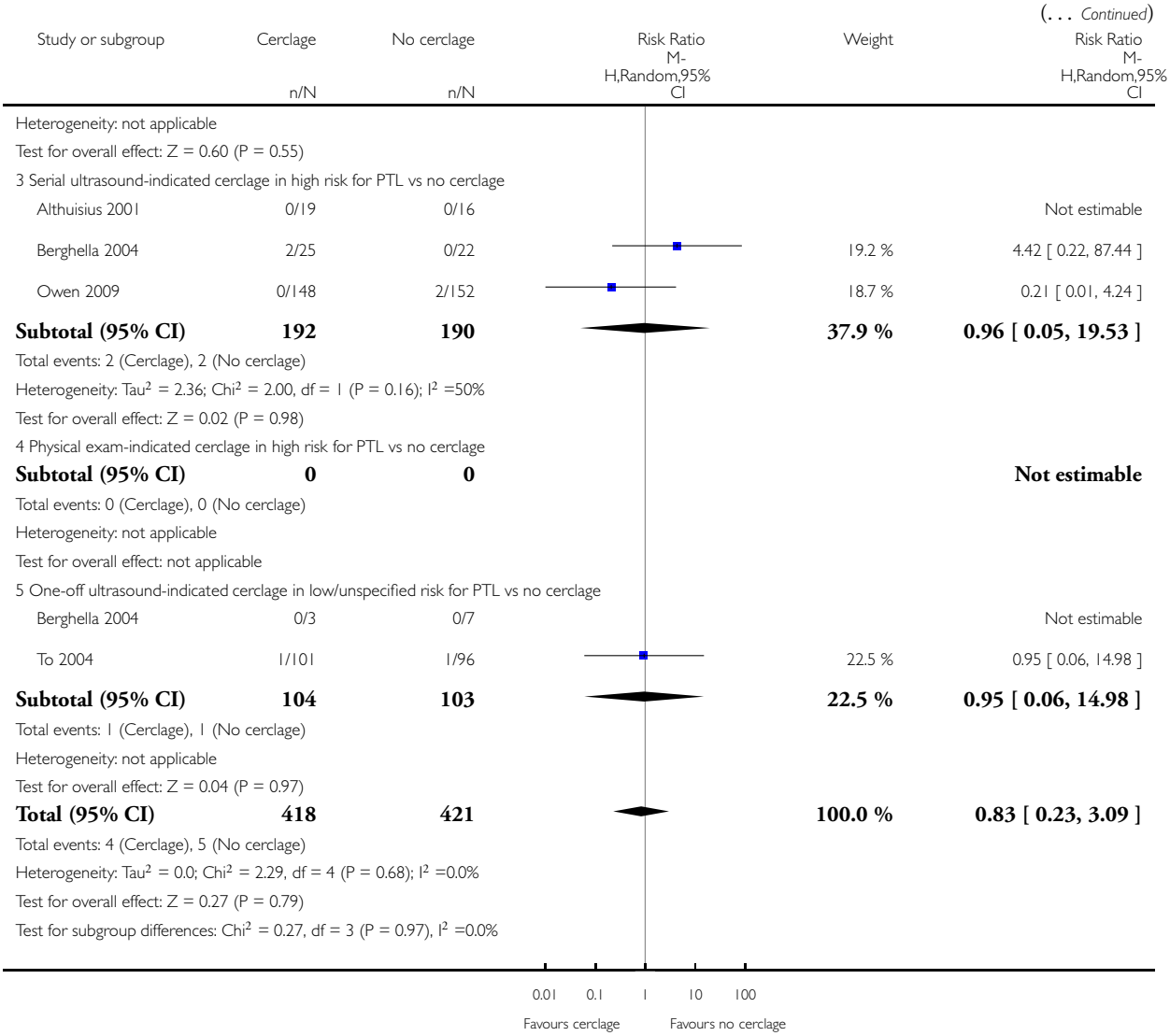

Analysis 1.11. Comparison 1 Cerclage versus no cerclage, Outcome 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)

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 History-indicated cerclage vs no cerclage					
Rush 1984	3/96	1/98		4.2 %	3.06 [0.32, 28.93]
Subtotal (95% CI)	**96**	**98**		**4.2 %**	**3.06 [0.32, 28.93]**
Total events: 3 (Cerclage), 1 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	1/26	2/30		7.9 %	0.58 [0.06, 6.00]
Subtotal (95% CI)	**26**	**30**		**7.9 %**	**0.58 [0.06, 6.00]**
Total events: 1 (Cerclage), 2 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	0/19	0/16			Not estimable
Berghella 2004	5/25	5/22		22.5 %	0.88 [0.29, 2.64]
Owen 2009	13/148	13/152		54.3 %	1.03 [0.49, 2.14]
Subtotal (95% CI)	**192**	**190**		**76.7 %**	**0.98 [0.53, 1.81]**
Total events: 18 (Cerclage), 18 (No cerclage)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	1/3	1/7		2.5 %	2.33 [0.21, 26.23]
To 2004	3/101	2/96		8.7 %	1.43 [0.24, 8.35]
Subtotal (95% CI)	**104**	**103**		**11.2 %**	**1.63 [0.39, 6.86]**
Total events: 4 (Cerclage), 3 (No cerclage)					
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 0.67 (P = 0.50)					

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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)	**418**	**421**		**100.0 %**	**1.11 [0.66, 1.88]**
Total events: 26 (Cerclage), 24 (No cerclage)					
Heterogeneity: Chi^2 = 1.74, df = 5 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi^2 = 1.51, df = 3 (P = 0.68), I^2 =0.0%					

Analysis 1.12. Comparison 1 Cerclage versus no cerclage, Outcome 12 Necrotising enterocolitis.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 12 Necrotising enterocolitis

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 History-indicated cerclage vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	0/19	0/16			Not estimable
Berghella 2004	1/25	0/2		31.2 %	0.35 [0.02, 6.74]
Owen 2009	2/148	2/152		68.8 %	1.03 [0.15, 7.20]
Subtotal (95% CI)	**192**	**170**		**100.0 %**	**0.81 [0.16, 4.12]**
Total events: 3 (Cerclage), 2 (No cerclage)					
Heterogeneity: Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%					

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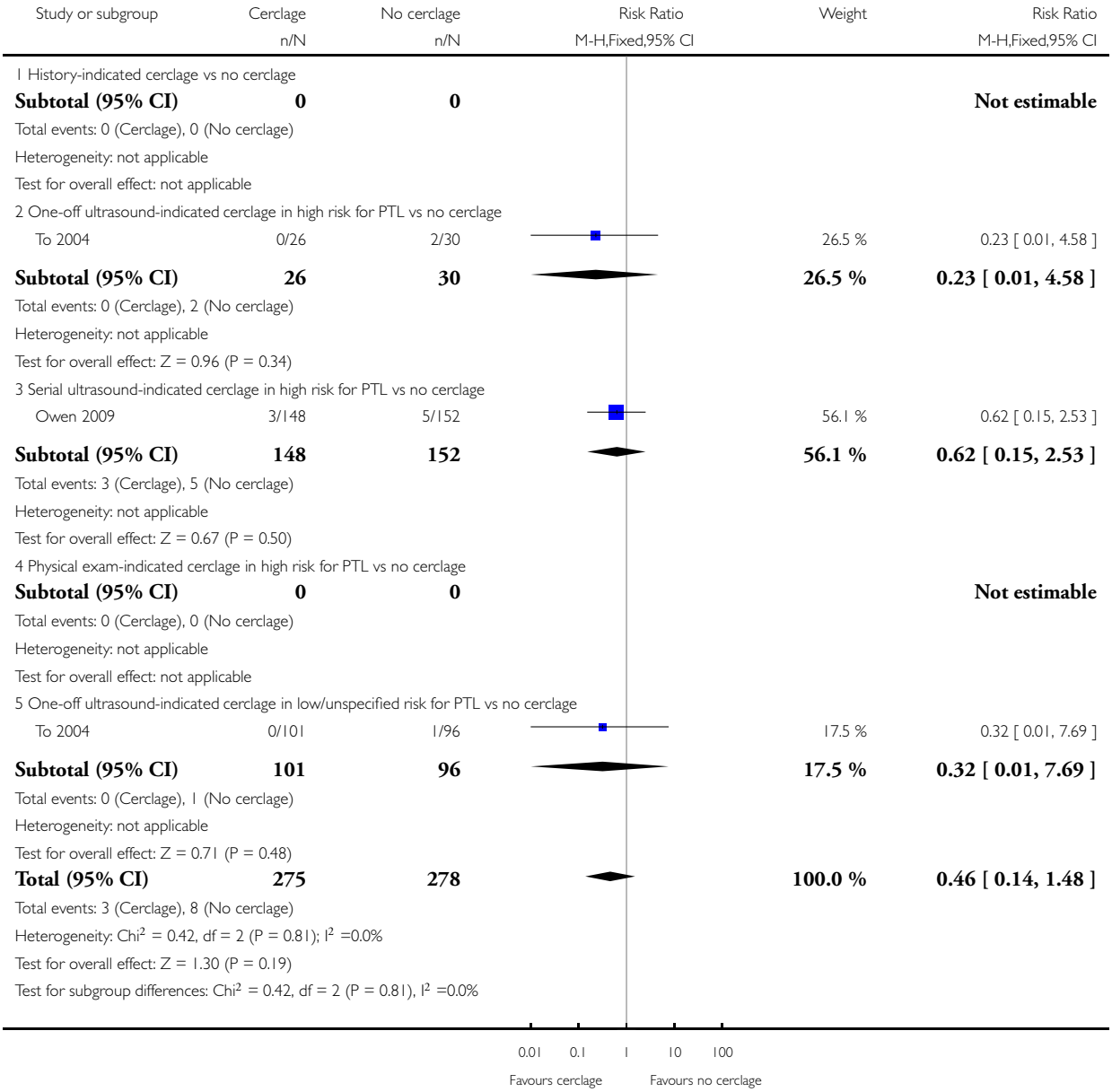
Study or subgroup	Cerclage n/N	No cerclage n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.25 (P = 0.80)					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	0/3	0/7			Not estimable
Subtotal (95% CI)	**3**	**7**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**195**	**177**		**100.0 %**	**0.81 [0.16, 4.12]**
Total events: 3 (Cerclage), 2 (No cerclage)					
Heterogeneity: Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					

Analysis 1.13. Comparison 1 Cerclage versus no cerclage, Outcome 13 Retinopathy of prematurity.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 13 Retinopathy of prematurity

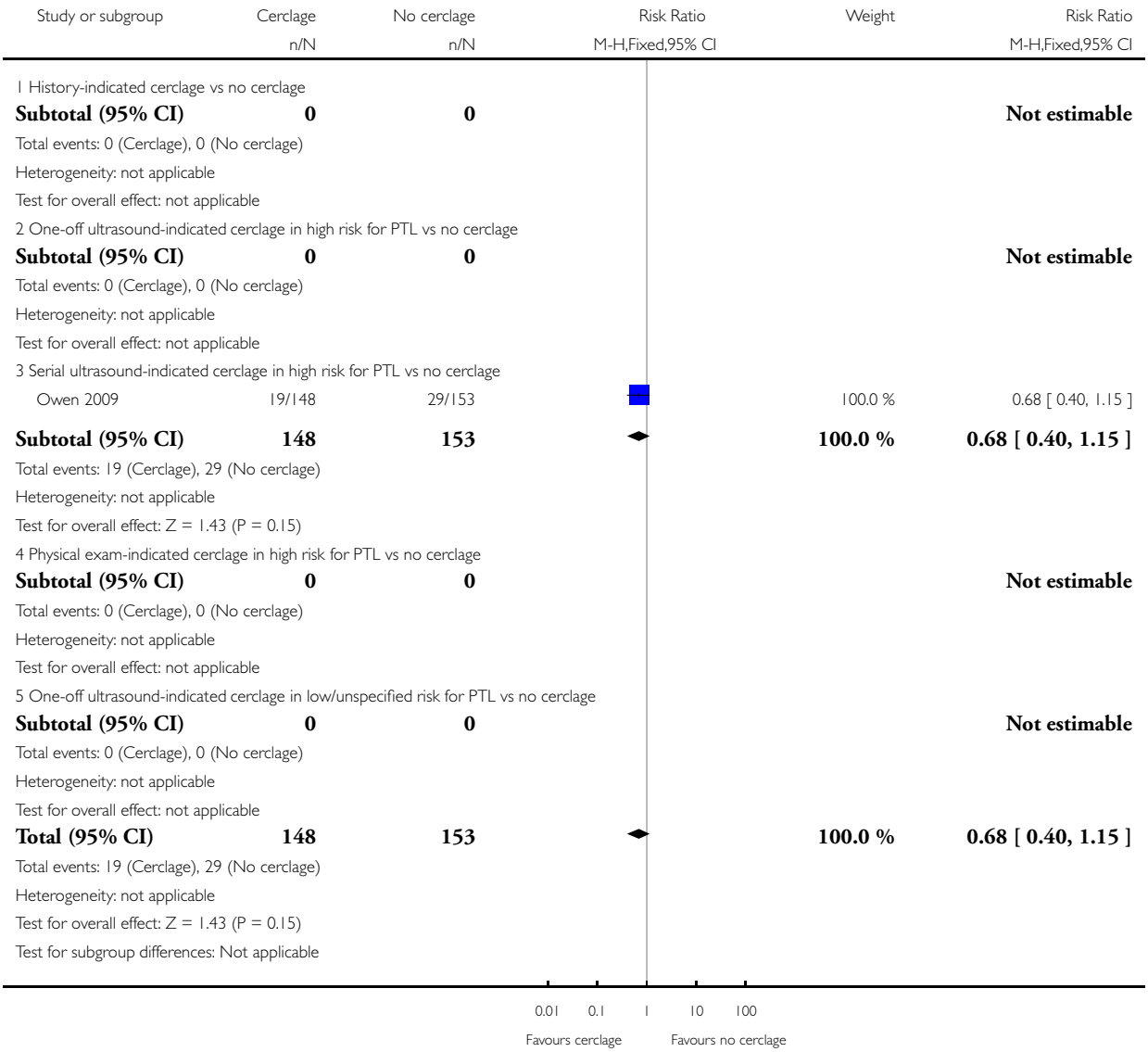


Analysis 1.14. Comparison 1 Cerclage versus no cerclage, Outcome 14 Apgar < 7 at 5 minutes.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 14 Apgar < 7 at 5 minutes



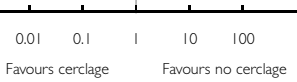
Analysis 1.15. Comparison 1 Cerclage versus no cerclage, Outcome 15 Caesarean section (elective and emergency).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 15 Caesarean section (elective and emergency)

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 History-indicated cerclage vs no cerclage					
Lazar 1984	33/268	22/238		10.9 %	1.33 [0.80, 2.22]
MRC/RCOG 1993	91/635	77/629		36.2 %	1.17 [0.88, 1.55]
Rush 1984	19/96	16/98		7.4 %	1.21 [0.66, 2.21]
Subtotal (95% CI)	**999**	**965**		**54.6 %**	**1.21 [0.96, 1.52]**
Total events: 143 (Cerclage), 115 (No cerclage)					
Heterogeneity: Chi^2 = 0.19, df = 2 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.62 (P = 0.10)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
To 2004	7/26	6/30		2.6 %	1.35 [0.52, 3.50]
Subtotal (95% CI)	**26**	**30**		**2.6 %**	**1.35 [0.52, 3.50]**
Total events: 7 (Cerclage), 6 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Althuisius 2001	4/19	3/16		1.5 %	1.12 [0.29, 4.29]
Berghella 2004	6/25	7/22		3.5 %	0.75 [0.30, 1.91]
Owen 2009	46/148	37/153		17.0 %	1.29 [0.89, 1.86]
Rust 2000	14/61	18/66		8.1 %	0.84 [0.46, 1.54]
Subtotal (95% CI)	**253**	**257**		**30.1 %**	**1.10 [0.82, 1.46]**
Total events: 70 (Cerclage), 65 (No cerclage)					
Heterogeneity: Chi^2 = 2.07, df = 3 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.62 (P = 0.53)					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
Berghella 2004	0/3	0/7			Not estimable
Rust 2000	11/43	9/37		4.5 %	1.05 [0.49, 2.26]



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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
To 2004	26/101	17/96		8.2 %	1.45 [0.84, 2.50]
Subtotal (95% CI)	**147**	**140**		**12.7 %**	**1.31 [0.84, 2.04]**
Total events: 37 (Cerclage), 26 (No cerclage)					
Heterogeneity: Chi^2 = 0.46, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Total (95% CI)	**1425**	**1392**		**100.0 %**	**1.19 [1.01, 1.40]**
Total events: 257 (Cerclage), 212 (No cerclage)					
Heterogeneity: Chi^2 = 3.25, df = 9 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 2.09 (P = 0.037)					
Test for subgroup differences: Chi^2 = 0.57, df = 3 (P = 0.90), I^2 =0.0%					

Analysis 1.16. Comparison 1 Cerclage versus no cerclage, Outcome 16 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics).

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

Comparison: 1 Cerclage versus no cerclage

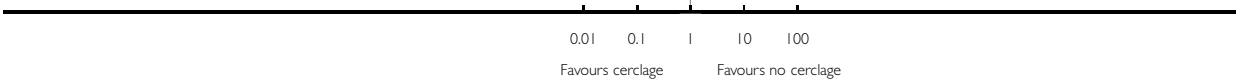
Outcome: 16 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)

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 History-indicated cerclage vs no cerclage					
Lazar 1984	60/268	43/238		47.9 %	1.24 [0.87, 1.76]
Rush 1984	11/96	4/98		29.7 %	2.81 [0.93, 8.51]
Subtotal (95% CI)	**364**	**336**		**77.6 %**	**1.57 [0.76, 3.24]**
Total events: 71 (Cerclage), 47 (No cerclage)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 1.92, df = 1 (P = 0.17); I^2 =48%					
Test for overall effect: Z = 1.21 (P = 0.23)					
2 One-off ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					

(*Continued* . . .)

(. . . *Continued*)

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
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Serial ultrasound-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Physical exam-indicated cerclage in high risk for PTL vs no cerclage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Cerclage), 0 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 One-off ultrasound-indicated cerclage in low/unspecified risk for PTL vs no cerclage					
To 2004	12/127	2/126		22.4 %	5.95 [1.36, 26.06]
Subtotal (95% CI)	**127**	**126**		**22.4 %**	**5.95 [1.36, 26.06]**
Total events: 12 (Cerclage), 2 (No cerclage)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
Total (95% CI)	**491**	**462**		**100.0 %**	**2.25 [0.89, 5.69]**
Total events: 83 (Cerclage), 49 (No cerclage)					
Heterogeneity: Tau^2 = 0.44; Chi^2 = 5.83, df = 2 (P = 0.05); I^2 =66%					
Test for overall effect: Z = 1.70 (P = 0.088)					
Test for subgroup differences: Chi^2 = 2.53, df = 1 (P = 0.11), I^2 =60%					

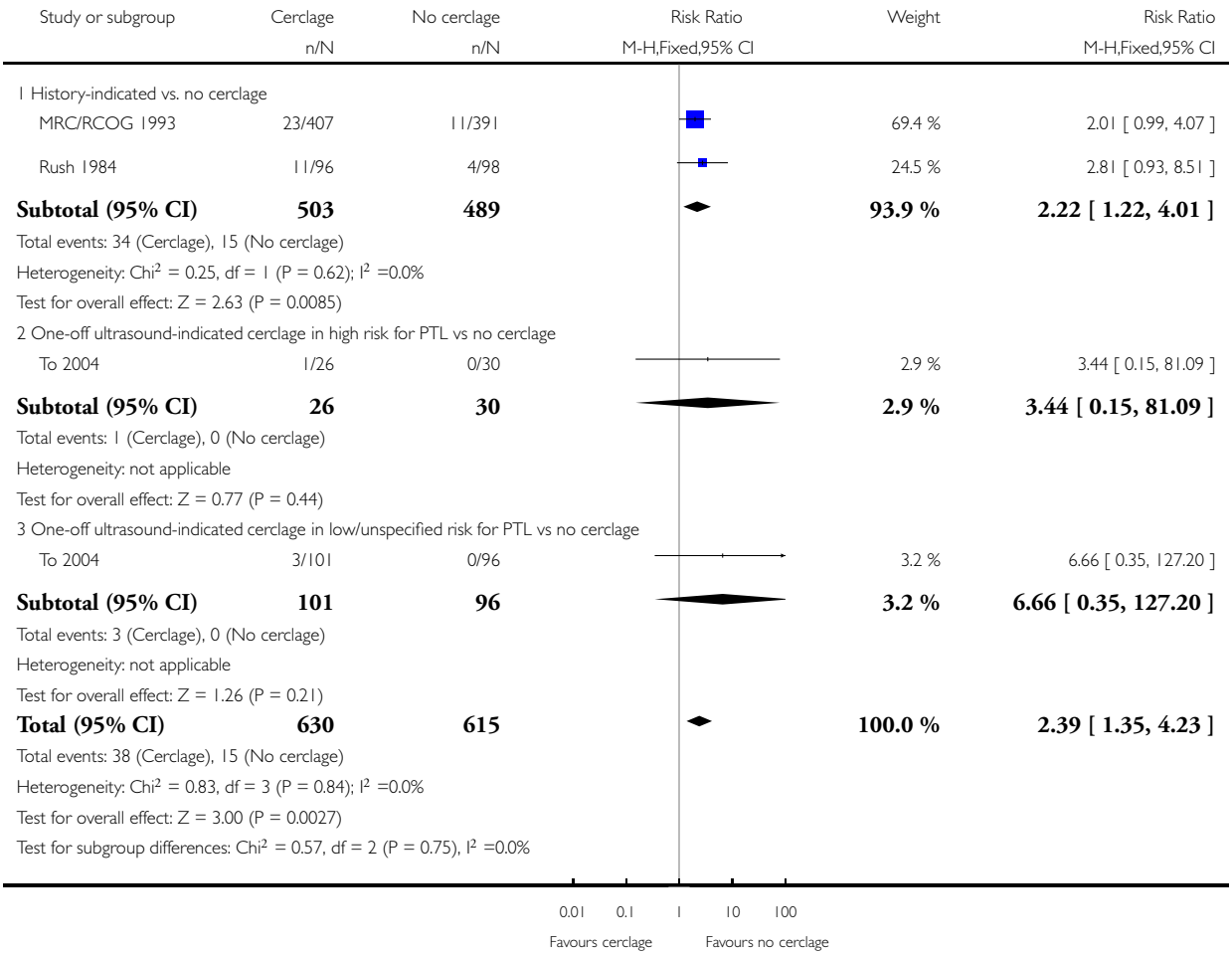


Analysis 1.17. Comparison 1 Cerclage versus no cerclage, Outcome 17 Pyrexia.

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 17 Pyrexia

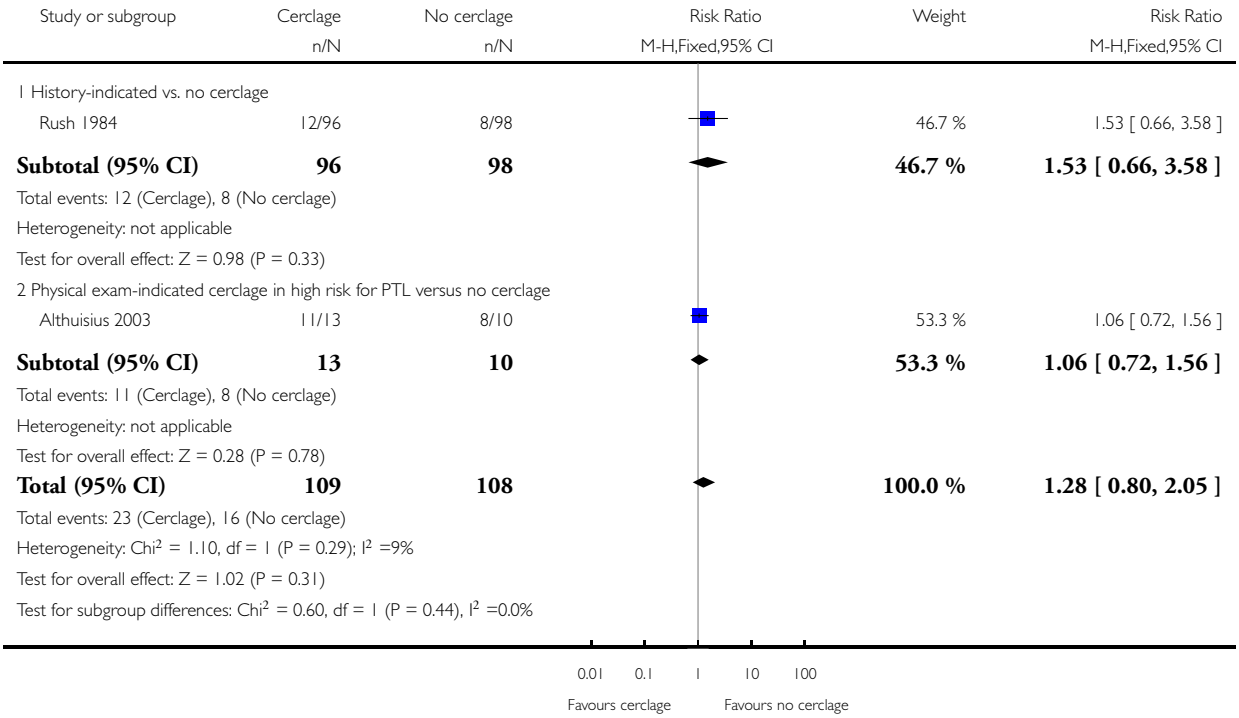


Analysis 1.18. Comparison 1 Cerclage versus no cerclage, Outcome 18 Any intravenous, oral or combined tocolysis (not prespecified).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 18 Any intravenous, oral or combined tocolysis (not prespecified)

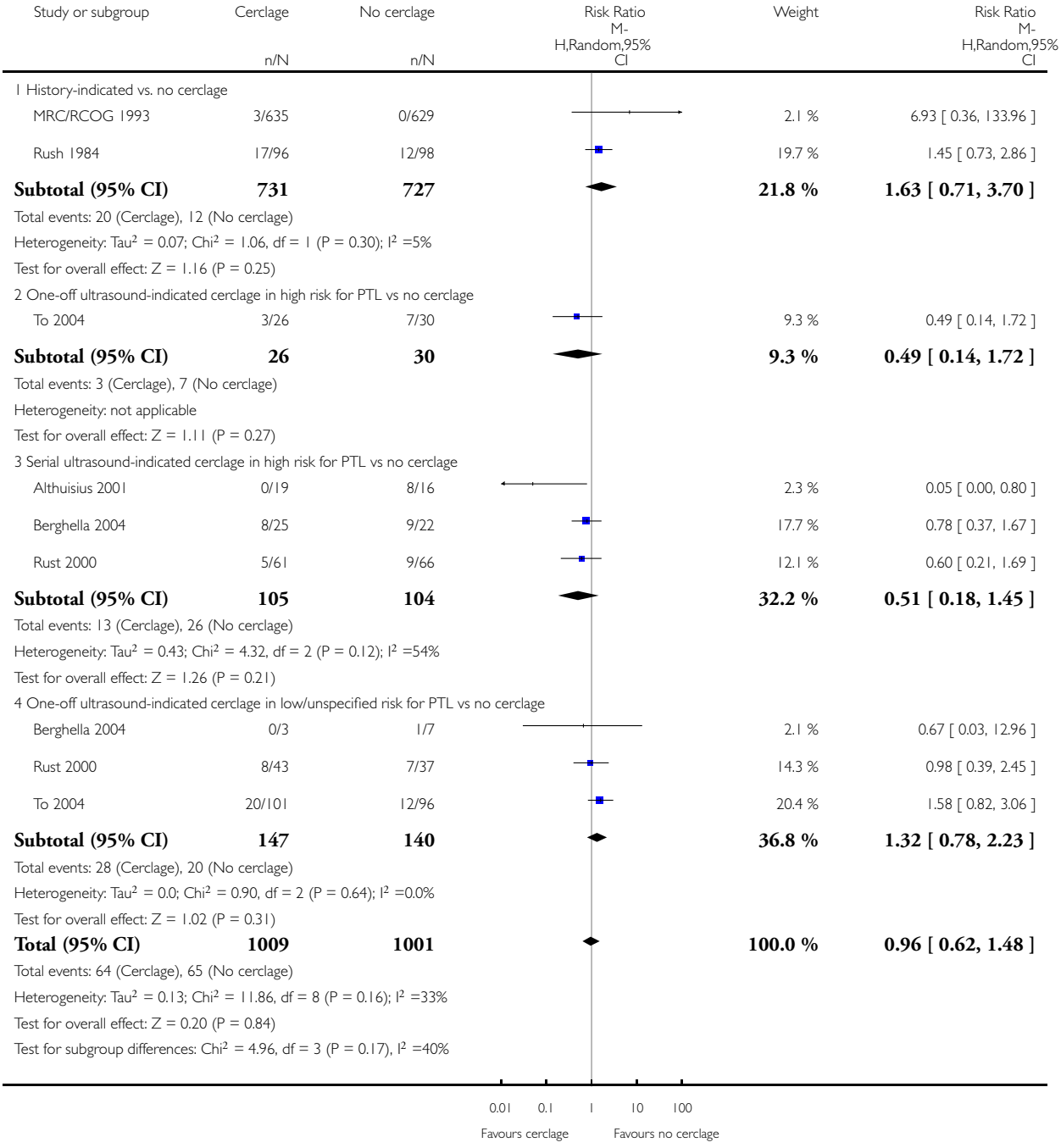


Analysis 1.19. Comparison 1 Cerclage versus no cerclage, Outcome 19 PPROM (not prespecified).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 19 PPROM (not prespecified)

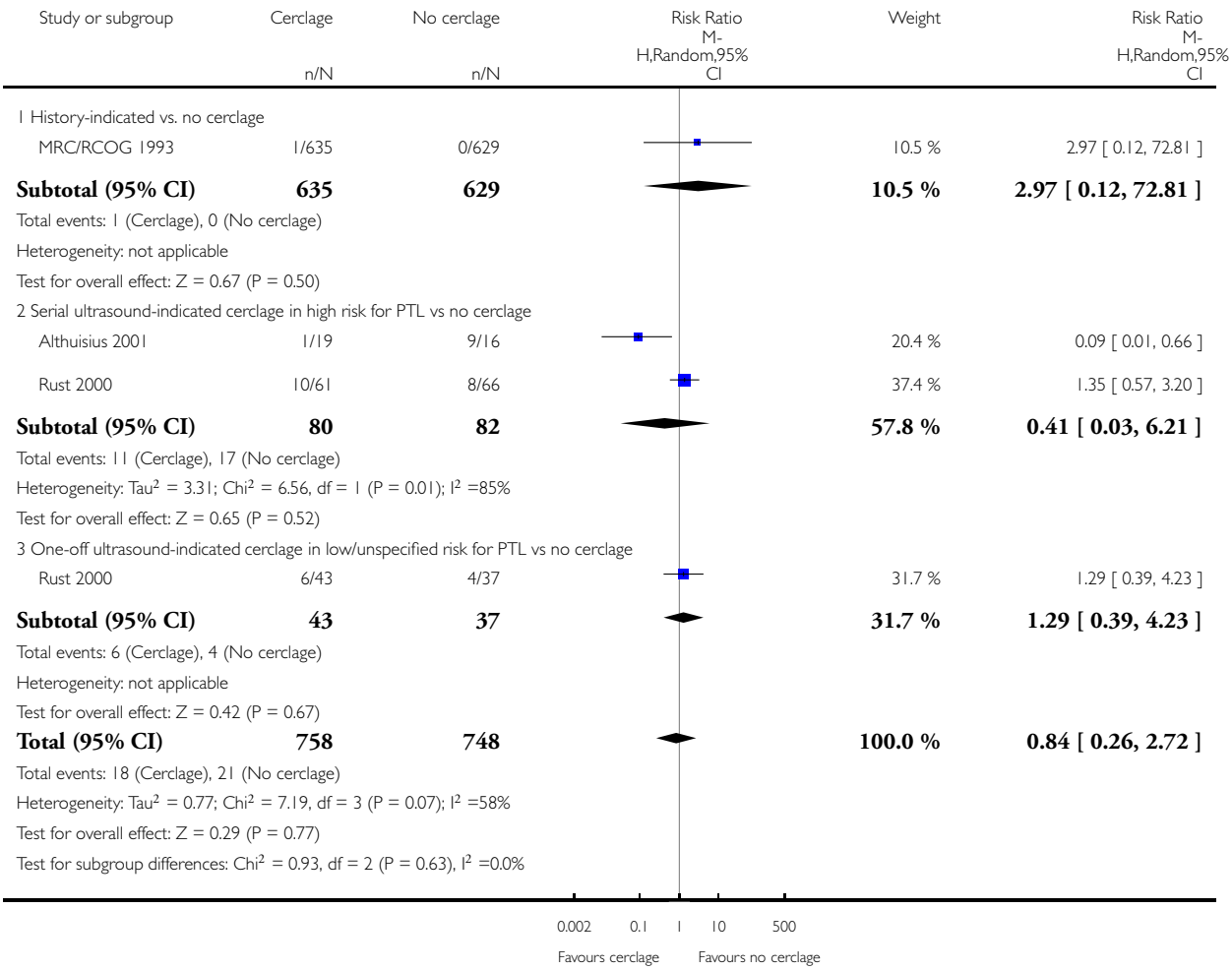


Analysis 1.20. Comparison 1 Cerclage versus no cerclage, Outcome 20 Chorioamnionitis (not prespecified).

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

Comparison: 1 Cerclage versus no cerclage

Outcome: 20 Chorioamnionitis (not prespecified)



Analysis 2.1. Comparison 2 Cerclage versus vaginal progesterone, Outcome 1 All perinatal losses.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 1 All perinatal losses

Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	5/19	5/17		80.5 %	0.89 [0.31, 2.56]
Ionescu 2012	2/46	1/26		19.5 %	1.13 [0.11, 11.87]
Total (95% CI)	**65**	**43**		**100.0 %**	**0.94 [0.36, 2.48]**

Total events: 7 (Cerclage), 6 (Vaginal progesterone)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.12 (P = 0.90)

Test for subgroup differences: Not applicable

Favours cerclage Favours vag progesterone

Analysis 2.2. Comparison 2 Cerclage versus vaginal progesterone, Outcome 2 Serious neonatal morbidity.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 2 Serious neonatal morbidity

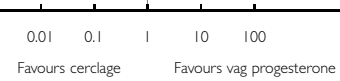
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chandiramani 2010 (1)	2/15	11/13		49.3 %	0.16 [0.04, 0.58]
Ionescu 2012	6/46	4/46		50.7 %	1.50 [0.45, 4.97]
Total (95% CI)	**61**	**59**		**100.0 %**	**0.49 [0.05, 4.52]**

Total events: 8 (Cerclage), 15 (Vaginal progesterone)

Heterogeneity: $Tau^2 = 2.14$; $Chi^2 = 6.22$, df = 1 (P = 0.01); $I^2 = 84\%$

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable



Favours cerclage Favours vag progesterone

(1) Includes neonatal infection (4 progesterone; 2 cerclage); RDS (4 progesterone); Brain abnormality on ultrasound (2 progesterone); IVH (1 progesterone).

Analysis 2.3. Comparison 2 Cerclage versus vaginal progesterone, Outcome 3 Baby discharged home healthy.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 3 Baby discharged home healthy

Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	14/15	11/12		21.7 %	1.02 [0.82, 1.27]
Ionescu 2012	42/46	44/46		78.3 %	0.95 [0.86, 1.06]
Total (95% CI)	**61**	**58**		**100.0 %**	**0.97 [0.88, 1.07]**

Total events: 56 (Cerclage), 55 (Vaginal progesterone)

Heterogeneity: $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 0.65 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Cerclage versus vaginal progesterone, Outcome 4 Stillbirths.

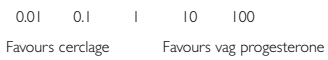
Review: Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 4 Stillbirths

Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	1/19	0/17		100.0 %	2.70 [0.12, 62.17]
Ionescu 2012	0/46	0/46			Not estimable
Total (95% CI)	**65**	**63**		**100.0 %**	**2.70 [0.12, 62.17]**

Total events: 1 (Cerclage), 0 (Vaginal progesterone)
Heterogeneity: not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 Cerclage versus vaginal progesterone, Outcome 5 Neonatal deaths before discharge.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 5 Neonatal deaths before discharge

Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	1/15	1/13		68.2 %	0.87 [0.06, 12.52]
Ionescu 2012	2/46	0/46		31.8 %	5.00 [0.25, 101.37]
Total (95% CI)	**61**	**59**		**100.0 %**	**2.18 [0.34, 13.86]**

Total events: 3 (Cerclage), 1 (Vaginal progesterone)
Heterogeneity: Chi^2 = 0.75, df = 1 (P = 0.39); I^2 =0.0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Cerclage versus vaginal progesterone, Outcome 6 Miscarriages.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 6 Miscarriages

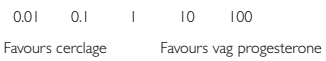
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	3/19	4/17		73.8 %	0.67 [0.17, 2.58]
Ionescu 2012	0/46	1/46		26.2 %	0.33 [0.01, 7.98]
Total (95% CI)	**65**	**63**		**100.0 %**	**0.58 [0.17, 2.01]**

Total events: 3 (Cerclage), 5 (Vaginal progesterone)

Heterogeneity: $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Cerclage versus vaginal progesterone, Outcome 7 Preterm birth before 37 completed weeks.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 7 Preterm birth before 37 completed weeks

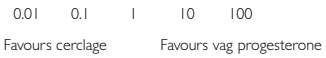
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	10/19	9/17		76.0 %	0.99 [0.54, 1.85]
Ionescu 2012	5/46	3/46		24.0 %	1.67 [0.42, 6.57]
Total (95% CI)	**65**	**63**		**100.0 %**	**1.16 [0.64, 2.08]**

Total events: 15 (Cerclage), 12 (Vaginal progesterone)

Heterogeneity: $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2 Cerclage versus vaginal progesterone, Outcome 8 Preterm birth before 34 completed weeks.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 8 Preterm birth before 34 completed weeks

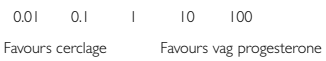
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chandiramani 2010	7/19	8/17		73.8 %	0.78 [0.36, 1.70]
Ionescu 2012	5/46	3/46		26.2 %	1.67 [0.42, 6.57]
Total (95% CI)	**65**	**63**		**100.0 %**	**1.01 [0.51, 2.01]**

Total events: 12 (Cerclage), 11 (Vaginal progesterone)

Heterogeneity: $Chi^2 = 0.93$, df = 1 (P = 0.33); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

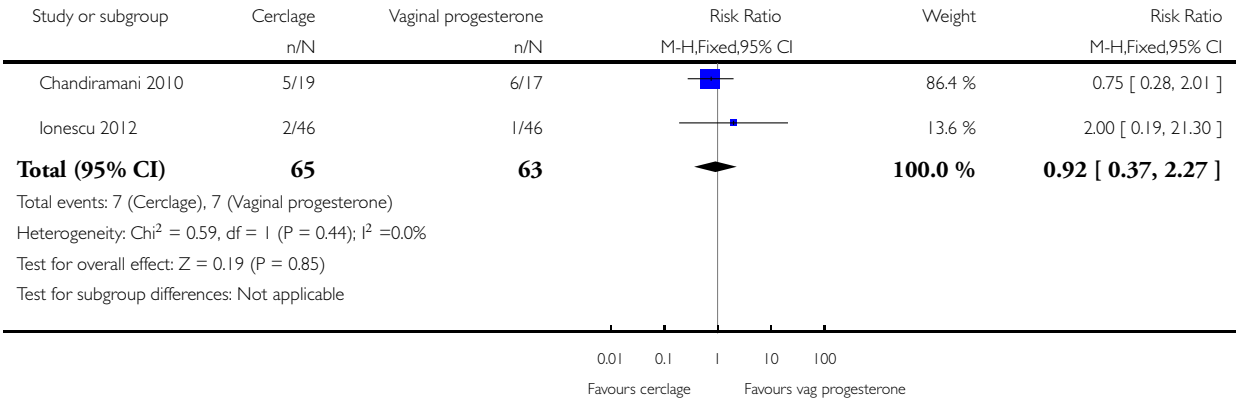


Analysis 2.9. Comparison 2 Cerclage versus vaginal progesterone, Outcome 9 Preterm birth before 28 completed weeks.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 9 Preterm birth before 28 completed weeks

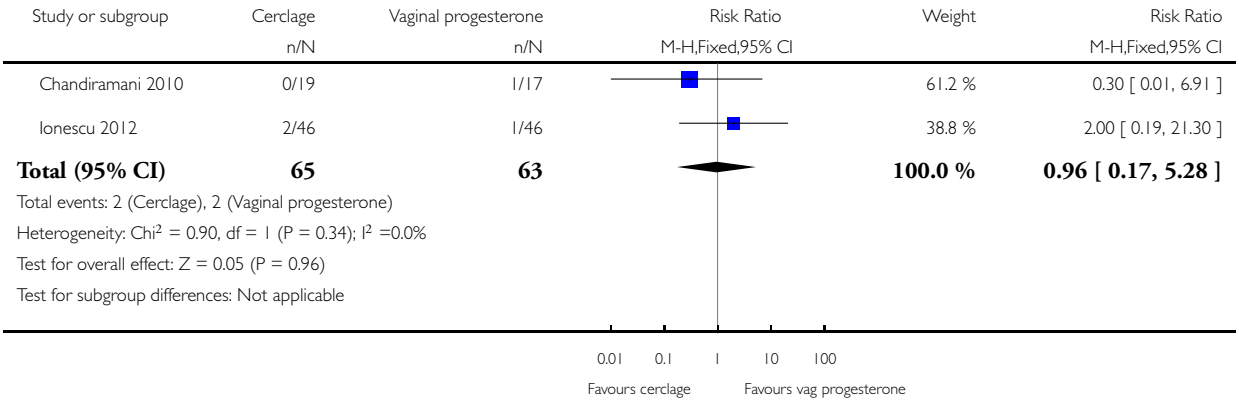


Analysis 2.10. Comparison 2 Cerclage versus vaginal progesterone, Outcome 10 Serious intracranial pathology (IVH or periventricular leucomalacia).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 10 Serious intracranial pathology (IVH or periventricular leucomalacia)

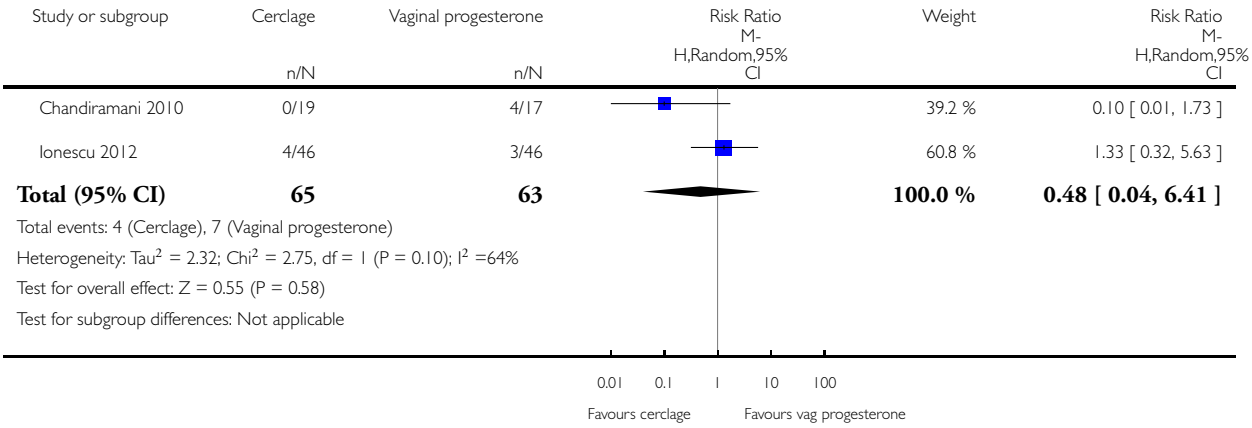


Analysis 2.11. Comparison 2 Cerclage versus vaginal progesterone, Outcome 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)

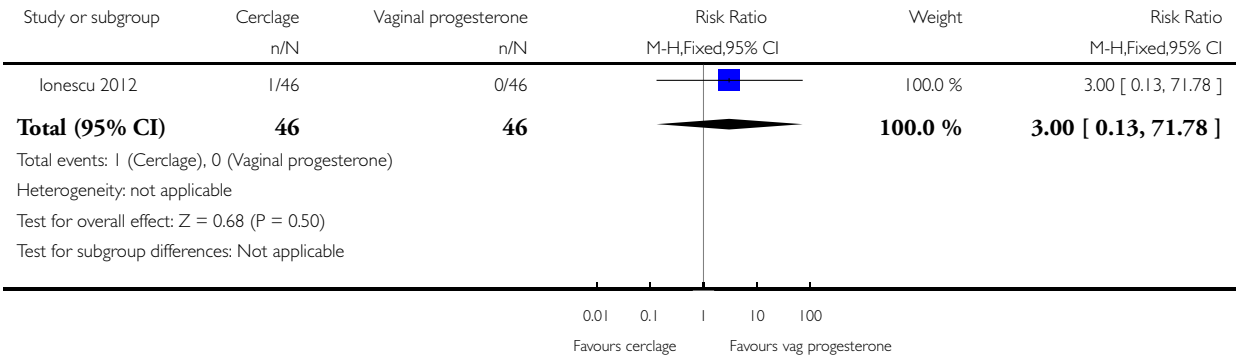


Analysis 2.12. Comparison 2 Cerclage versus vaginal progesterone, Outcome 12 Necrotising enterocolitis.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 12 Necrotising enterocolitis

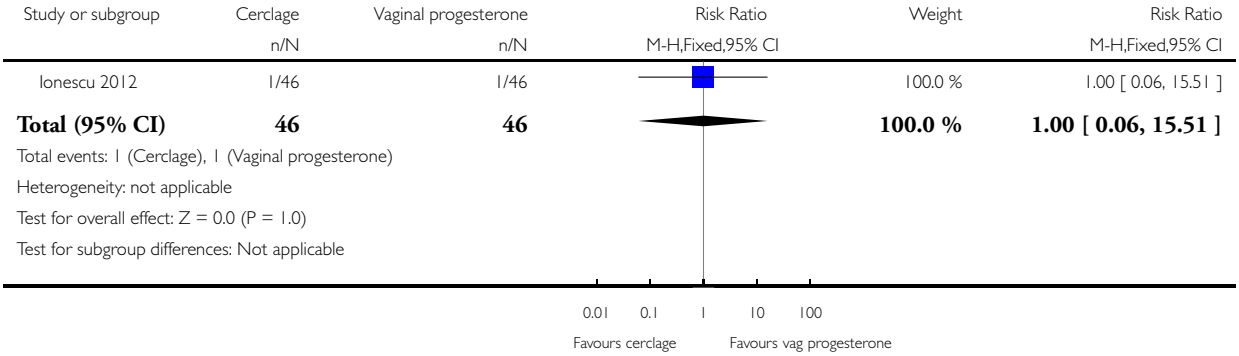


Analysis 2.13. Comparison 2 Cerclage versus vaginal progesterone, Outcome 13 Retinopathy of prematurity.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 13 Retinopathy of prematurity

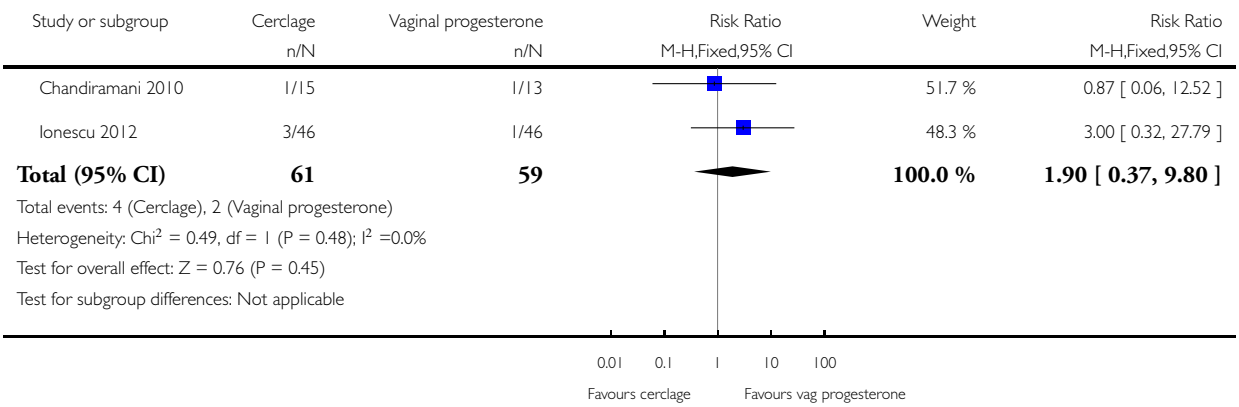


Analysis 2.14. Comparison 2 Cerclage versus vaginal progesterone, Outcome 14 Apgar < 7 at 5 minutes.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 14 Apgar < 7 at 5 minutes



Analysis 2.15. Comparison 2 Cerclage versus vaginal progesterone, Outcome 15 Caesarean section (elective and emergency).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 15 Caesarean section (elective and emergency)

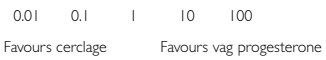
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chandiramani 2010	2/19	6/17		35.9 %	0.30 [0.07, 1.28]
Ionescu 2012	35/46	33/46		64.1 %	1.06 [0.83, 1.35]
Total (95% CI)	**65**	**63**		**100.0 %**	**0.67 [0.18, 2.47]**

Total events: 37 (Cerclage), 39 (Vaginal progesterone)

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 3.35$, df = 1 (P = 0.07); $I^2 = 70\%$

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable



Analysis 2.17. Comparison 2 Cerclage versus vaginal progesterone, Outcome 17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)

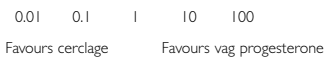
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ionescu 2012	3/46	1/46		100.0 %	3.00 [0.32, 27.79]
Total (95% CI)	**46**	**46**		**100.0 %**	**3.00 [0.32, 27.79]**

Total events: 3 (Cerclage), 1 (Vaginal progesterone)

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



Analysis 2.18. Comparison 2 Cerclage versus vaginal progesterone, Outcome 18 Pyrexia.

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 18 Pyrexia

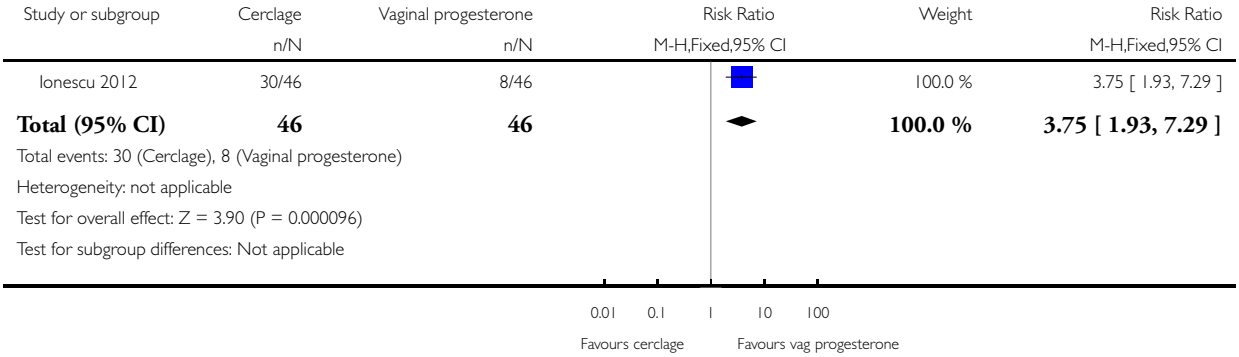
Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ionescu 2012	0/46	0/46			Not estimable
Total (95% CI)	**46**	**46**			**Not estimable**
Total events: 0 (Cerclage), 0 (Vaginal progesterone)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 2.19. Comparison 2 Cerclage versus vaginal progesterone, Outcome 19 Any intravenous, oral or combined tocolysis (not prespecified).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 19 Any intravenous, oral or combined tocolysis (not prespecified)

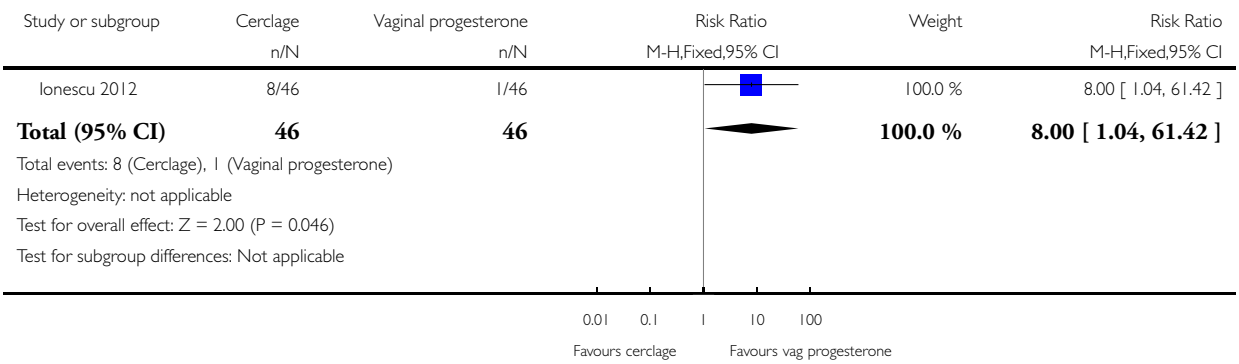


Analysis 2.20. Comparison 2 Cerclage versus vaginal progesterone, Outcome 20 PPROM (not prespecified).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 20 PPROM (not prespecified)



Analysis 2.21. Comparison 2 Cerclage versus vaginal progesterone, Outcome 21 Chorioamnionitis (not prespecified).

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

Comparison: 2 Cerclage versus vaginal progesterone

Outcome: 21 Chorioamnionitis (not prespecified)

Study or subgroup	Cerclage n/N	Vaginal progesterone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chandiramani 2010	1/19	2/17		55.4 %	0.45 [0.04, 4.50]
Ionescu 2012	3/46	0/46		44.6 %	7.00 [0.37, 131.81]
Total (95% CI)	**65**	**63**		**100.0 %**	**1.53 [0.10, 23.61]**

Total events: 4 (Cerclage), 2 (Vaginal progesterone)

Heterogeneity: $Tau^2 = 2.14$; $Chi^2 = 2.18$, df = 1 (P = 0.14); $I^2 = 54\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 1 All perinatal losses.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 1 All perinatal losses

Study or subgroup	Cerclage n/N	IM Progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keeler 2009	14/42	11/37		100.0 %	1.12 [0.58, 2.16]
Total (95% CI)	**42**	**37**		**100.0 %**	**1.12 [0.58, 2.16]**

Total events: 14 (Cerclage), 11 (IM Progesterone)

Heterogeneity: not applicable

Test for overall effect: Z = 0.34 (P = 0.73)

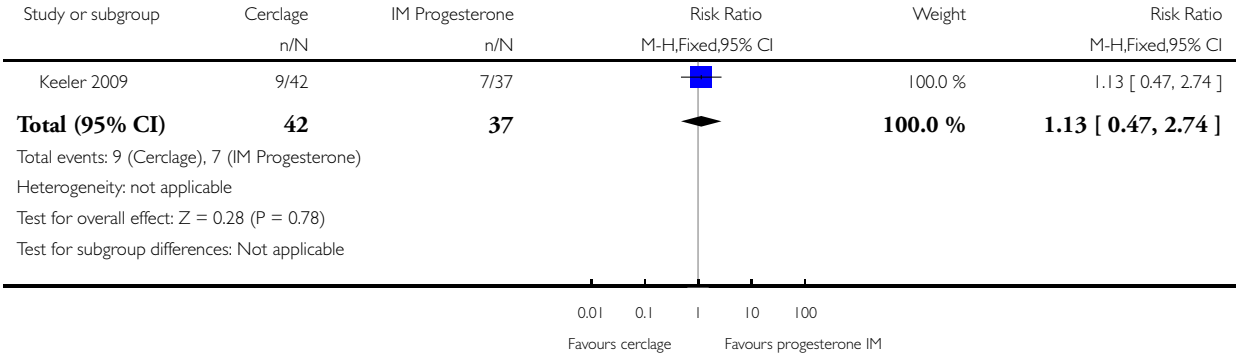
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 2 Serious neonatal morbidity.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 2 Serious neonatal morbidity

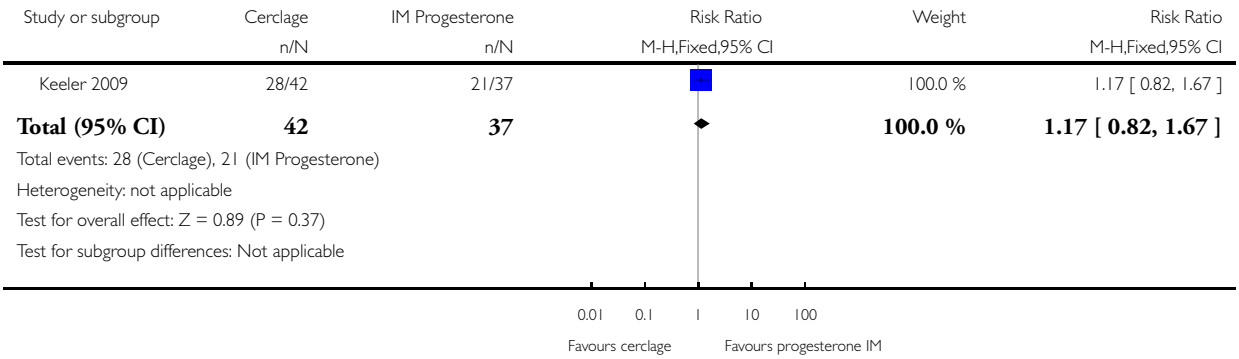


Analysis 3.3. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 3 Baby discharged home healthy.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 3 Baby discharged home healthy

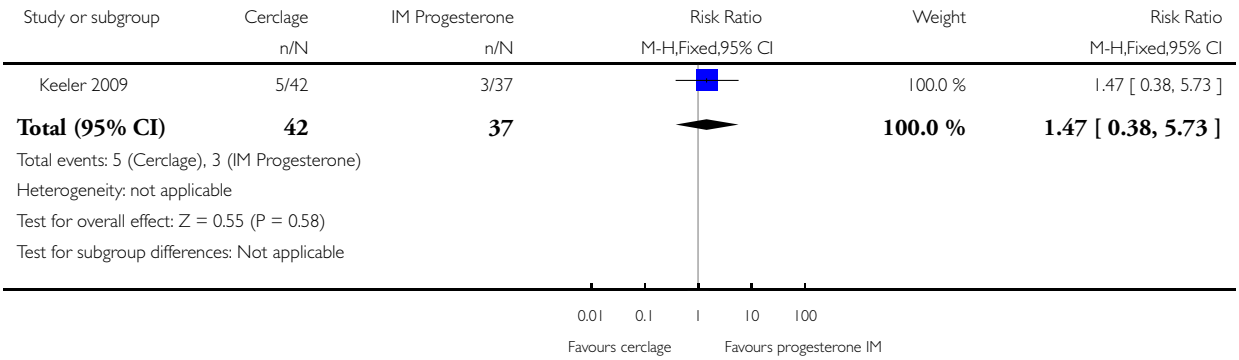


Analysis 3.6. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 6 Miscarriages.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 6 Miscarriages

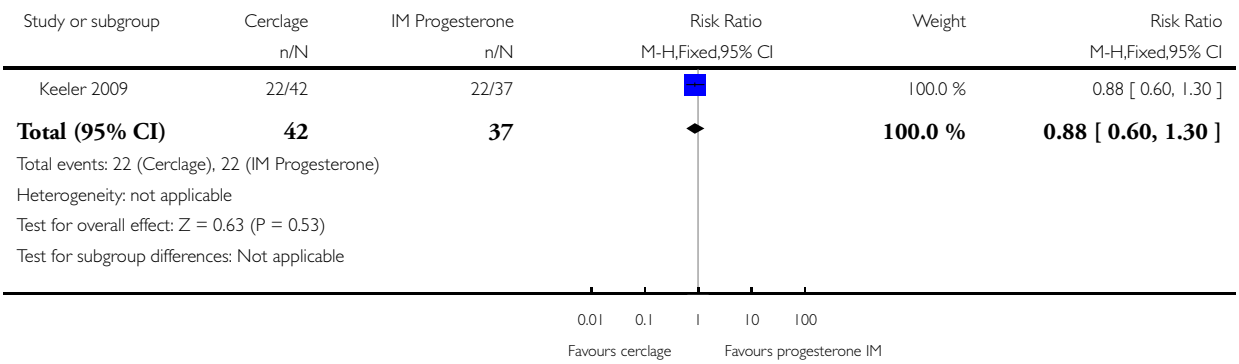


Analysis 3.7. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 7 Preterm birth before 37 completed weeks.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 7 Preterm birth before 37 completed weeks



Analysis 3.9. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 9 Preterm birth before 28 completed weeks.

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 9 Preterm birth before 28 completed weeks

Study or subgroup	Cerclage n/N	IM Progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keeler 2009	10/42	7/37		100.0 %	1.26 [0.53, 2.97]
Total (95% CI)	**42**	**37**		**100.0 %**	**1.26 [0.53, 2.97]**

Total events: 10 (Cerclage), 7 (IM Progesterone)
Heterogeneity: not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable

Analysis 3.19. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 19 PPROM (not prespecified).

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 19 PPROM (not prespecified)

Study or subgroup	Cerclage n/N	IM Progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keeler 2009	13/42	13/37		100.0 %	0.88 [0.47, 1.65]
Total (95% CI)	**42**	**37**		**100.0 %**	**0.88 [0.47, 1.65]**

Total events: 13 (Cerclage), 13 (IM Progesterone)
Heterogeneity: not applicable
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable

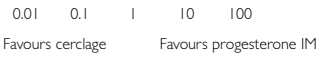
Analysis 3.20. Comparison 3 Cerclage versus intramuscular progesterone, Outcome 20 Chorioamnionitis (not prespecified).

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

Comparison: 3 Cerclage versus intramuscular progesterone

Outcome: 20 Chorioamnionitis (not prespecified)

Study or subgroup	Cerclage n/N	IM Progesterone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keeler 2009	12/42	8/37		100.0 %	1.32 [0.61, 2.88]
Total (95% CI)	**42**	**37**		**100.0 %**	**1.32 [0.61, 2.88]**
Total events: 12 (Cerclage), 8 (IM Progesterone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Not applicable					



Analysis 5.1. Comparison 5 Any comparison of different cerclage protocols, Outcome 1 All perinatal losses.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 1 All perinatal losses

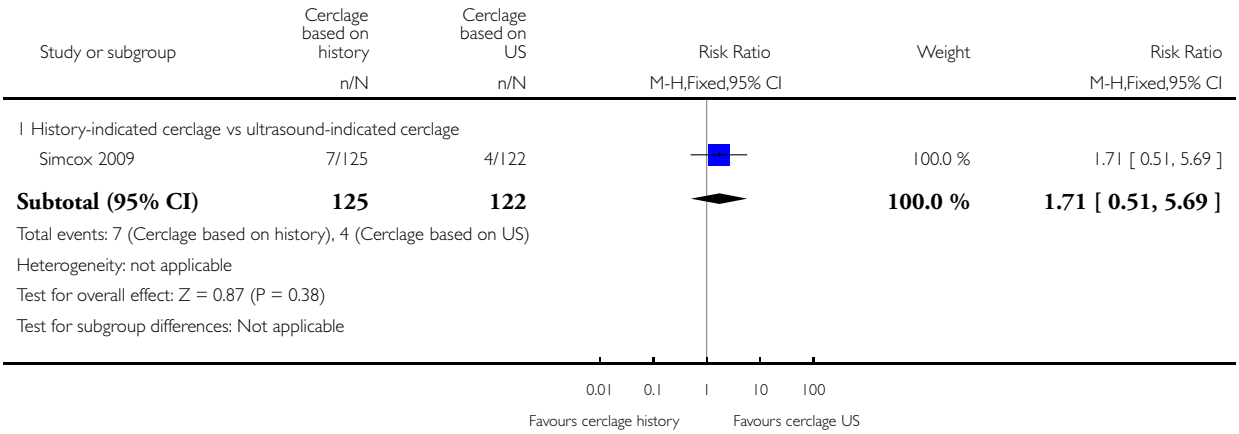
Study or subgroup	Cerclage based on history n/N	Cerclage based on US n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 History-indicated cerclage vs ultrasound-indicated cerclage					
Simcox 2009	14/125	10/122		100.0 %	1.37 [0.63, 2.96]
Subtotal (95% CI)	**125**	**122**		**100.0 %**	**1.37 [0.63, 2.96]**
Total events: 14 (Cerclage based on history), 10 (Cerclage based on US)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Any comparison of different cerclage protocols, Outcome 2 Serious neonatal morbidity.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 2 Serious neonatal morbidity

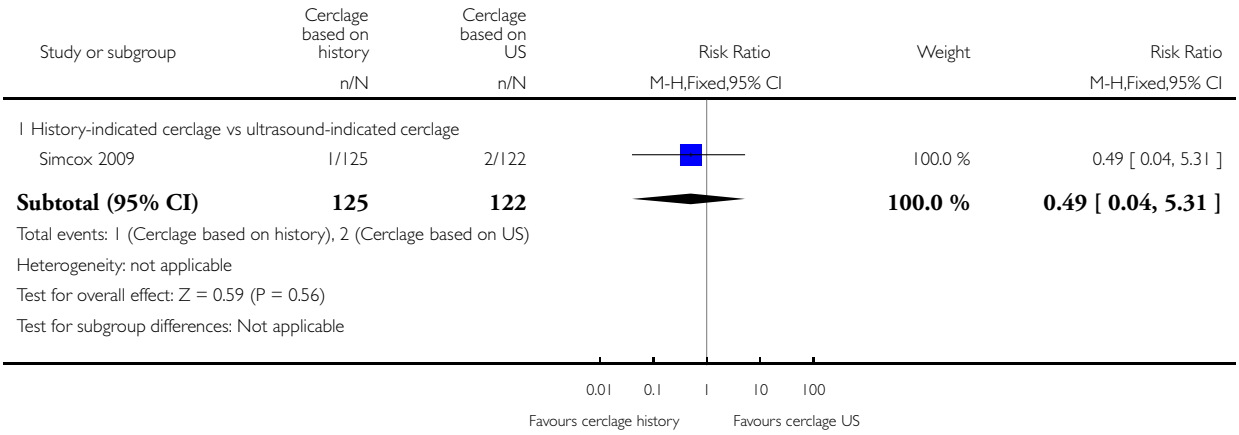


Analysis 5.4. Comparison 5 Any comparison of different cerclage protocols, Outcome 4 Stillbirths.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 4 Stillbirths

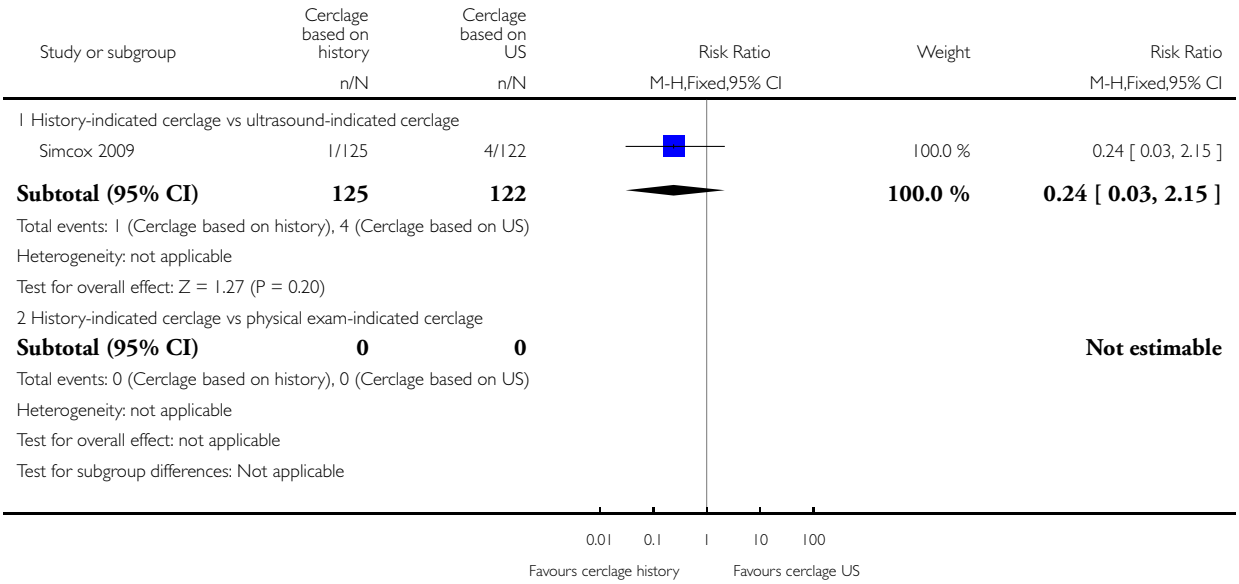


Analysis 5.5. Comparison 5 Any comparison of different cerclage protocols, Outcome 5 Neonatal deaths before discharge.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 5 Neonatal deaths before discharge

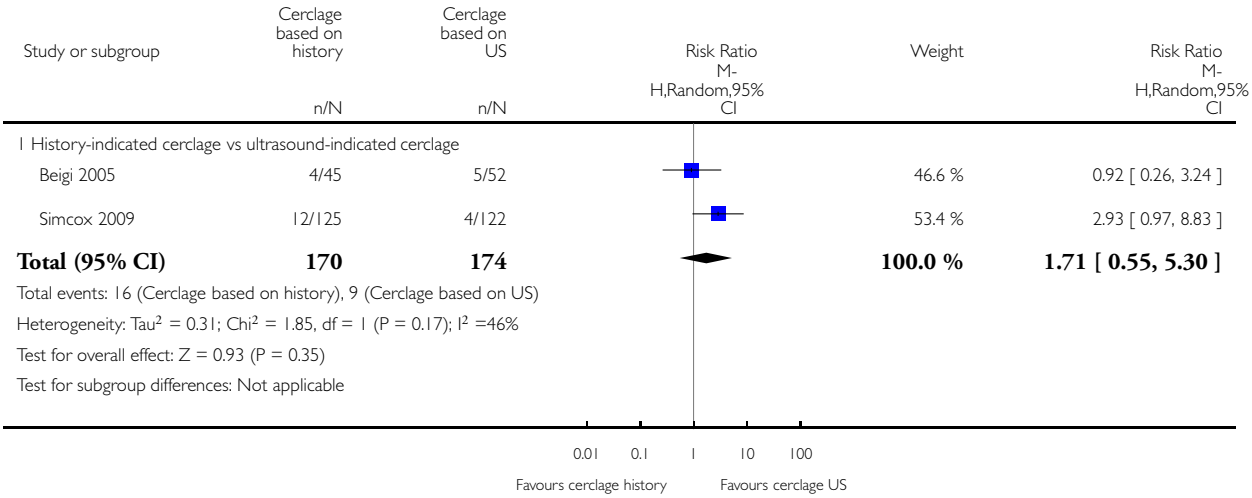


Analysis 5.6. Comparison 5 Any comparison of different cerclage protocols, Outcome 6 Miscarriages.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 6 Miscarriages

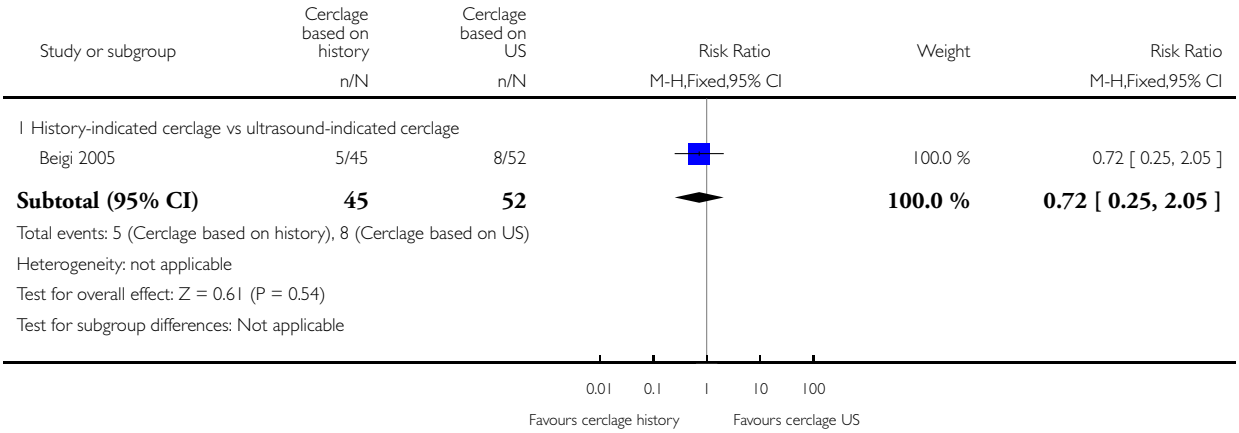


Analysis 5.7. Comparison 5 Any comparison of different cerclage protocols, Outcome 7 Preterm birth before 37 completed weeks.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 7 Preterm birth before 37 completed weeks

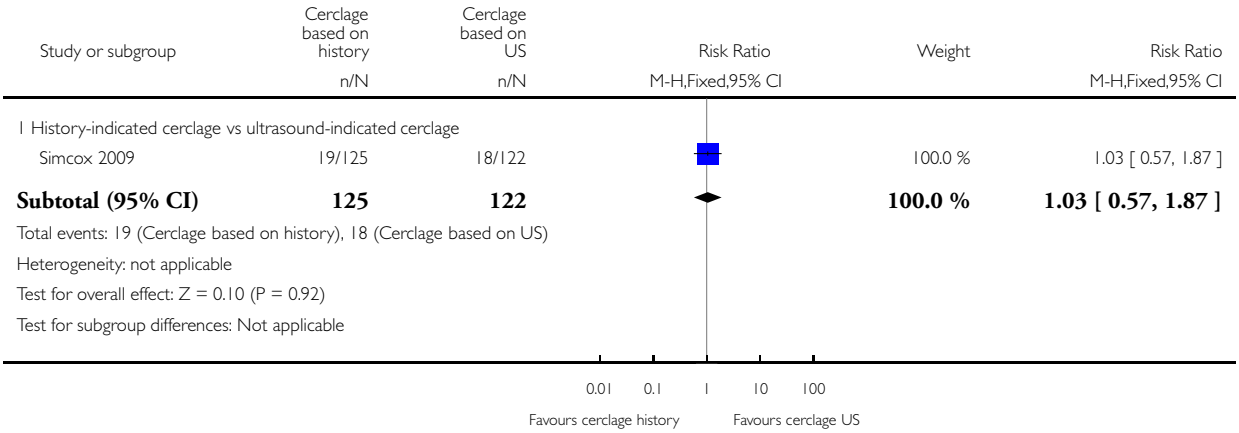


Analysis 5.8. Comparison 5 Any comparison of different cerclage protocols, Outcome 8 Preterm birth before 34 completed weeks.

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 8 Preterm birth before 34 completed weeks

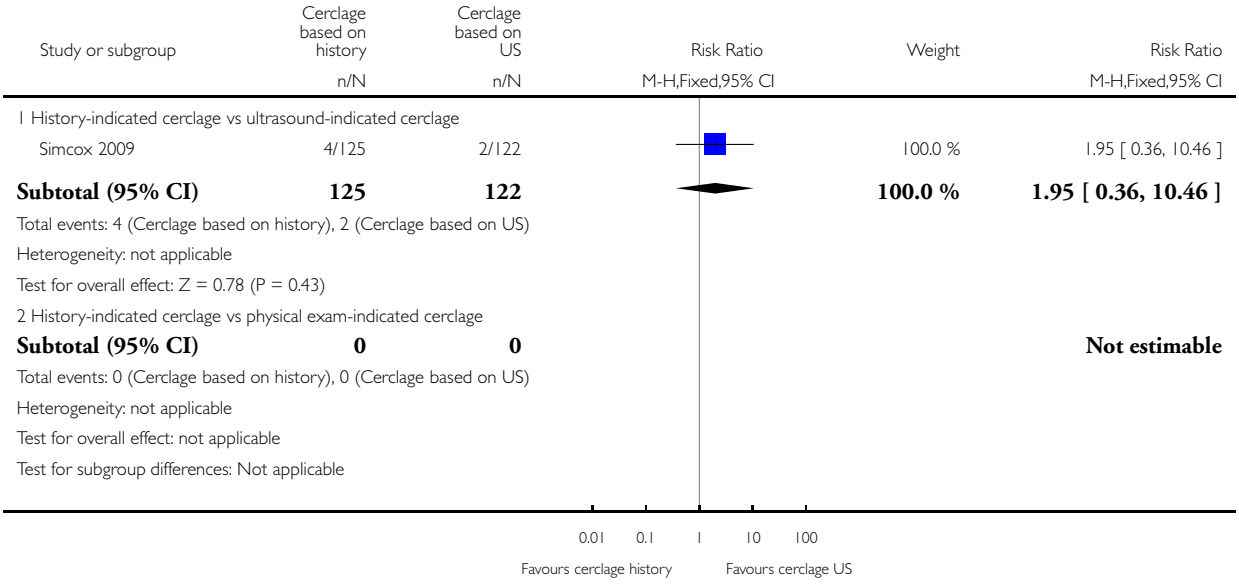


Analysis 5.10. Comparison 5 Any comparison of different cerclage protocols, Outcome 10 Serious intracranial pathology (IVH or periventricular leucomalacia).

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 10 Serious intracranial pathology (IVH or periventricular leucomalacia)

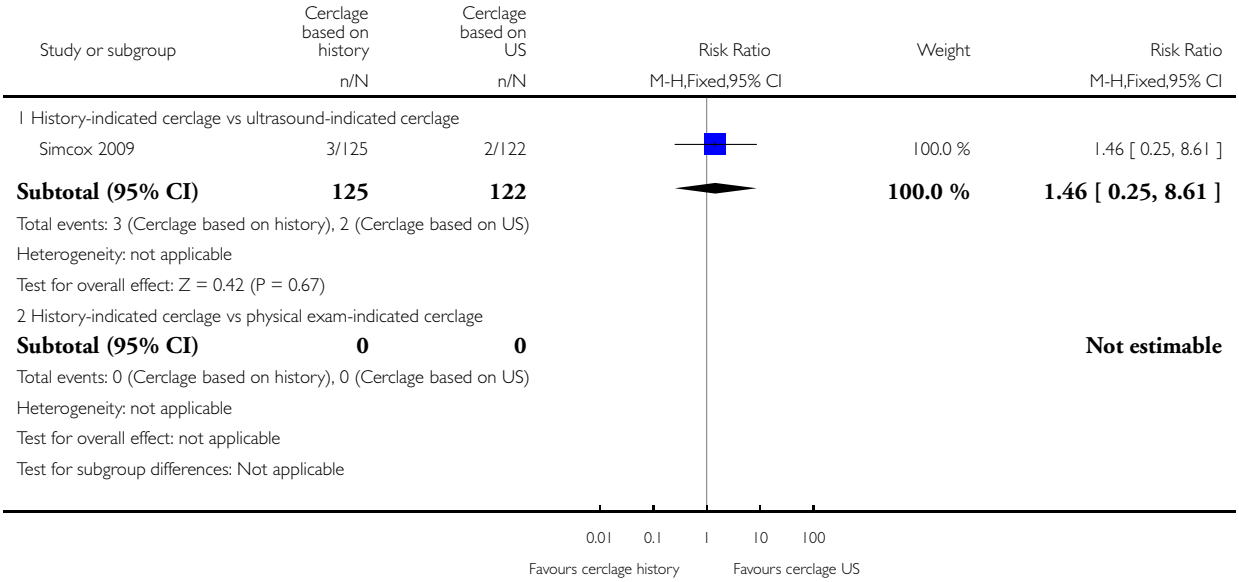


Analysis 5.11. Comparison 5 Any comparison of different cerclage protocols, Outcome 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life).

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 11 Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)

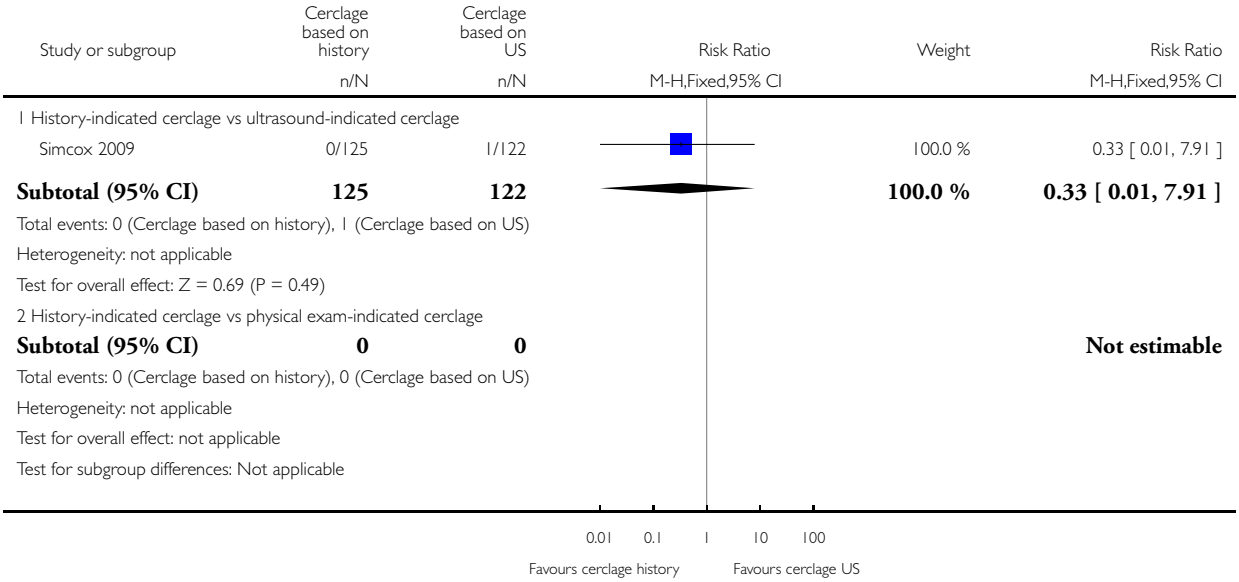


Analysis 5.16. Comparison 5 Any comparison of different cerclage protocols, Outcome 16 Maternal infection requiring intervention(antibiotics or delivery).

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 16 Maternal infection requiring intervention(antibiotics or delivery)

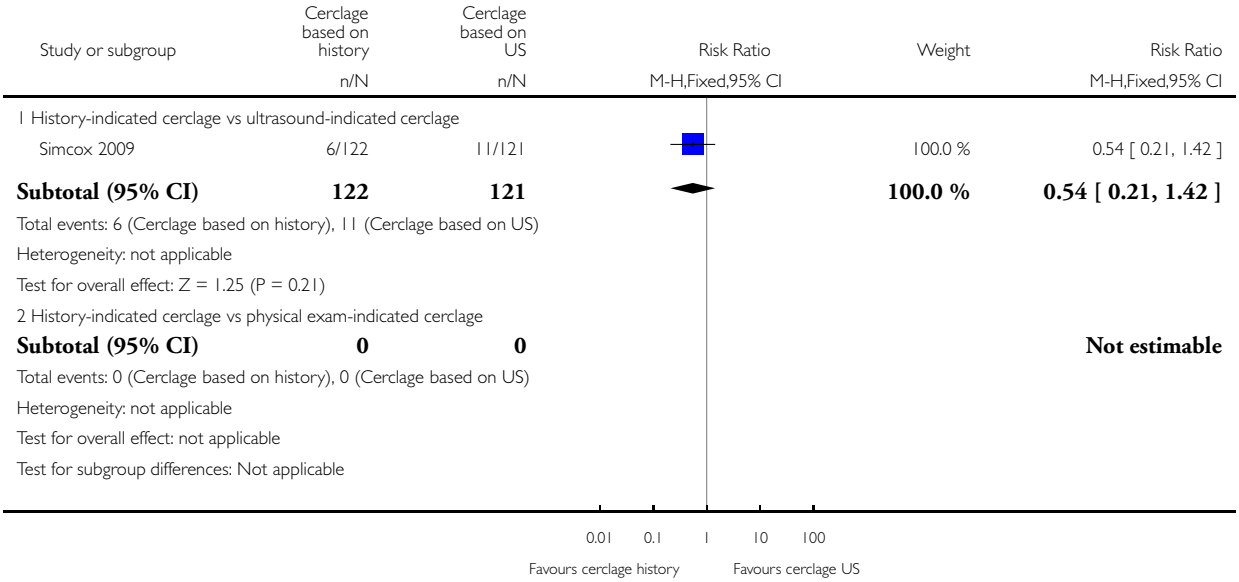


Analysis 5.17. Comparison 5 Any comparison of different cerclage protocols, Outcome 17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics).

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 17 Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)

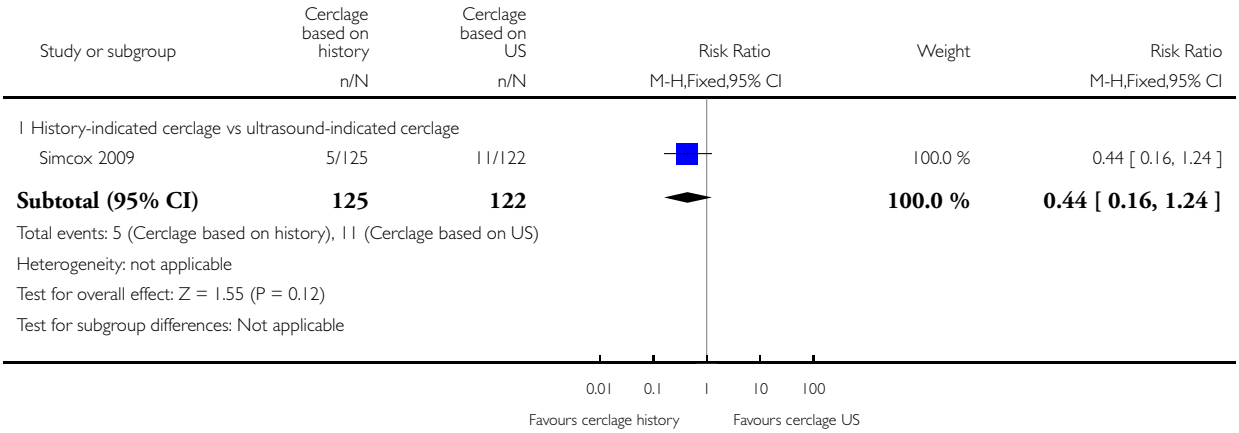


Analysis 5.18. Comparison 5 Any comparison of different cerclage protocols, Outcome 18 Tocolysis (not prespecified).

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

Comparison: 5 Any comparison of different cerclage protocols

Outcome: 18 Tocolysis (not prespecified)



Analysis 6.1. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 1 All perinatal losses.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 1 All perinatal losses

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	0/3	0/7			Not estimable
Lazar 1984	2/268	1/238		0.8 %	1.78 [0.16, 19.46]
Rust 2000	5/43	2/37		1.6 %	2.15 [0.44, 10.44]
Ezechi 2004	0/39	2/42		1.8 %	0.22 [0.01, 4.34]
To 2004	2/26	3/30		2.1 %	0.77 [0.14, 4.25]
Althuisius 2001	0/19	3/16		2.8 %	0.12 [0.01, 2.19]
Berghella 2004	4/25	4/22		3.2 %	0.88 [0.25, 3.11]
Althuisius 2003	9/16	4/14		3.2 %	1.97 [0.77, 5.01]
Rust 2000	7/61	5/66		3.6 %	1.51 [0.51, 4.52]
Rush 1984	9/96	9/98		6.6 %	1.02 [0.42, 2.46]
To 2004	7/101	9/96		6.9 %	0.74 [0.29, 1.91]
Owen 2009	13/148	25/152		18.3 %	0.53 [0.28, 1.00]
MRC/RCOG 1993	53/635	66/629		49.3 %	0.80 [0.56, 1.12]
Total (95% CI)	**1480**	**1447**		**100.0 %**	**0.82 [0.65, 1.04]**

Total events: 111 (Cerclage), 133 (No cerclage)

Heterogeneity: Chi^2 = 10.95, df = 11 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 6.2. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 2 Serious neonatal morbidity.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 2 Serious neonatal morbidity

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
Althuisius 2001 (1)	1/19	5/16		10.7 %	0.17 [0.02, 1.30]
Althuisius 2003 (2)	1/16	4/14		8.4 %	0.22 [0.03, 1.73]
Berghella 2004	6/25	6/22		12.6 %	0.88 [0.33, 2.33]
Berghella 2004	1/3	2/7		2.4 %	1.17 [0.16, 8.48]
Owen 2009	16/148	18/153		34.8 %	0.92 [0.49, 1.73]
Rust 2000	3/61	6/66		11.3 %	0.54 [0.14, 2.07]
Rust 2000	4/43	3/37		6.3 %	1.15 [0.27, 4.80]
To 2004	2/26	3/30		5.5 %	0.77 [0.14, 4.25]
To 2004	7/101	4/96		8.1 %	1.66 [0.50, 5.50]
Total (95% CI)	**442**	**441**		**100.0 %**	**0.80 [0.55, 1.18]**

Total events: 41 (Cerclage), 51 (No cerclage)

Heterogeneity: $Chi^2 = 6.10$, df = 8 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable

(1) NEW data from Althusius 2001 why not included last time?; serious morbidity defined as NICU admission.

(2) Defined as admission to NICU.

Analysis 6.3. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 3 Baby discharged home healthy.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 3 Baby discharged home healthy

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 (1)	19/25	17/25		5.7 %	1.12 [0.79, 1.58]
Rush 1984 (2)	85/90	88/93		28.9 %	1.00 [0.93, 1.07]
Rust 2000 (3)	85/92	87/96		28.4 %	1.02 [0.93, 1.11]
To 2004 (4)	114/120	109/116		37.0 %	1.01 [0.95, 1.08]
Total (95% CI)	**327**	**330**		**100.0 %**	**1.02 [0.97, 1.06]**
Total events: 303 (Cerclage), 301 (No cerclage)					
Heterogeneity: Chi^2 = 0.56, df = 3 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

(1) From Jorgenson 2007 (excluding deaths from denominator. One-off and serial ultrasound together).

(2) Included women had a history of at least one preterm delivery < 37 weeks; women with cervical dilation > 2mm were excluded.

(3) From Jorgenson 2007 (excluding deaths from denominator).

(4) From Jorgenson 2007 (excluding deaths; both risk groups together.)

Analysis 6.4. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 4 Stillbirths.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 4 Stillbirths

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
Althuisius 2001	0/19	0/16			Not estimable
Berghella 2004	0/25	0/22			Not estimable
Berghella 2004	0/3	0/7			Not estimable
MRC/RCOG 1993	8/635	10/629		57.6 %	0.79 [0.31, 1.99]
Rush 1984	4/96	2/98		11.4 %	2.04 [0.38, 10.89]
To 2004	3/101	3/96		17.6 %	0.95 [0.20, 4.59]
To 2004	0/26	2/30		13.4 %	0.23 [0.01, 4.58]
Total (95% CI)	**905**	**898**		**100.0 %**	**0.89 [0.45, 1.75]**

Total events: 15 (Cerclage), 17 (No cerclage)

Heterogeneity: Chi^2 = 1.80, df = 3 (P = 0.61); I^2 =0.0%

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

Analysis 6.5. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 5 Neonatal deaths before discharge.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 5 Neonatal deaths before discharge

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
Althuisius 2001	0/19	1/14		5.4 %	0.25 [0.01, 5.72]
Althuisius 2003	9/16	4/14		13.4 %	1.97 [0.77, 5.01]
Berghella 2004	1/22	0/18		1.7 %	2.48 [0.11, 57.40]
Berghella 2004	0/3	0/7			Not estimable
MRC/RCOG 1993	8/590	14/577		44.6 %	0.56 [0.24, 1.32]
Rush 1984	3/90	4/93		12.4 %	0.78 [0.18, 3.37]
To 2004	2/26	1/28		3.0 %	2.15 [0.21, 22.37]
To 2004	4/101	6/96		19.4 %	0.63 [0.18, 2.18]
Total (95% CI)	**867**	**847**		**100.0 %**	**0.85 [0.53, 1.39]**

Total events: 27 (Cerclage), 30 (No cerclage)

Heterogeneity: Chi^2 = 5.88, df = 6 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 0.64 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 6.6. Comparison 6 Cerclage versus no cerclage (Summary of findings outcomes), Outcome 6 Preterm birth before 34 completed weeks.

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

Comparison: 6 Cerclage versus no cerclage (Summary of findings outcomes)

Outcome: 6 Preterm birth before 34 completed weeks

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
Althuisius 2001	0/19	7/16		0.3 %	0.06 [0.00, 0.92]
Althuisius 2003	7/13	10/10		9.0 %	0.56 [0.34, 0.93]
Berghella 2004	0/3	1/7		0.3 %	0.67 [0.03, 12.96]
Berghella 2004	10/25	11/22		5.6 %	0.80 [0.42, 1.51]
Ezechi 2004	0/39	11/42		0.3 %	0.05 [0.00, 0.77]
MRC/RCOG 1993	92/635	113/629		36.0 %	0.81 [0.63, 1.04]
Owen 2009	42/148	57/153		21.2 %	0.76 [0.55, 1.06]
Rush 1984	14/96	14/98		4.9 %	1.02 [0.51, 2.03]
Rust 2000	11/43	12/37		4.8 %	0.79 [0.40, 1.57]
Rust 2000	13/61	15/66		5.3 %	0.94 [0.49, 1.81]
To 2004	22/101	25/96		9.1 %	0.84 [0.51, 1.38]
To 2004	6/26	11/30		3.2 %	0.63 [0.27, 1.46]
Total (95% CI)	**1209**	**1206**		**100.0 %**	**0.77 [0.66, 0.89]**

Total events: 217 (Cerclage), 287 (No cerclage)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.31$, df = 11 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 3.41 (P = 0.00065)

Test for subgroup differences: Not applicable

WHAT'S NEW

Last assessed as up-to-date: 30 June 2016.

Date	Event	Description
30 June 2016	New search has been performed	Search updated and three trials added data to the review (Chandiramani 2010; Ionescu 2012; Althuisius 2003). We added a 'Summary of findings' table with GRADE assessments
30 June 2016	New citation required but conclusions have not changed	Conclusions have not changed. There is still a lack of evidence comparing cervical cerclage with cervical pessary or vaginal progesterone

CONTRIBUTIONS OF AUTHORS

Nancy Medley assessed reports for inclusion, extracted and entered data, created the SoF table and contributed to writing the text of the review.

Tamara Stampilija assessed reports for inclusion, extracted and entered data, created the SoF table and contributed to writing the text of the review.

Zarko Alfirevic assessed reports for inclusion and contributed to writing the text of the review.

DECLARATIONS OF INTEREST

Zarko Alfirevic: My employer (University of Liverpool) has received grants from UK National Institute of Health Research, Wellbeing of Women charity and Perkin Elmer to support my research group's work related to preterm birth prevention and my Cochrane editorial work.

Tamara Stampalija: none known.

Nancy Medley: Nancy Medley's work was financially supported by the University of Liverpool's Harris-Wellbeing of Women Preterm Birth Centre research award.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK.

External sources

- Harris-Wellbeing of Women Preterm Birth Centre, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2012 update we replaced 'any preventable perinatal loss' with 'all perinatal losses'. We also added the non-prespecified outcomes:

- Any intravenous, oral or combined tocolysis.
- Preterm premature rupture of membranes (PPROM).
- Chorioamnionitis.

For the 2017 update, we removed the primary outcome of composite perinatal deaths and serious neonatal morbidity. We were concerned about the possible double counting of babies with serious morbidity who also died. A clearer indicator of efficacy and safety together is whether or not babies go home without serious morbidity. Therefore, we moved the outcome of baby discharged home healthy to primary outcomes. Methods have been updated to current Cochrane Pregnancy and Childbirth standards and a 'Summary of findings' table was added for this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Cerclage, Cervical [adverse effects; *methods]; Cesarean Section [utilization]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Suture Techniques

MeSH check words

Female; Humans; Pregnancy