9-25-2019

Cervical assessment by ultrasound for preventing preterm delivery.

Vincenzo Berghella
Thomas Jefferson University

Gabriele Saccone
University of Naples Federico II

Cochrane Library

Cochrane Database of Systematic Reviews

Cervical assessment by ultrasound for preventing preterm delivery (Review)

Berghella V, Saccone G

Berghella V, Saccone G.
Cervical assessment by ultrasound for preventing preterm delivery.
Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD007235.
DOI: 10.1002/14651858.CD007235.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Cervical assessment by ultrasound for preventing preterm delivery

Vincenzo Berghella[1], Gabriele Saccone[2]

[1]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA. [2]Department of Neuroscience, Reproductive Science and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Contact address: Vincenzo Berghella, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Thomas Jefferson University, 833 Chestnut Street, Level 1, Philadelphia, Pennsylvania, PA 19107, USA. vincenzo.berghella@jefferson.edu.

Editorial group: Cochrane Pregnancy and Childbirth Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2019.

Citation: Berghella V, Saccone G. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database of Systematic Reviews* 2019, Issue 9. Art. No.: CD007235. DOI: 10.1002/14651858.CD007235.pub4.

ABSTRACT

Background

Measurement of cervical length by ultrasound is predictive of preterm birth (PTB). There are three methods of ultrasound cervical assessment: transvaginal (TVU), transabdominal (TAU), and transperineal (TPU, also called translabial). Cervical length measured by TVU is a relatively new screening test, and has been associated with better prediction of PTB than previously available tests. It is unclear if cervical length measured by ultrasound is effective for preventing PTB. This is an update of a review last published in 2013.

Objectives

To assess the effectiveness of antenatal management based on transvaginal, transabdominal, and transperineal (also called translabial) ultrasound screening of cervical length for preventing preterm birth.

Search methods

For this update, we searched the Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) to 30 August 2018; reviewed the reference lists of all articles, and contacted experts in the field for additional and ongoing trials.

Selection criteria

We included published and unpublished randomised controlled trials (RCT) including pregnant women between the gestational ages of 14 to 32 weeks, for whom the cervical length was screened for risk of PTB with TVU, TAU, or TPU. This review focused on studies based on knowledge versus no knowledge of cervical length results, or ultrasound versus no ultrasound for cervical length. We excluded studies based on interventions (e.g. progesterone, cerclage) for short cervical length.

Data collection and analysis

We followed standard Cochrane methods.

Main results

We included seven RCTs (N = 923): one examined asymptomatic women with twin pregnancies; four included women with singleton pregnancies and symptoms of preterm labour (PTL); one included women with singleton pregnancies and symptoms of preterm premature rupture of membranes (PPROM); and one included asymptomatic singletons. All trials used TVU for screening.

We assessed the risk of bias of the included studies as mixed, and the quality of the evidence for primary outcomes as very low for all populations.

For asymptomatic women with twin pregnancies, it is uncertain whether knowledge of TVU-measured cervical length compared to no knowledge reduces PTB at less than 34 weeks (risk ratio (RR) 0.62, 95% confidence intervals (CI) 0.30 to 1.25; 1 study, 125 participants) because the quality of the evidence is very low. The results were also inconclusive for preterm birth at 36, 32, or 30 weeks; gestational age at birth, and other maternal and perinatal outcomes.

Four trials examined knowledge of TVU-measured cervical length of singletons with symptoms of PTL versus no knowledge. We are uncertain of the effects because of inconclusive results and very low-quality evidence for: preterm births at less than 37 weeks (average RR 0.59, 95% CI 0.26 to 1.32; 2 studies, 242 participants; I^2 = 66%; Tau^2 = 0.23). Birth occurred about four days later in the knowledge groups (mean difference (MD) 0.64 weeks, 95% CI 0.03 to 1.25; 3 trials, 290 women). The results were inconclusive for the other outcomes for which there were available data: PTB at less than 34 or 28 weeks; birthweight less than 2500 g; perinatal death; maternal hospitalisation; tocolysis; and steroids for fetal lung maturity.

The trial of singletons with PPROM (N = 92) evaluated safety of using TVU to measure cervical length in this population as its primary outcome, not its effect on management. The results were inconclusive for incidence of maternal and neonatal infections between the TVU and no ultrasound groups.

In the trial of asymptomatic singletons (N = 296), in which women either received TVU or not, the results were inconclusive for preterm birth at less than 37 weeks (RR 1.27, 95% CI 0.61 to 2.61; I^2 = 0%), gestational age at birth, and other perinatal and maternal outcomes.

We downgraded evidence for limitations in study design, inconsistency between the trials, and imprecision, due to small sample size and wide confidence intervals crossing the line of no effect.

No trial compared the effect of knowledge of the CL with no knowledge of CL in other populations, such as asymptomatic women with singleton pregnancies, or symptomatic women with twin pregnancies.

Authors' conclusions

There are limited data on the effects of knowing the cervical length, measured by ultrasound, for preventing preterm births, which preclude us from drawing any conclusions for women with asymptomatic twin or singleton pregnancies, singleton pregnancies with PPROM, or other populations and clinical scenarios.

Limited evidence suggests that knowledge of transvaginal ultrasound-measured cervical length, used to inform the management of women with singleton pregnancies and symptoms of preterm labour, appears to prolong pregnancy by about four days over women in the no knowledge groups.

Future studies could look at specific populations separately (e.g. singleton versus twins; symptoms versus no symptoms of PTL), report on all pertinent maternal and perinatal outcomes, and include cost-effectiveness analyses. Most importantly, future studies should include a clear protocol for management of women based on TVU-measured cervical length.

PLAIN LANGUAGE SUMMARY

Cervical assessment by ultrasound for preventing preterm delivery

We set out to assess the effectiveness of knowing the cervical length, measured with ultrasound, for preventing preterm birth compared with not knowing the cervical length.

What is the issue?

The cervix is the lower part of the uterus that connects to the vagina. When women are not pregnant, it is normally at least 3 cm long. During pregnancy, a short cervical length is associated with a risk of spontaneous preterm birth. The shorter the cervical length, the greater the risk. Therefore, measuring cervical length by ultrasound can help predict spontaneous preterm birth. The cervical length is measured by an ultrasound scan through the vagina (transvaginal or TVU), abdomen (transabdominal), or the perineum (transperineal). The most common causes of spontaneous preterm birth are preterm labour or preterm premature rupture of the membranes. Many of the interventions used to prevent preterm birth are used once symptoms develop.

Why is this important?

Preterm birth before 37 weeks is the main cause of a newborn baby being sick and disabled, or dying. The cervix is the opening or passage through which the baby must pass before being born vaginally. Ultrasound can detect early changes of the cervix, such as shortening of the cervical length, to predict preterm birth. On identifying a short cervical length, interventions can be applied to prevent preterm birth. These interventions include giving the expectant mother progesterone to relax the uterus, or applying a stitch, known as a cerclage, to tighten the opening of the cervix.

What evidence did we find?

This review assessed if knowing the cervical length can prevent preterm birth. We included seven randomised controlled studies, which involved 923 pregnant women at 14 to 32 weeks' gestation. One study included expectant mothers with twins, without any symptoms of preterm birth or labour, and looked at the number of babies born prematurely before 36 weeks. Four studies included expectant mothers of single babies with threatened preterm labour, and one study involving women with premature rupture of the membranes looked at the safety of transvaginal ultrasound. One trial included expectant mothers with singleton pregnancies who did not have any symptoms of preterm birth or labour to look at the efficacy of transvaginal ultrasound cervical length screening. All studies used transvaginal ultrasound to assess cervical length.

For women with twin pregnancies and not showing symptoms of preterm birth, we are unclear of the impact of knowing the cervical length on whether babies are born before 34 weeks' gestation, or their gestational age at birth (1 study, 125 women), because we assessed the quality of the evidence to be very low. For women with a single baby and threatened preterm labour, knowledge of their cervical length may have led to a longer pregnancy by about four days (4 studies, 410 women), but the evidence on the number of babies born before 37 weeks was unclear (2 studies, 242 women). For women whose waters had broken, it is unclear whether healthcare provider knowledge makes any difference to whether the women gave birth preterm, or on the number of infections, again because we judged the quality of evidence as very low. For women with singleton pregnancies not showing symptoms of preterm birth, it is unclear whether an ultrasound to measure cervical length made any difference to whether their babies were born before 37 weeks' gestation (1 study, 296 women; very low-quality evidence).

What does this mean?

We found a limited number of studies including small numbers of women. The studies varied in their design and had a broad spread of results. Women were not blinded to whether they had an ultrasound or not. Currently, there is not enough high quality research to show if knowledge of cervical length in women with twin or singleton pregnancies has any effect. Future studies could include ways of managing women as a result of the cervical length results, and it would be useful to look at specific populations separately, such as single babies versus twins and women with and without symptoms of preterm labour. They could also report on all important maternal and perinatal outcomes, and include cost-effectiveness analyses.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Asymptomatic women with twins (no preterm labour (PTL) or preterm premature rupture of membranes (PPROM))

Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length

Patient or population: women carrying twins, asymptomatic for PTL or PPROM
Setting: USA, setting not specified
Intervention: knowledge of TVU-measured cervical length (CL)
Comparison: no knowledge of CL

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no knowledge of CL	Risk with knowledge of CL				
Preterm birth < 34 weeks	Study population (asymptomatic women carrying twins)		RR 0.62 (0.30 to 1.25)	125 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]	
	258 per 1000	160 per 1000 (77 to 323)				

***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

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

[a]We downgraded 2 levels for very serious imprecision due to wide CI crossing the line of no effect, few events, and small sample size
[b]We downgraded 1 level for serious limitations in study design, due to unclear risk of bias for several domains, and high risk of performance bias

Summary of findings 2. Symptomatic singletons (with preterm labour (PTL))

Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length

Patient or population: singleton pregnancy with symptoms of PTL
Setting: hospital settings in Spain and USA

Intervention: knowledge of TVU-measured cervical length (CL)
Comparison: no knowledge of CL

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no knowledge of CL	Risk with knowledge of CL				
Preterm birth < 37 weeks	Study population (symptomatic singletons)		Average RR 0.59 (0.26 to 1.32)	242 (2 RCTs)	⊕⊝⊝⊝ VERY LOW[a,b,c]	
	347 per 1000	222 per 1000 (146 to 337)				

***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

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

[a]We downgraded 1 level for serious inconsistency due to high statistical heterogeneity (66%)
[b]We downgraded 2 levels for very serious imprecision due to a small sample size and wide confidence intervals crossing the line of no effect
[c]We downgraded 1 level for serious limitations in study design due to high risk of bias for several domains

BACKGROUND

Description of the condition

Preterm birth (PTB) is defined by the World Health Organization (WHO) as birth between 20 and 36 6/7 weeks. PTB can be spontaneous, and follow preterm labour (PTL (50%)), or preterm premature rupture of membranes (PPROM (30%)). It can also be iatrogenic (caused by health worker intervention (20%). Its incidence is about 5% to 12% in most countries, accounting for over a million deaths per year in the world. PTB is the main cause of neonatal morbidity and mortality in most countries. In the USA, 75% of perinatal mortality occurs in preterm babies; 60% of total perinatal mortality occurs in infants born before 32 weeks. Mortality and morbidities are inversely associated with gestational age at birth. Morbidities include respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis, sepsis, retinopathy, etc. The whole family suffers greatly in several aspects when a baby has been born prematurely, including medically, socially, psychologically, and financially.

Description of the intervention

Many of the interventions studied have been aimed at tertiary prevention, i.e. prevention once symptoms (e.g. PTL or PPROM) develop. Interventions based on risk factors, usually based on prior history, have been more recently developed. There are three methods of ultrasound cervical assessment: transvaginal (TVU), transabdominal (TAU), and transperineal (TPU, also called translabial). Cervical length measured by transvaginal ultrasound (TVU) is a relatively new screening test, and has been associated with better prediction of PTB than previously available tests (Berghella 2003, Berghella 2017,Navathe 2019). Interventions based on this screening test have now been tested in randomised trials.

How the intervention might work

Cervical assessment by ultrasound has been correlated with the prediction of spontaneous PTB (Berghella 2003). The most objective and effective ultrasound method is TVU (Hernandez-Andrade 2012; Khalifeh 2016). The most predictive and reproducible variable that can be measured on TVU is cervical length. The gestational age at which TVU cervical length is most predictive of PTB is 14 to 34 weeks, but shortening at earlier and later gestational ages is also associated with PTB. The shorter the cervical length, the higher the risk of PTB becomes (Grimes-Dennis 2007). The earlier in gestation the shortening is detected, the higher the risk of PTB (Berghella 2007). This prediction has been confirmed in all populations screened with TVU cervical length so far, including singleton and multiple pregnancies, women with or without risk factors for PTB (e.g. prior PTB, mullerian anomalies, cervical surgery, etc.), asymptomatic women, as well as those with PTL or PPROM (Grimes-Dennis 2007). In fact, TVU cervical length is one of the best predictors of PTB in all populations studied so far. The overall sensitivity and specificity vary according to the cervical length cut-off used (e.g. 25 mm versus 20 mm versus 15 mm); gestational age at screening; population studied; prevalence of PTB; single versus serial screening; etc. Its positive predictive value also varies depending on the incidence of PTL in the population studied. The intervention of cervical length assessment by ultrasound has been studied in combination with other interventions (e.g. cerclage, progesterone, pessary, etc.) for prevention of PTB, and the reader is encouraged to read these specific Cochrane Reviews (e.g. progesterone (Dodd 2017a; Dodd 2017b), cerclage (Alfirevic 2017; Rafael 2014); or pessary (Abdel-Aleem 2013). Knowledge of cervical length assessment by ultrasound per se can also be considered an intervention, and is the topic of this review. In addition, cervical length assessment could also reduce the need for other interventions (e.g. activity restriction, tocolytics, steroids, etc.).

Why it is important to do this review

PTB is the main cause of neonatal morbidity and mortality in most countries. It account for a neonatal death every 30 seconds globally, and millions of babies are affected by its consequences every year. Mortality and morbidities are inversely associated with gestational age at birth. Morbidities include respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis, sepsis, retinopathy, etc. The whole family suffers greatly in several aspects when a baby has been born prematurely, including medically, socially, psychologically, and financially. This is an update of a review last published in 2013 (Berghella 2013).

OBJECTIVES

To assess the effectiveness of antenatal management based on transvaginal, transabdominal, and transperineal (also called translabial) ultrasound screening of cervical length for preventing preterm birth.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials. We had planned to include cluster-randomised and quasi-randomised trials, if available. Abstracts were eligible for inclusion if sufficient information was provided to judge the quality and potential for bias of these trials.

Types of participants

Pregnant women between the gestational ages of 14 to 34 weeks, screened with transvaginal (TVU), transabdominal (TAU), or transperineal (TPU) cervical length for risk of preterm birth (PTB). Given the different characteristics of singleton versus twin pregnancies; women with asymptomatic versus symptomatic preterm labour (PTL) or preterm premature rupture of membranes (PPROM); and PTL versus PPROM; we divided comparisons into:

- asymptomatic singletons
- asymptomatic with twins
- singletons with PTL
- singleton with PPROM
- twins with PTL
- twins with PPROM

We had planned to divide the analysis by the type of cervical length ultrasound screening, i.e. TVU versus TAU versus TPU. We carried out analysis of other participants by type of population, as described under 'subgroup analyses'.

Trials that did not measure the outcome of interest, as well as trials using manual digital cervical examination as control group were excluded.

Types of interventions

A screening test such as clinical length can only be considered effective if the interventions based on screening results reduce the outcome of preterm birth. For this review, we included the following screening cervical length modalities on which interventions were based.

- Knowledge versus no knowledge of cervical length results (i.e. cervical length is assessed for all women, but women are randomised so that in about 50% of them, the result is available to the managing obstetrician, while in about 50%, the managing obstetrician is blind to the result).
- Cervical length screening versus no cervical length screening (TVU/TAU/TPU cervical length screening is only performed on half of the women).

Types of outcome measures

Primary outcomes

1. Preterm birth (less than 37 weeks for singleton pregnancies; less than 34 weeks for twin pregnancies)

Secondary outcomes

1. Preterm birth (less than 36 weeks)
2. Preterm birth (less than 34 weeks)
3. Preterm birth (less than 32 weeks)
4. Preterm birth (less than 30 weeks)
5. Preterm birth (less than 28 weeks)
6. Gestational age at delivery
7. Birthweight less than 2500 g
8. Birthweight (g)
9. Composite perinatal outcome (perinatal death, respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, and sepsis)
10. Perinatal death (fetal death and neonatal death)
11. Fetal death
12. Neonatal death
13. Neonatal infection
14. Respiratory distress syndrome
15. Intraventricular haemorrhage
16. Necrotizing enterocolitis
17. Sepsis
18. Neonatal intensive care unit (NICU) admission
19. NICU days
20. Maternal hospitalisation
21. Maternal well-being (e.g. stress level, etc.)
22. Economic analysis (cost effectiveness, cost utility)
23. Tocolysis
24. Cervical cerclage
25. Steroids for fetal maturity
26. Chorioamnionitis
27. Endometritis

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

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (30 August 2018).

The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current 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.

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 that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned, and ongoing trial reports (30 August 2018), using the search methods detailed in Appendix 1.

Searching other resources

We reviewed the reference list of all retrieved articles. If necessary, we contacted researchers to provide further information. We contacted experts in the field for additional and ongoing trials.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Berghella 2013.

For this update, the following methods were used to assess the reports that were identified as a result of the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion. Two ongoing studies are being conducted by one of the authors of this review, so these were assessed by the Cochrane Pregancy and Childbirth Group staff (NCT02923973; NCT02928302).

Data extraction and management

We designed a form to extract data. Data were entered into Review Manager 5 software, and checked for accuracy (Review Manager 2014). One of the authors of this Cochrane Review (Vincenzo Berghella) is a co-author of one of the included trials (Ness 2007), and the other author (Gabriele Saccone) is lead author on two ongoing trials (NCT02923973; NCT02928302). Gabriele Saccone assessed the eligibility and risk of bias for Ness 2007; the Cochrane Pregancy and Childbirth editorial staff assessed the eligibility of NCT02923973 and NCT02928302. The two review authors independently assessed the other potential studies, identified as a result of the search strategy for inclusion. We resolved any disagreement through discussion.

When information regarding any of the above was unclear, we had 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.

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

For each included study, we described 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)

For each included study, we described 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)

For each included study, we described 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 was 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)

For each included study, we described 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)

For each included study, and for each outcome or class of outcomes, we described 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)

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

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were report-

ed incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

For each included study, we described 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 *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we had planned to assess the likely magnitude and direction of the bias and whether we considered it was 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 used the GRADE approach, as outlined in the *GRADE Handbook,* in order to assess the quality of the body of evidence relating to the primary outcome (preterm birth less than 37 weeks for singleton pregnancies; less than 34 weeks for twin pregnancies) for the following comparisons (GRADE Handbook).

1. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (asymptomatic women with twins)
2. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (symptomatic singletons with preterm labour (PTL))

We used GRADEpro GDT to import data from Review Manager 5 to create 'Summary of findings' tables (GRADEpro GDT; Review Manager 2014). 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

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

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. In future updates, as appropriate, we plan to use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We had planned to include cluster-randomised trials in the analyses along with individually-randomised trials, however, all included studies were individually-randomised trials.

Dealing with missing data

For included studies, we noted levels of attrition. We had planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis, however, because most trials had a unique comparison, there were too few data available to carry out a meaningful sensitivity analysis.

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

Assessment of heterogeneity

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

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 it.

Data synthesis

We carried out statistical analysis using Review Manager 5 software (Review Manager 2014). We used a fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect, i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used a random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects, with 95% confidence intervals, and the estimates of Tau^2 and I^2, and discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses, classifying whole trials by interaction tests as described by Deeks 2001.

1. Women with singleton pregnancies without prior spontaneous PTB
2. Women with singleton pregnancies with prior spontaneous PTB

We had planned to restrict subgroup analyses to the primary outcome.

We had planned to assess subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2014).

None of the included studies reported results separately for singleton pregnancies based on prior or no prior spontaneous PTB, so we could not perform the planned subgroup analysis. In future updates, assuming we have sufficient data, we will report the results of subgroup analyses, quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We had planned to carry out sensitivity analyses to explore the effect of the trials' methodological quality, assessed by concealment of allocation, high attrition rates, or both, when studies with high risk of bias were excluded from the analyses, to assess whether this made any difference to the overall result.

We did not carry out a sensitivity analysis because most meta-analyses only included data from one or two studies.

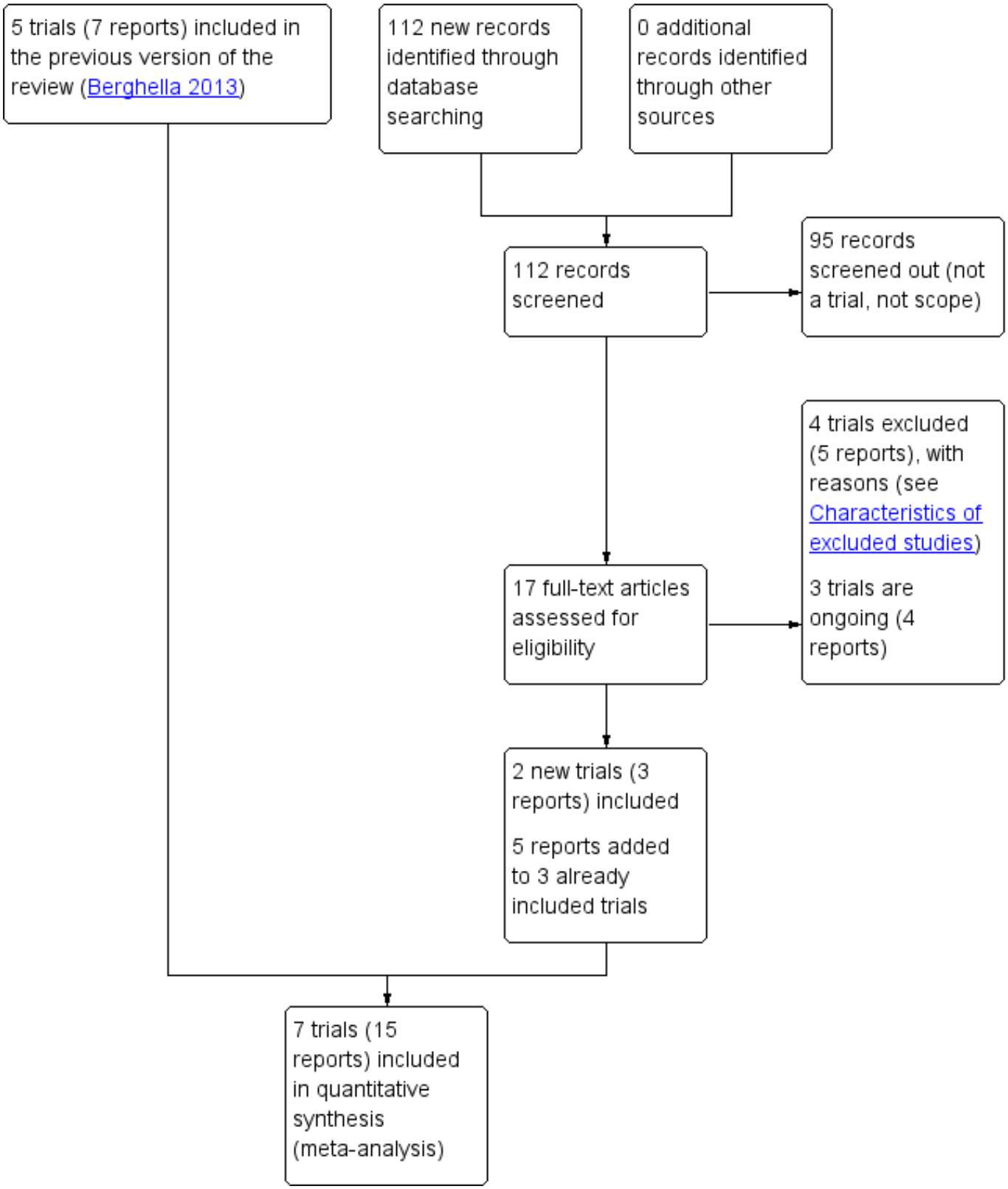
RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram



For this 2018 update, we identified 17 trial reports to assess. We included two new trials in three reports (Mishra 2018; Vafaei 2017); and five reports related to three already included studies (Gordon 2016; Ness 2007; Palacio 2018). We excluded four new trials in five reports (Gauthier 2014; Hosseini 2012; Romero 2014; Sch-

nettler 2013); and added three ongoing studies in four reports (NCT01431885; NCT02923973; NCT02928302).

In this update, we included a total of seven trials (N = 923). We identified no quasi-randomised trials. All seven included studies used transvaginal (TVU) cervical length screening, versus either no TVU cervical length screening, or no knowledge of the results of TVU cervical length screening. We did not identify any studies that used transabdominal or transperineal ultrasound for cervical length screening.

Included studies

The seven included studies included: one trial on women with twins, who were asymptomatic for preterm labour (PTL (Gordon 2016)); four trials on women with singleton pregnancies, who had symptoms of PTL (Alfirevic 2007; Ness 2007; Palacio 2018; Vafaei 2017); one trial on women with singleton pregnancies, who had preterm premature rupture of membranes (PPROM (Carlan 1997)); no trials included women with twin pregnancies, who were symptomatic for either PTL or had PPROM.

Five studies did not measure cervical length with TVU in the control groups (Alfirevic 2007; Carlan 1997; Gordon 2016; Mishra 2018; Vafaei 2017); and two studies used TVU to measure cervical length on all women, but only disclosed knowledge of cervical length to women and physicians in the intervention group (Ness 2007; Palacio 2018).

We requested patient-level data from most of the trial authors, and obtained them from one (Ness 2007).

In the one trial of women with twin pregnancies, who were asymptomatic for PTL, the analysis included 63 women who had TVU-measured cervical length and 62 who did not (Gordon 2016).

In the three trials of women with singleton pregnancies, who had symptoms of PTL, 410 women were randomised; 212 to knowledge, and 198 to no knowledge of TVU-measured cervical length (Alfirevic 2007; Ness 2007; Palacio 2018). Ness 2007 used knowledge of the cervical length in the management protocol; for women with cervical length 20 mm to 29 mm, they also used fetal fibronectin levels (FFN).

In the one trial of women with singleton pregnancies and PPROM, the analysis included 47 women who had TVU measurement of cervical length, and 45 who did not (Carlan 1997).

Funding

Only one trial reported on funding, and reported that the study was funded by The Fetal Medicine Foundation (Registered Charity 1037116 (Alfirevic 2007)), and one trial reported support from the Vice-Chancellor of Research, Shiraz University of Medical Sciences, Shiraz, Iran (Vafaei 2017). None of the other trials reported on funding.

Declarations of interest

Two studies reported that the authors had no conflicts of interest (Mishra 2018; Vafaei 2017). In the remaining studies, they did not report on declarations of interest.

Dates of study

Dates were not reported in two studies (Gordon 2016; Vafaei 2017). The dates were reported as follows in the remaining studies: 2003 to 2005 (Alfirevic 2007); May 1993 to June 1996 (Carlan 1997); July 2014 to December 2015 (Mishra 2018); November 2004 to April 2006 (Ness 2007); and January 2002 to April 2005 (Palacio 2018).

Excluded studies

We excluded a total of 12 trials (14 reports); three because they compared history-indicated to ultrasound-indicated cerclage (Beigi 2005; Kassanos 2001; Simcox 2009); one because the TVU-measured cervical length information was blinded and not used for management (Matijevic 2006); one because TVU information was not used for clinical care and no data on outcomes were provided (Owen 1999); two trials were excluded because control group was not 'no ultrasound' or 'no knowledge', but was manual digital cervical examination, interestingly, these studies utilized transabdominal ultrasound (Lorenz 1990; Van Dijken 1991); one because it used Cervilenz, which measures the vaginal part of the cervix rather than cervical length (Burwick 2011); one because TVU was compared to TPU, therefore with no 'no knowledge' group (Gauthier 2014); one because it was unclear if women were randomised to knowledge versus no knowledge of cervical length groups, and no outcome of interest was reported (Hosseini 2012); and one because no data on any outcomes of interest were measured and available, as this was a trial assessing only visit length and patient attitudes (Romero 2014).

Risk of bias in included studies

See Figure 2 and Figure 3 for summaries of 'Risk of bias' assessments.

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

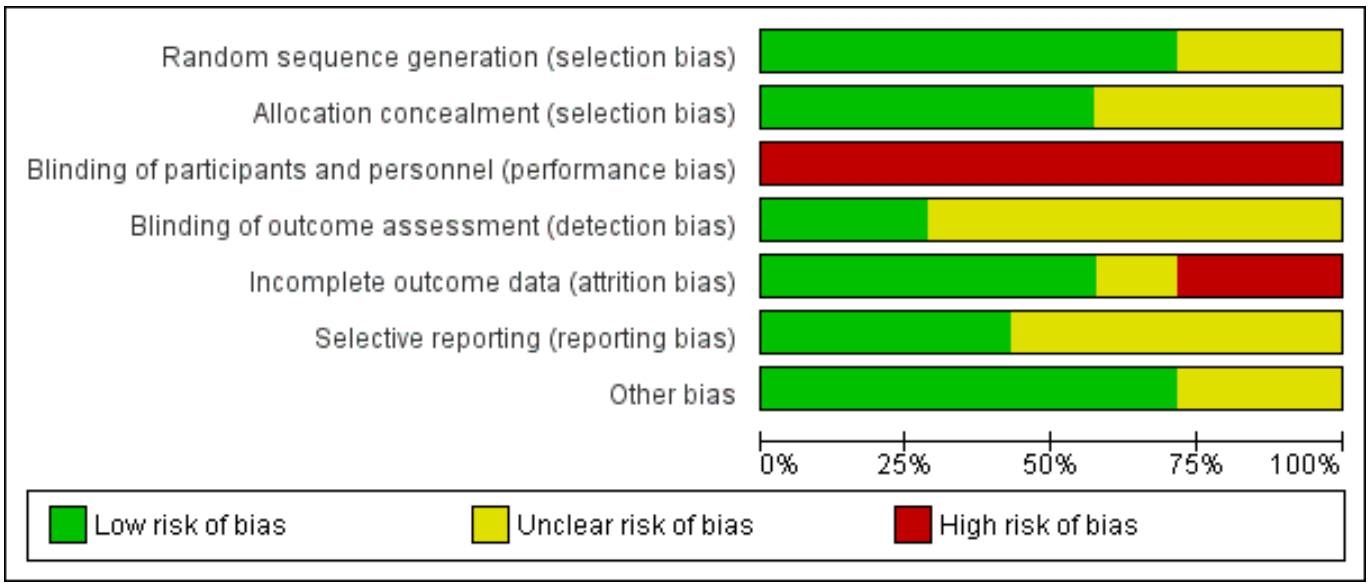
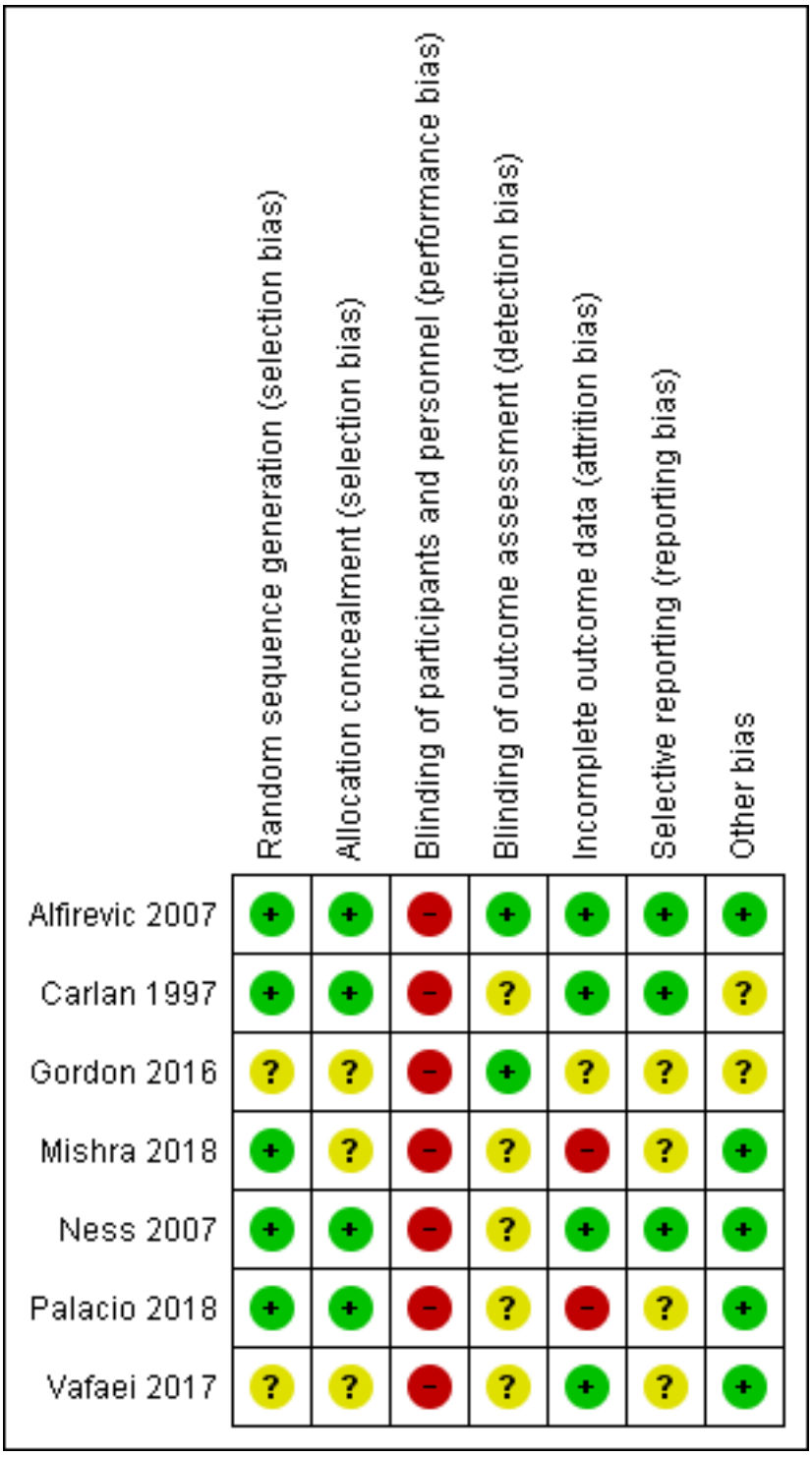


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study



Allocation

We assessed risk of selection bias as low in four trials (Alfirevic 2007; Carlan 1997; Ness 2007; Palacio 2018). Alfirevic 2007, Ness 2007, and Palacio 2018 used computer-generated random numbers for sequence generation, and Carlan 1997 reported that they used randomly-generated assignment in sealed envelopes.

Alfirevic 2007, Carlan 1997, and Gordon 2016 reported using consecutively numbered, sealed envelopes and Palacio 2018 used a central telephone operated platform.

Although Mishra 2018 used computer-generated randomisation, they reported no details related to allocation concealment, so we assessed it as unclear. The other two studies reported no information on methods of randomisation or allocation concealment, so

we assessed them as unclear for selection bias (Gordon 2016;Vafaei 2017).

Blinding

We assessed risk of performance bias as high in all trials, as participants and researchers were aware of the arm to which they were randomised, but this was inevitable.

In two trials, the primary outcomes were objective measures, so we assessed detection bias at low risk (Alfirevic 2007; Gordon 2016). It was unclear in other trials if outcome assessment had been blinded.

Incomplete outcome data

Information regarding an intention-to-treat analysis was available for three of the seven trials. Two trials included all women randomised in the intention-to-treat analysis (Alfirevic 2007; Ness 2007). In Carlan 1997, one of the 93 (1%) women randomised was excluded from the analysis because she delivered immediately. In one study, there were no losses to follow-up (Vafaei 2017). We assessed these four studies at low risk of attrition bias. We assessed two trials as high risk because women lost to follow-up were excluded from the analysis (Mishra 2018; Palacio 2018). We could not assess incomplete outcome data in one trial because the trial was only reported as an abstract, so data were limited (Gordon 2016).

Selective reporting

We assessed risk of selective reporting as unclear in four trials due to a lack of information (Gordon 2016; Mishra 2018; Palacio 2018; Vafaei 2017); and at low risk of bias in the remaining trials as they reported all expected specified outcomes.

Other potential sources of bias

We assessed the risk of other potential sources of bias as unclear in two trials; one did not include a baseline characteristics table (Carlan 1997), and another did not provide sufficient information to allow us to assess (Gordon 2016). We judged the remaining studies at low risk of bias from other sources.

Effects of interventions

See: **Summary of findings for the main comparison** Asymptomatic women with twins (no preterm labour (PTL) or preterm premature rupture of membranes (PPROM)); **Summary of findings 2** Symptomatic singletons (with preterm labour (PTL))

We included seven trials in this review (N = 923).

We found the risk of bias of the included studies to be mixed. For selected important comparisons for the primary outcome, we graded the quality of the evidence as very low, see Summary of findings for the main comparison and Summary of findings 2.

Knowledge of transvaginal ultrasound (TVU)-measured cervical length versus no knowledge (asymptomatic women with twins)

The effect of knowing the TVU-measured cervical length is unclear due to very low-quality evidence from a single trial (Summary of findings for the main comparison; Gordon 2016).

In women with twin pregnancies, and without symptoms of preterm labour (PTL), it is uncertain whether TVU-measured cervical length reduces preterm birth at less than 36 weeks' gestation (risk ratio (RR) 1.27, 95% confidence interval (CI) 0.85 to 1.90; 125 participants; Analysis 1.1); at less than 34 weeks (RR 0.62, 95% CI 0.30 to 1.25; 125 participants; Analysis 1.2; Summary of findings for the main comparison); at less than 32 weeks (RR 0.56, 95% CI 0.17 to 1.83; 125 participants; Analysis 1.3); or at less than 30 weeks' gestation (RR 0.20, 95% CI 0.02 to 1.64; 125 participants; Analysis 1.4), because the quality of the evidence is very low.

The results were also inconclusive for gestational age at delivery (weeks) (mean difference (MD) 0.20, 95% CI -0.74 to 1.14; 125 participants; Analysis 1.5), maternal hospitalisation (RR 1.29, 95% CI 0.75 to 2.23; 125 participants; Analysis 1.6), tocolysis (RR 1.34, 95% CI 0.74 to 2.42; 125 participants; Analysis 1.7), steroids for fetal lung maturity (RR 0.79, 95% CI 0.49 to 1.26; 125 participants; Analysis 1.8), or cervical cerclage (RR 4.92, 95% CI 0.24 to 100.49; 125 participants; Analysis 1.9); or perinatal outcomes: birthweight (MD 142.00, 95% CI -9.95 to 293.95; 250 participants; Analysis 1.10), NICU admission (RR 1.14, 95% CI 0.83 to 1.55; 250 participants; Analysis 1.11),

No other outcomes were reported in this trial.

Knowledge of transvaginal ultrasound (TVU)-measured cervical length versus no knowledge (singletons with symptoms of preterm labour (PTL))

In women with a singleton pregnancy who have symptoms of PTL, we are uncertain of the effects of knowledge of TVU-measured cervical length on preterm births (PTB) at less than 37 weeks' gestation (average RR 0.59, 95% CI 0.26 to 1.32; 2 studies, 242 participants; I^2 = 66%; Tau^2 = 0.23; very low-quality evidence; Analysis 2.1; Summary of findings 2); and at less than 34 weeks (RR 0.55, 95% CI 0.25 to 1.20; 3 studies, 256 participants; Analysis 2.2. There were no preterm births at less than 28 weeks' gestation.

Birth occurred at a slightly later gestational age in the cervical length knowledge groups compared to the no knowledge groups (weeks) (MD 0.64, 95% CI 0.03 to 1.25; 3 studies, 290 participants; Analysis 2.4).

These results were determined mostly by the Ness 2007 trial, which used TVU-measured cervical length as the main screening test for guiding management, adding FFN levels to help determine management in women with a cervical length of 20 mm to 29 mm. There were inconclusive results and often substantial heterogeneity for all other outcomes for which there were available data: birthweight less than 2500 g (RR 0.71, 95% CI 0.21 to 2.44; 1 study, 70 participants; Analysis 2.5); maternal hospitalisation (RR 2.94, 95% CI 0.85 to 10.16; 1 study, 93 participants; Analysis 2.7), tocolysis (average RR 0.85, 95% CI 0.11 to 6.58; 2 studies, 102 participants; I^2 = 86%; Tau^2 = 1.89; Analysis 2.8); and steroids for fetal lung maturity (average RR 1.72, 95% CI 0.15 to 19.64; 2 studies, 114 participants; I^2 = 91%; Tau^2 = 2.83; Analysis 2.9); there were no perinatal deaths reported in either group. Appropriateness of treatment with steroids for fetal lung maturity was higher in the knowledge versus the no knowledge group in the one trial that evaluated this outcome (Alfirevic 2007).

Other maternal and fetal outcomes were not reported, or insufficient data were available for meaningful analysis.

Knowledge of transvaginal ultrasound (TVU)-measured cervical length versus no knowledge (singletons with preterm premature rupture of membranes (PPROM))

One trial of women with a singleton pregnancy and PPROM evaluated the safety of using TVU to measure cervical length in this population, and not the effect on management of knowing the cervical length (Carlan 1997). They did not report the incidence of preterm births or gestational age at delivery. The results were inconclusive for birthweight (MD 31.00 g, 95% CI -162.16 to 224.16; 92 participants; Analysis 3.1), incidence of maternal infections (chorioamnionitis: RR 0.72, 95% CI 0.34 to 1.52; 92 participants; Analysis 3.2, or endometritis: RR 1.39, 95% CI 0.33 to 5.88; 92 participants; Analysis 3.3), and neonatal infections (RR 1.18, 95% CI 0.50 to 2.78; 92 participants; Analysis 3.4).

The trials did not report other outcomes.

Knowledge of transvaginal ultrasound (TVU)-measured cervical length versus no knowledge (asymptomatic singletons)

One trial examined the effects of the knowledge of TVU-measured cervical length for women with a singleton pregnancy, no symptoms of PTL, and no history of spontaneous preterm birth or second trimester loss (Mishra 2018). The results were inconclusive for maternal outcomes: preterm birth less than 37 weeks (RR 1.27, 95% CI 0.61 to 2.61; 296 participants; Analysis 4.1); and for neonatal outcomes: birthweight (MD -10.00 g, 95% CI -135.17 to 115.17; 296 participants; Analysis 4.2); respiratory distress syndrome (RR 2.03, 95% CI 0.38 to 10.90; 296 participants; Analysis 4.3); NICU admission (RR 2.03, 95% CI 0.19 to 22.12; 296 participants; Analysis 4.4); intraventricular haemorrhage (RR 0.51, 95% CI 0.05 to 5.53; 296 participants; Analysis 4.5); and neonatal death (RR 0.20, 95% CI 0.01 to 4.19; 296 participants; Analysis 4.6).

The trial did not report other outcomes.

Other comparisons

We did not identify any trials that assessed knowledge versus no knowledge of TVU-measured cervical length in women with twins who had symptoms of PTL or PPROM.

We did not identify any trials that compared different types of ultrasound.

Subgroup analysis and sensitivity analysis

None of the seven included trials reported data separately for singleton pregnancies with and without prior spontaneous preterm births, so we could not perform that planned subgroup analysis.

We did not carry a sensitivity analysis because most meta-analyses included data from only one or two studies.

DISCUSSION

Summary of main results

There are limited data on the effects of knowing the cervical length, measured by ultrasound for preventing preterm births.

We were unable to determine the effects of the knowledge of transvaginal ultrasound (TVU)-measured cervical length in the management of asymptomatic women with either singleton or twin pregnancies, because we found only one small trial that examined each population.

Knowledge of TVU-measured cervical length to inform the management of women with singleton pregnancies and symptoms of preterm labour (PTL) appeared to result in births that occurred about four days later than those born to women in the no knowledge groups. Evidence on other outcomes such as the incidence of preterm birth before 37 weeks, was unclear. We were unable to determine the effect of knowledge of TVU-measured cervical length in the management of women with singleton pregnancies and preterm premature rupture of membranes (PPROM) because we found just one small trial on this population. We identified no trials of women with twin pregnancies with symptoms of either PTL or PPROM.

There is limited and inconclusive evidence on how the knowledge of cervical length, assessed by ultrasound could avoid unnecessary interventions (e.g. tocolytics, steroids, etc.) in women with a normal cervical length.

Overall completeness and applicability of evidence

All included trials used TVU to measure cervical length; no included trials used transabdominal (TAU) or transperitoneal (TPU) ultrasound. There were no trials comparing knowledge versus no knowledge of TVU-measured cervical length in symptomatic women with twin pregnancies.

Ness 2007 suggested a protocol of no intervention for women with a TVU-measured cervical length of at least 30 mm; the addition of FFN levels for the management of women with a cervical length of 20 mm to 29 mm; and the administration of steroids for fetal lung maturity and tocolysis for women with a cervical length less than 20 mm (Ness 2007).

By design, our review did not include an assessment of the effectiveness of interventions based on positive TVU-measured cervical length (short cervical length), or negative TVU-measured cervical length screening (normal or long cervical length). These are examined in Cochrane Reviews of the specific intervention (e.g. progesterone (Dodd 2017a; Dodd 2017b), cerclage (Alfirevic 2017; Rafael 2014); and pessary (Abdel-Aleem 2013).

All the included trials took place in high-income settings and countries, therefore, our findings are limited to this type of setting.

Quality of the evidence

The seven included randomised studies were all relatively small, and blinding was not possible; see Figure 2 and Figure 3.

For the comparison, knowledge of TVU-measured cervical length versus no knowledge (asymptomatic women with twins), we assessed the evidence to be very low quality for preterm birth less than 34 weeks. We downgraded the quality for limitations in study design, small sample size, and wide confidence intervals that crossed the line of no effect; see Summary of findings for the main comparison.

For the comparison, knowledge of TVU-measured cervical length versus no knowledge (singletons with symptoms of PTL), we assessed the evidence to be very low quality for preterm birth less than 37 weeks. We downgraded the quality for limitations in study

design, high statistical heterogeneity, small sample size, and wide confidence intervals that crossed the line of no effect; see Summary of findings 2.

Potential biases in the review process

One of the authors of this Cochrane Review (Vincenzo Berghella) is a co-author of one of the included trials (Ness 2007), and the other author (Gabriele Saccone) is lead author on two ongoing trials (NCT02923973; NCT02928302). Gabriele Saccone assessed the eligibility and risk of bias for Ness 2007; the Cochrane Pregancy and Childbirth editorial staff assessed the eligibility of NCT02923973 and NCT02928302. The two review authors independently assessed the other potential studies, identified as a result of the search strategy for inclusion. We resolved any disagreement through discussion.

Agreements and disagreements with other studies or reviews

The evidence presented in this current update has added two new trials (Mishra 2018; Vafaei 2017). Our overall conclusions remain the same as those in the previous version (Berghella 2013). The results of this Cochrane review concur with another IPD meta-analysis of three trials including a total of 287 singleton gestations with threatened preterm labour between 24 + 0 and 35 + 6 weeks, that showed that there is a significant association between knowledge of transvaginal ultrasound cervical length and later gestational age at delivery (Berghella 2017). However, our review found no good quality evidence that there was an association between knowledge of transvaginal ultrasound cervical length and a lower incidence of preterm birth in women with singleton pregnancies and threatened PTB, whereas Berghella 2017 did report an association. A retrospective cohort study of women with asymptomatic singleton gestations also suggested an association between TVU screening and a reduction in preterm labour (Navathe 2019). Our review did not find the same finding in the single study identified of asymptomatic women with a singleton gestation (Mishra 2018).

AUTHORS' CONCLUSIONS

Implications for practice

There are limited data on the effects of knowing the cervical length, measured by ultrasound, for preventing preterm births, which preclude us from drawing any conclusions.

Limited evidence suggests that knowledge of transvaginal ultrasound-measured cervical length, used to inform the management of women with singleton pregnancies and symptoms of preterm labour, appears to prolong pregnancy by about four days over women in the no knowledge groups.

Implications for research

This review found limited evidence that suggested knowledge of TVU-measured cervical length might increase slightly the age at birth, but it had an unclear effect on preterm births at less than 37 weeks, and there were no clear differences in other outcomes, possibly due to the small number of women with symptoms of PTL. The review authors encourage further research. Future studies could look at specific populations separately (e.g. singleton versus twins; symptoms of PTL or no symptoms), report on all pertinent maternal and perinatal outcomes, and include cost-effectiveness analyses. Most importantly, future studies should include a clear protocol for the management of women's pregnancies, based on TVU-measured cervical length results, so that it can be easily evaluated and replicated.

ACKNOWLEDGEMENTS

JK Baxter and NW Hendrix helped with the first Cochrane Review on this topic.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), and the Group's Statistical Adviser. The authors are grateful to the following peer reviewer for his time and comments: Dr Mohammad Othman, Assistant Professor and Consultant of Obstetrics and Gynaecology, Faculty of Medicine Al-Baha University, Saudi Arabia.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Alfirevic 2007 *{published data only}*

Alfirevic Z, Allen-Coward H, Molina F, Vinuesa CP, Nicolaides K. Targeted therapy for threatened preterm labor based on sonographic measurement of the cervical length: a randomized controlled trial. *Ultrasound in Obstetrics & Gynecology* 2007;**29**(1):47-50.

Carlan 1997 *{published data only}*

Carlan SJ, Richmond LB, O'Brien WF. Randomized trial of endovaginal ultrasound in preterm premature rupture of membranes. *Obstetrics & Gynecology* 1997;**89**:458-61.

Gordon 2016 *{published data only}*

Gordon M, Robbins A, McKenna D, Howard B, Barth W. Cervical length assessment as a resource to identify twins at risk for preterm delivery (clarity study). *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S55.

* Gordon MC, McKenna DS, Stewart TL, Howard BC, Foster KF, Higby K, et al. Transvaginal cervical length scans to prevent prematurity in twins: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2016;**214**:227.e 1-7.

NCT02372422. Use of transvaginal ultrasound cervical length measurements in twin gestations. clinicaltrials.gov/ct2/show/NCT02372422 (first received 26 February 2015).

Mishra 2018 *{published data only}*

Mishra S, Bagga R, Kalra J, Jain V, Dutta S. Routine second trimester cervical length screening in low risk women identified women at risk of a 'very' preterm birth but did not reduce the preterm birth rate: a randomised study from India. *Journal of Obstetrics and Gynaecology* 2018;**38**(6):789-95.

Ness 2007 *{published data only}*

NCT00371046. The use of fetal fibronectin and transvaginal ultrasound cervical length in women with threatened preterm labor: a randomized trial. clinicaltrials.gov/ct2/show/NCT00371046 (first received 1 Septmber 2006).

* Ness A, Visintine J, Ricci E, Berghella V. Does knowledge of cervical length and fetal fibronectin affect management of women with threatened preterm labor? A randomized trial. *American Journal of Obstetrics and Gynecology* 2007;**197**(4):426.e 1-7.

Ness A, Visintine J, Ricci E, Boyle K, Berghella V. Use of fetal fibronectin and transvaginal ultrasound cervical length to triage women with suspected preterm labor: a randomized trial. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S67.

Palacio 2018 *{published data only}*

NCT00432250. The use of cervical length to reduce hospital stay in women admitted because of preterm labor. clinicaltrials.gov/ct2/show/NCT00432250 (first posted 7 February 2007).

* Palacio M, Caradeux J, Sanchez M, Cobo T, Figueras F, Coll O, et al. Uterine cervical length measurement to reduce length of stay in patients admitted for threatened preterm labor: a randomized trial. *Fetal Diagnosis and Therapy* 2018;**43**(3):184-90.

Palacio M, Sanchez M, Cobo T, Figueras F, Coll O, Cararach V. Uterine cervical length to reduce length of stay in patients admitted because of preterm labor. Prospective and randomized trial. Preliminary results. *Ultrasound in Obstetrics & Gynecology* 2003;**22**(Suppl 1):47.

* Palacio M, Sanchez M, Cobo T, Figueras F, Coll O, Cararach V, et al. Cervical length measurement to reduce length of stay in patients admitted because of preterm labor. Prospective and randomized trial. Final results. *Ultrasound in Obstetrics & Gynecology* 2006;**28**(4):485.

Vafaei 2017 *{published data only}*

IRCT2017092317034N5. Targeted therapy for threatened preterm labor based on sonographic measurements of the cervical length in women. en.irct.ir/trial/15770 (first received 16 October 2017).

* Vafaei H, Rahimirad N, Hosseini SM, Kasraeian M, Asadi N, Raeisi Shahraki H, et al. Triage by cervical length sonographic measurements for targeted therapy in threatened preterm labor: a double blind randomized clinical trial. *International Journal of Reproductive Biomedicine* 2017;**15**(11):697-702.

References to studies excluded from this review

Beigi 2005 *{published data only}*

Beigi A, Zarrinkoub F. Elective versus ultrasound-indicated cervical cerclage in women at risk for cervical incompetence. *Medical Journal of the Islamic Republic of Iran* 2005;**19**(2):103-7.

Burwick 2011 *{published data only}*

Burwick RM, Zork NM, Lee GT, Ross MG, Kjos SL. Cervilenz assessment of cervical length compared to fetal fibronectin in the prediction of preterm delivery in women with threatened preterm labor. *Journal of Maternal-Fetal & Neonatal Medicine* 2011;**24**(1):127-31.

Gauthier 2014 *{published data only}*

Gauthier T, Marin B, Garuchet-Bigot A, Kanoun D, Catalan C, Caly H, et al. Transperineal versus transvaginal ultrasound cervical length measurement and preterm labor. *Archives of Gynecology and Obstetrics* 2014;**290**:465-9.

Hosseini 2012 *{published data only}*

Hosseini SM, Vafaei F, Vafaei H. Management of threatened preterm labor based on sonographic measurements of the cervical length. *International Journal of Gynecology and Obstetrics* 2012;**119**(Suppl 3):S510.

Kassanos 2001 *{published data only}*

Kassanos D, Salamalekis E, Vitoratos N, Panayotopoulos N, Loghis C, Creatsas C. The value of transvaginal ultrasonography

in diagnosis and management of cervical incompetence. *Clinical and Experimental Obstetrics & Gynecology* 2001;**28**:266-8.

Lorenz 1990 *{published data only}*

Lorenz RP, Comstock CH, Bottoms SF, Marx SR. Randomized prospective trial comparing ultrasonography and pelvic examination for preterm labor surveillance. *American Journal of Obstetrics and Gynecology* 1990;**162**:1603-10.

Matijevic 2006 *{published data only}*

Matijevic R, Grgic O, Vasilj O. Is sonographic assessment of cervical length better than digital examination in screening for preterm delivery in a low-risk population?. *Acta Obstetricia et Gynecologica Scandinavica* 2006;**85**(11):1342-7.

Owen 1999 *{published data only}*

Owen J, Neely C, Northen A. Transperineal versus endovaginal ultrasonographic examination of the cervix in the midtrimester: a blinded comparison. *American Journal of Obstetrics and Gynecology* 1999;**181**(4):780-3.

Romero 2014 *{published data only}*

NCT01482039. Patient attitudes regarding abdominal versus transvaginal ultrasonography for assessment of the cervical length in low risk patients: a randomized trial. clinicaltrials.gov/ct2/show/record/NCT01482039 (first received 30 November 2011).

* Romero ST, Holmgren CC, Feltovich H, Porter TF, Esplin MS. Cervical length screening: a randomized trial assessing the impact on visit length and patient attitudes. *Journal of Ultrasound in Medicine* 2014;**33**(12):2159-63.

Schnettler 2013 *{published data only}*

Schnettler W, March M, Hacker MR, Modest AM, Rodriguez D. Impaired ultrasonographic cervical assessment after voiding: a randomized controlled trial. *Obstetrics and Gynecology* 2013;**121**(4):798-804. [NCT01513395]

Simcox 2009 *{published data only}*

Shennan A, Maternal and Fetal Research Unit (MFRU). CIRCLE study: cerclage in relation to cervical length. Maternal and Fetal Research Unit (www.mfru.org.uk/CIRCLE.htm) (accessed 25 February 2004).

Simcox R, Bennett F, Teoh TG, Shennan AH. A randomised controlled trial of cervical scanning vs history to determine cerclage in high risk women (circle trial). *Journal of Obstetrics and Gynaecology* 2007;**27**(Suppl 1):S18.

* Simcox R, Seed PT, Bennett P, Teoh TG, Poston L, Shennan AH. A randomized controlled trial of cervical scanning vs history to determine cerclage in women at high risk of preterm birth (CIRCLE trial). *American Journal of Obstetrics and Gynecology* 2009;**200**(6):623.e1-6.

Van Dijken 1991 *{published data only}*

Van Dijken DKE, Wolf H, Boer K, Treffers PE. Preliminary results of a randomized trial comparing abdominal ultrasonography and digital examination. 13th World Congress of Gynaecology and Obstetrics (FIGO); 1991 Sept 15-20; Singapore. 1991:289.

References to ongoing studies

NCT01431885 *{published data only}*

NCT01431885. Randomized controlled trial of two methods of diagnosing preterm labor. clinicaltrials.gov/ct2/show/NCT01431885 (first received 12 September 2011).

NCT02923973 *{published data only}*

NCT02923973. Transvaginal ultrasound cervical length screening in singleton pregnancy with prior spontaneous preterm birth. clinicaltrials.gov/ct2/show/NCT02923973 (first received 5 October 2016).

NCT02928302 *{published data only}*

NCT02928302. Transvaginal ultrasound cervical length screening in singleton pregnancy without prior spontaneous preterm birth. clinicaltrials.gov/ct2/show/NCT02928302 (10 October 2016) (first received 10 October 2016).

NCT03591042. Universal transvaginal cervical length screening program for prevention of preterm birth in singletons without prior preterm birth: a randomized controlled trial. clinicaltrials.gov/ct2/show/NCT03591042 (first received 18 July 2018).

Additional references

Abdel-Aleem 2013

Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD007873.pub2]

Alfirevic 2017

Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database of Systematic Reviews* 2017, Issue 6. [DOI: 10.1002/14651858.CD008991.pub3]

Berghella 2003

Berghella V, Bega G, Tolosa JE, Berghella M. Ultrasound assessment of the cervix. *Clinical Obstetrics and Gynecology* 2003;**46**:947-62.

Berghella 2007

Berghella V, Roman A, Daskalakis C, Ness A, Baxter JK. Gestational age at cervical length measurement and incidence of preterm birth. *Obstetrics and Gynecology* 2007;**110**:311-7.

Berghella 2017

Berghella V, Palacio M, Ness A, Alfirevic Z, Nicolaides KH, Saccone G. Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. *Ultrasound in Obstetrics & Gynecology* 2017;**49**:322-329.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG

editor(s). Systematic Reviews in Health Care: Meta-analysis in Context. London: BMJ Books, 2001.

Dodd 2017a

Dodd JM, Grivell RM, OBrien CM, Deussen AR. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a singleton pregnancy. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: 10.1002/14651858.CD012531]

Dodd 2017b

Dodd JM, Grivell RM, OBrien CM, Dowswell T, Deussen AR. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. *Cochrane Database of Systematic Reviews* 2017, Issue 10. [DOI: 10.1002/14651858.CD012024.pub2]

GRADE Handbook

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version Accessed 11 May 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grimes-Dennis 2007

Grimes-Dennis J, Berghella V. Cervical length and prediction of preterm birth. *Current Opinion in Obstetrics and Gynecology* 2007;**19**:191-5.

Hernandez-Andrade 2012

Hernandez-Andrade E, Romero R, Ahn H, Hussein Y, Yeo L, Korzeniewski SJ, et al. Transabdominal evaluation of uterine cervical length during pregnancy fails to identify a substantial number of women with a short cervix. *Journal of Maternal-Fetal and Neonatal Medicine* 2012;**25**(9):1682-9.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Khalifeh 2016

Khalifeh A, Berghella V. Universal cervical length screening in singleton gestations without a previous preterm birth: ten reasons why it should be implemented. *American Journal of Obstetrics and Gynecology* 2016;**214**:e1-5.

Navathe 2019

Navathe R, Saccone G, Villani M, Knapp J, Cruz Y, Boelig R, Roman A, Berghella V. Decrease in the incidence of threatened preterm labor after implementation of transvaginal ultrasound cervical length universal screening. *The Journal of Maternal-Fetal & Neonatal Medicine* 2019;**32**:1853-1858.

Rafael 2014

Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD009166.pub2]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

References to other published versions of this review

Berghella 2008

Berghella V, Baxter J, Harvey C, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD007235]

Berghella 2009

Berghella V, Baxter JK, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007235.pub2]

Berghella 2013

Berghella V, Baxter JK, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD007235.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alfirevic 2007

Methods	RCT
Participants	Singleton pregnancies; uterine contractions at < 34 weeks; and clinical decision to use steroids and tocolytics. N = 41
Interventions	TVU CL knowledge or not (the control group did not receive TVU CL)

Alfirevic 2007 *(Continued)*

	Time TVU CL results available: not specified
	Protocol for TVU knowledge group: yes
Outcomes	Primary: incidence of women still pregnant at 7 days
Notes	Intention-to-treat; only singletons; protocol for management of TVU CL group
	Short TVU CL (< 15 mm): 7/21 (33%) in knowledge group; not done in other group
	Funding: the study was funded by The Fetal Medicine Foundation (Registered Charity 1037116)
	Dates of trial: from 2003 to 2005
	Setting: 5 hospitals in the United Kingdom, 1 in Spain
	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Consecutively numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and physicians knew which group was randomised to 'knowledge' or 'no knowledge'.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Some blinding attempted – "Women allocated to the experimental group had a transvaginal scan to measure the CL, which was performed by a member of the research team who was not involved in the care of the patient" – but the control group did not have a transvaginal scan. Primary outcome – is an objective outcome (delivery within 7 days)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcomes. Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Primary outcome was delivery within 7 days. All other outcomes reported
Other bias	Low risk	Baseline characteristics similar

Carlan 1997

Methods	RCT
Participants	Singleton pregnancies; PPROM; 24 to 34 weeks. N = 92
Interventions	TVU CL or not (the control group did not receive TVU CL)
	Time TVU CL results available: not specified

Carlan 1997 *(Continued)*

	Protocol for TVU knowledge group: no
Outcomes	Primary: maternal infection
Notes	Intention-to-treat; only singletons; PPROM; no protocol (really a safety study for TVU CL in women with PPROM) Short TVU CL (< 25 mm): 14/45 (31%) in knowledge group; not done in other group Funding: not reported Dates of trial: from May 1993 to June 1996 Setting: Arnold Palmer Hospital for Children and Women, Floride, United States Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly-generated assignment"
Allocation concealment (selection bias)	Low risk	"Randomly-generated" assignments in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study group had weekly US while controls had none
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% explained
Selective reporting (reporting bias)	Low risk	Primary outcome was chorioamnionitis. All other outcomes reported
Other bias	Unclear risk	No baseline characteristics table

Gordon 2016

Methods	RCT
Participants	Twin pregnancies; asymptomatic and with PTL symptoms; 15 to 34 weeks. N = 125
Interventions	TVU CL screening at 15 to 28 weeks, and if PTL symptoms develop or not (the control group did not receive TVU CL) Time TVU CL results available: not specified Protocol for TVU knowledge group: yes

Gordon 2016 *(Continued)*

Outcomes	Primary: length of gestation
Notes	Only abstract published; unclear if intention-to-treat; only twins; protocol for management of TVU CL group Short TVU CL not available Funding: not reported Dates of trial: not reported Setting: not reported, assumed United States Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different protocols for study and control groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome objective – length of gestation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No incomplete outcomes mentioned
Selective reporting (reporting bias)	Unclear risk	Primary outcome was gestational age at delivery
Other bias	Unclear risk	Abstract only, so data reported are limited

Mishra 2018

Methods	RCT
Participants	Asymptomatic singleton pregnancies at 16 to 24 6/7 weeks. N = 296
Interventions	TVU CL performed or not (the control group did not receive TVU CL) at the time of the routine anatomy screening Protocol for TVU group: yes
Outcomes	Primary: PTB < 37 weeks
Notes	Funding: not reported

Mishra 2018 *(Continued)*

	Dates of trial: July 2014 to December 2015 Setting: Department of Obstetrics & Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, North India Conflicts of interest: the authors reported no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and physicians knew which group was randomised to 'TVU CL performed' or 'not performed'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Lost to follow-up removed from the analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Baseline characteristics similar

Ness 2007

Methods	RCT
Participants	Singleton (and 3 twin) pregnancies; uterine contractions or symptoms suggestive of PTL at 24 to 33 6/7 weeks. N = 100
Interventions	TVU CL knowledge or not (the control group did receive TVU CL, but results were blinded to managing physicians) Time TVU CL results available: not specified Protocol for TVU knowledge group: yes
Outcomes	Primary: time from initial evaluation to discharge
Notes	Intention to treat; 97% singletons; protocol for management of TVU CL group, which included management based on FFN for women with CL 20 to 29 mm Short TVU CL (< 20 mm): 11/51 (22%) in knowledge group; 7/49 (15%) in the control group Funding: not reported

Ness 2007 *(Continued)*

	Dates of trial: between November 2004 and April 2006
	Setting: Thomas Jefferson University Hospital, Philadelphia
	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and physicians knew which group was randomised to 'knowledge' or 'no knowledge'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses
Selective reporting (reporting bias)	Low risk	Primary outcome time from evaluation to discharge. All other outcomes reported
Other bias	Low risk	Baseline characteristics similar

Palacio 2018

Methods	RCT
Participants	Singleton pregnancies; PTL at 24 to 35 6/7 weeks. N = 149
Interventions	TVU CL knowledge or not (the control group did receive TVU CL, but results were blinded to managing physicians) Time TVU CL results available: not specified Protocol for TVU knowledge group: yes
Outcomes	Primary: hospital length of stay
Notes	7 women lost to follow-up; only singletons; protocol for management of TVU CL group Short TVU CL (< 25 mm): 22/75 (29%) in knowledge group; 20/74 (27%) in the control group Funding: not reported Dates of trial: from January 2002 to April 2005 Setting: Hospital Clinic of Barcelona, Spain

Palacio 2018 *(Continued)*

	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Telephone-operated platform
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and physicians knew which group was randomised to 'knowledge' or 'no knowledge'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	5% of data removed from final analysis
Selective reporting (reporting bias)	Unclear risk	Length of hospital stay primary outcome
Other bias	Low risk	Baseline characteristics similar

Vafaei 2017

Methods	RCT
Participants	Singleton pregnancies; PTL before 34 weeks. N = 120
Interventions	TVU CL performed or not Protocol for TVU group: yes
Outcomes	Primary: Delivery within 7 days
Notes	No outcome of interest Funding: Supported by Vice-Chancellor of Research, Shiraz University of Medical Sciences, Shiraz, Iran Dates of trial: not reported Setting: Hafez Hospital, Shiraz University of Medical Sciences, Shiraz, Iran Conflicts of interest: authors declare no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement

Vafaei 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and physicians knew which group was randomised to 'TVU CL performed' or 'not performed'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Baseline characteristics similar

CL: cervical length
FFN: fetal fibronectin
PPROM: preterm premature rupture of membranes
PTL: preterm labour
RCT: randomised controlled trial
TVU: transvaginal ultrasound
US: ultrasound

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

Study	Reason for exclusion
Beigi 2005	Compared history – indicated to ultrasound-indicated cerclage
Burwick 2011	Used Cervilenz, which is a plastic instrument to measure the vaginal part of the cervix. This is outside the scope of our review, which focuses on CL measured exclusively by TVU.
Gauthier 2014	Compared TVU CL screening to transperineal ultrasound CL screening, with no control group with 'no knowledge' of CL.
Hosseini 2012	Unclear if randomised to knowledge versus no knowledge of CL. No outcome of interest was reported in cases versus controls. Only published as an abstract, with no other information available.
Kassanos 2001	Compared history-indicated to ultrasound-indicated cerclage.
Lorenz 1990	Control group was not 'no ultrasound' or 'no knowledge', but was manual digital cervical exam. Interestingly, the study group utilized transabdominal ultrasound.
Matijevic 2006	The TVU CL information was blinded and not used for management.
Owen 1999	TVU information was not used for clinical care and no data on outcomes were provided.

Study	Reason for exclusion
Romero 2014	No data on any outcomes of interest for this Cochrane Review were available, even upon direct request, as this was a trial assessing only visit length and patient attitudes.
Schnettler 2013	Compared TVU CL immediately after urination to TVU CL at least 15 minutes after urination, with no control group with 'no knowledge' of CL.
Simcox 2009	Compared history – indicated to ultrasound-indicated cerclage.
Van Dijken 1991	Control group was not 'no ultrasound' or 'no knowledge', but was manual digital cervical exam. Interestingly, the study group utilized transabdominal, not TVU.

CL: cervical length
TVU: transvaginal ultrasound

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

NCT01431885

Trial name or title	Two methods of diagnosing preterm labor
Methods	Parallel open label randomised controlled trial
Participants	Symptomatic complaints suggestive of preterm labour, greater than 6 contractions per hour
Interventions	Symptomatic preterm labor patients will be randomised to diagnosis of preterm labor by serial digital examination versus an algorithm incorporating transvaginal ultrasound measurement of cervical length and vaginal fetal fibronectin.
Outcomes	Preterm birth < 37 weeks
Starting date	August 2011
Contact information	Conrad R Chao, University of California, San Francisco. e-mail: cchao@fresno.ucsf.edu
Notes	Estimated primary completion date: August 2015 Estimated study completion date: August 2015

NCT02923973

Trial name or title	Transvaginal ultrasound cervical length screening in singleton pregnancy with prior spontaneous preterm birth
Methods	Parallel open label randomised trial
Participants	Women 18 to 50 years of age, with prior spontaneous preterm delivery 16 0/7 to 36 6/7 weeks and singleton pregnancies
Interventions	Transvaginal ultrasound cervical length screening versus no screening
Outcomes	Primary: Preterm birth (less than 37 weeks)

NCT02923973 *(Continued)*

	Secondary: Gestational age at delivery Preterm birth (less than 24, 28, 32, 30, and 34 weeks' gestation) Birthweight Low birth weight (< 2500g) Neonatal death Composite of adverse perinatal outcomes (necrotizing enterocolitis, intraventricular haemorrhage (grade 3 or higher), respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy, blood-culture proven sepsis and neonatal death) Admission to neonatal intensive care unit
Starting date	June 1, 2018
Contact information	Gabriele Saccone, Federico II University, Naples, Italy, e-mail: gabriele.saccone.1990@gmail.com
Notes	Estimated primary completion date: December 1, 2020 Estimated study completion date: March 1, 2021

NCT02928302

Trial name or title	Transvaginal ultrasound cervical length screening in singleton pregnancy without prior spontaneous preterm birth
Methods	Non-blinded randomised screening trial
Participants	Asymptomatic singleton pregnancies without prior spontaneous preterm birth
Interventions	Transvaginal ultrasound cervical length screening versus no screening
Outcomes	Primary: Preterm birth (less than 37 weeks) Secondary: Preterm birth (less than 24, 28, 32, 30, and 34 weeks' gestation) Admission to neonatal intensive care unit Neonatal death Birthweight Composite of adverse perinatal outcomes (necrotizing enterocolitis, intraventricular haemorrhage (grade 3 or higher), respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy, blood-culture proven sepsis and neonatal death) Perinatal death
Starting date	July 15, 2018
Contact information	Gabriele Saccone, Federico II University, Naples, Italy, e-mail: gabriele.saccone.1990@gmail.com

NCT02928302 *(Continued)*

Notes	Estimated primary completion date: September 2019 Estimated study completion date: January 2020

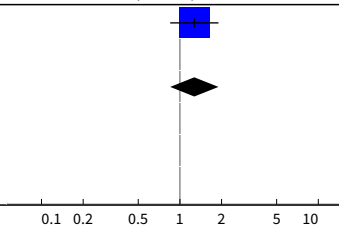
DATA AND ANALYSES

Comparison 1. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins

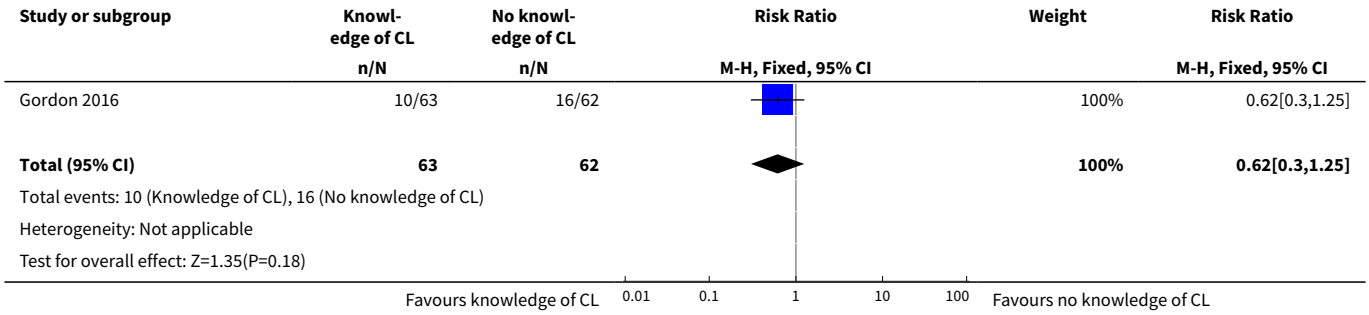
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth < 36 weeks	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.85, 1.90]
2 Preterm birth < 34 weeks	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.30, 1.25]
3 Preterm birth < 32 weeks	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.17, 1.83]
4 Preterm birth < 30 weeks	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.64]
5 Gestational age at delivery	1	125	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.74, 1.14]
6 Maternal hospitalisation for PTL	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.75, 2.23]
7 Tocolysis	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.74, 2.42]
8 Steroids for fetal lung maturity	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.49, 1.26]
9 Cervical cerclage	1	125	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [0.24, 100.49]
10 Birthweight (g)	1	250	Mean Difference (IV, Fixed, 95% CI)	142.0 [-9.95, 293.95]
11 NICU admission	1	250	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.83, 1.55]

Analysis 1.1. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 1 Preterm birth < 36 weeks.

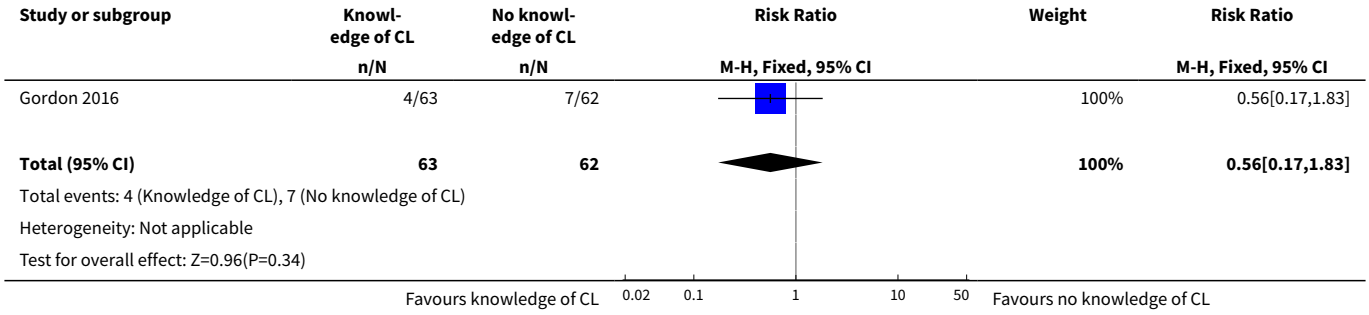
Study or subgroup	Knowledge of CL n/N	No knowledge of CL n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gordon 2016	31/63	24/62		100%	1.27[0.85,1.9]
Total (95% CI)	**63**	**62**		**100%**	**1.27[0.85,1.9]**
Total events: 31 (Knowledge of CL), 24 (No knowledge of CL)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					



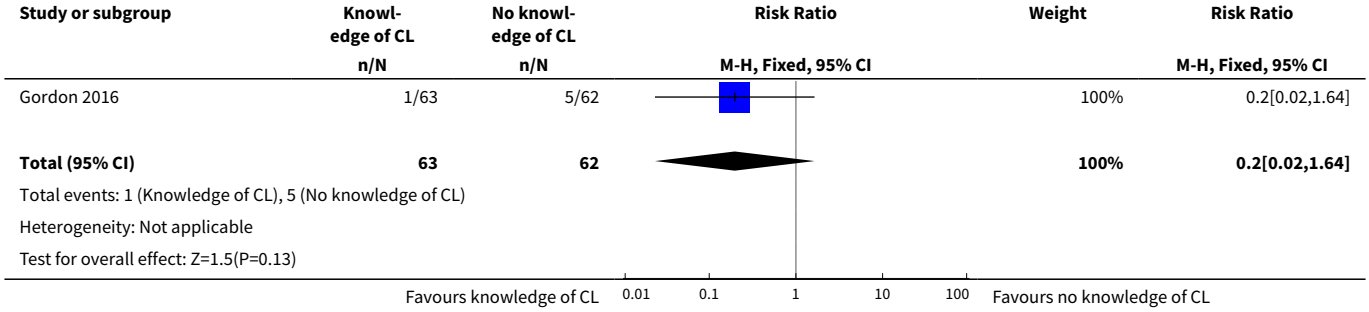
Analysis 1.2. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 2 Preterm birth < 34 weeks.



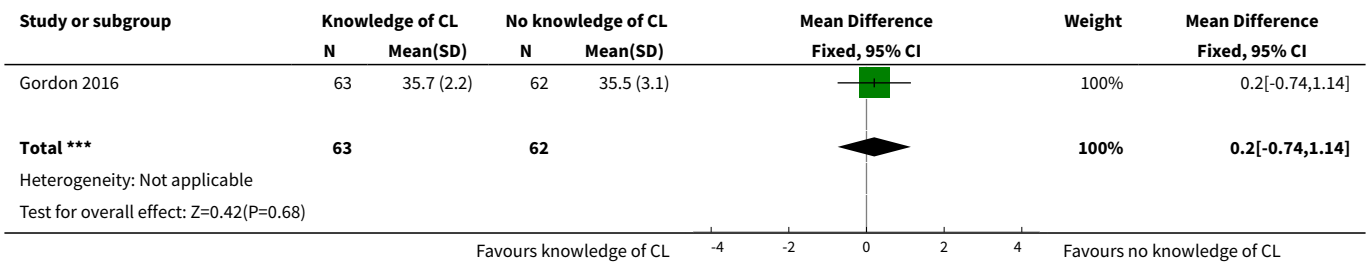
Analysis 1.3. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 3 Preterm birth < 32 weeks.



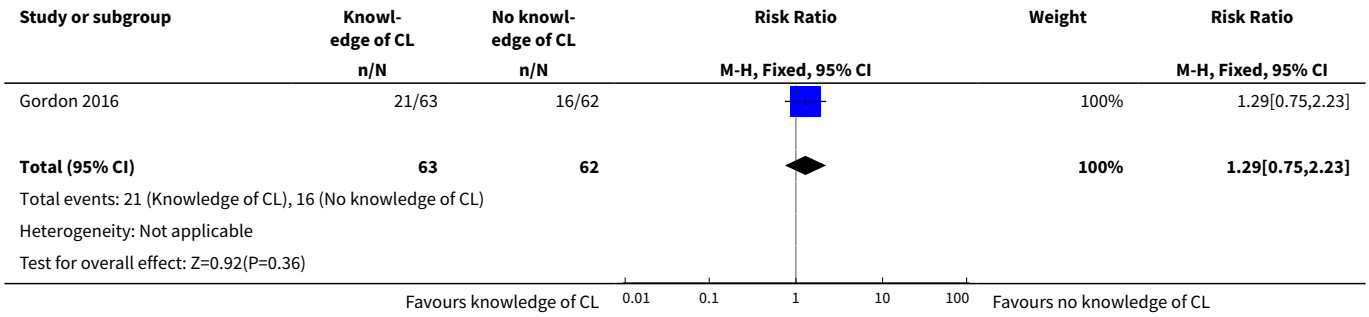
Analysis 1.4. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 4 Preterm birth < 30 weeks.



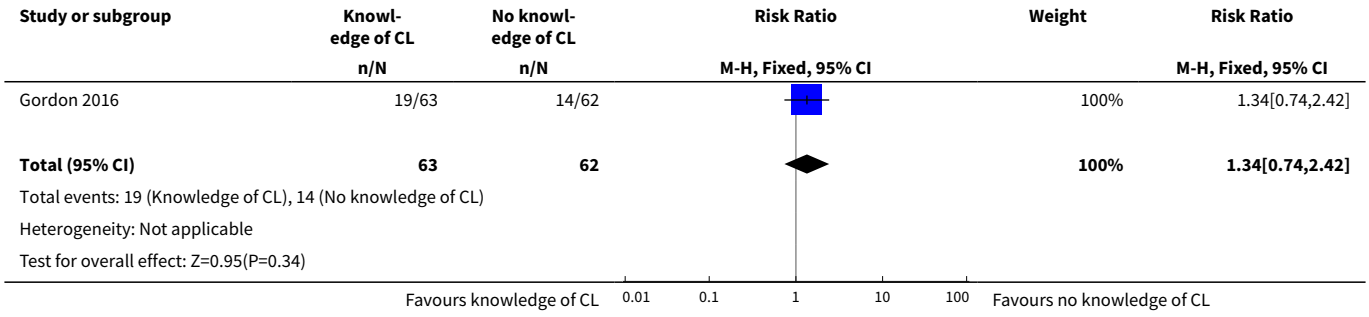
Analysis 1.5. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 5 Gestational age at delivery.



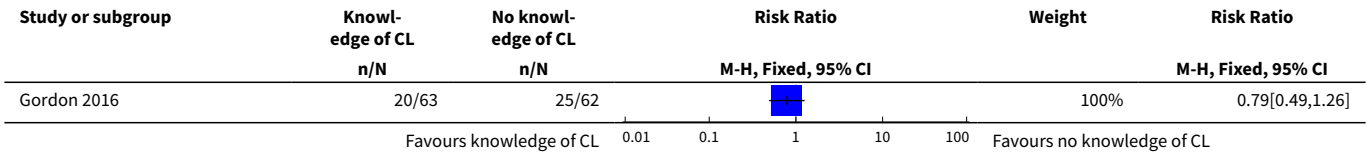
Analysis 1.6. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 6 Maternal hospitalisation for PTL.

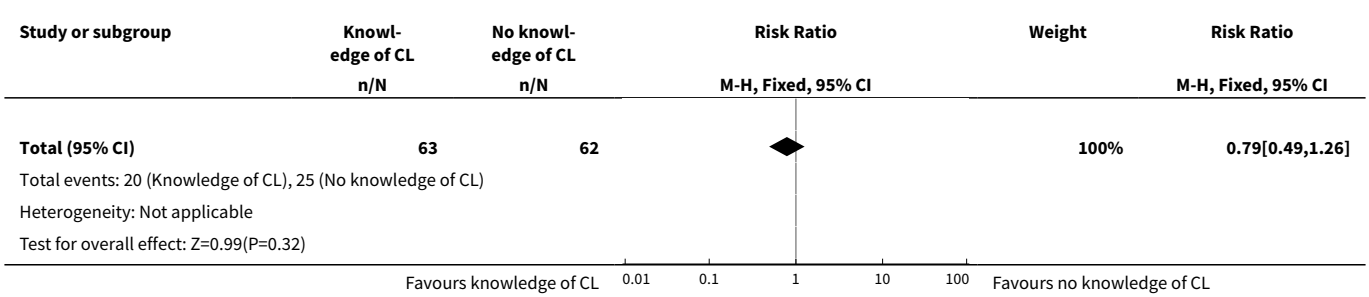


Analysis 1.7. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 7 Tocolysis.

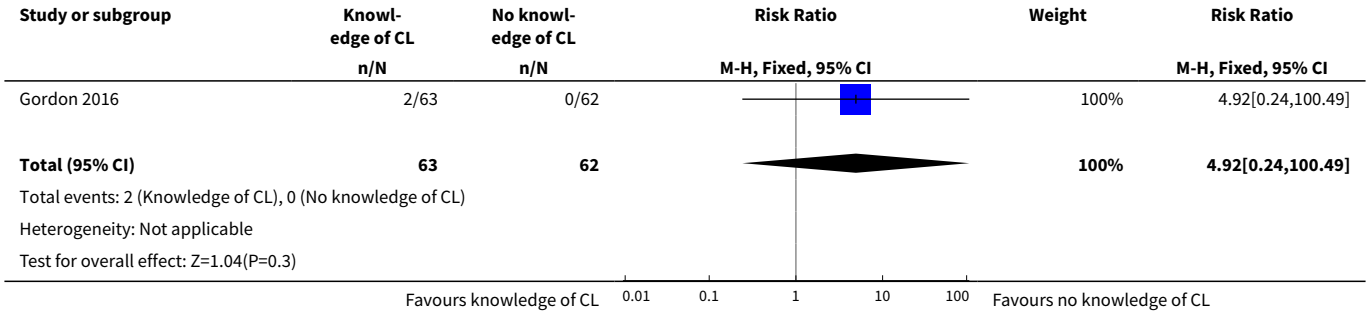


Analysis 1.8. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 8 Steroids for fetal lung maturity.

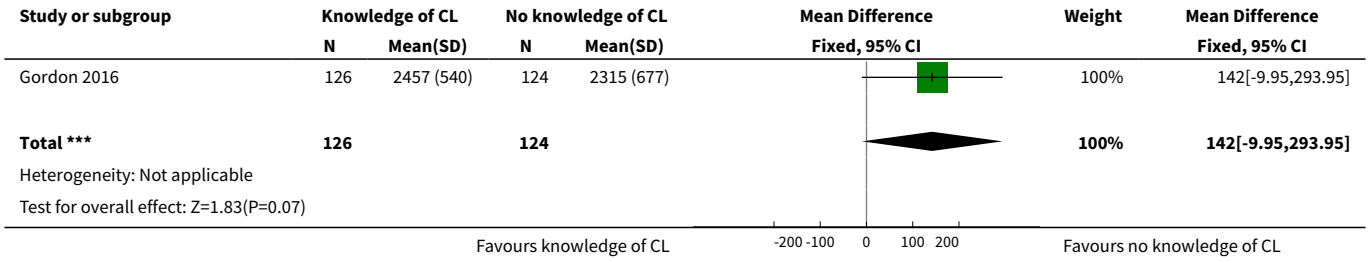




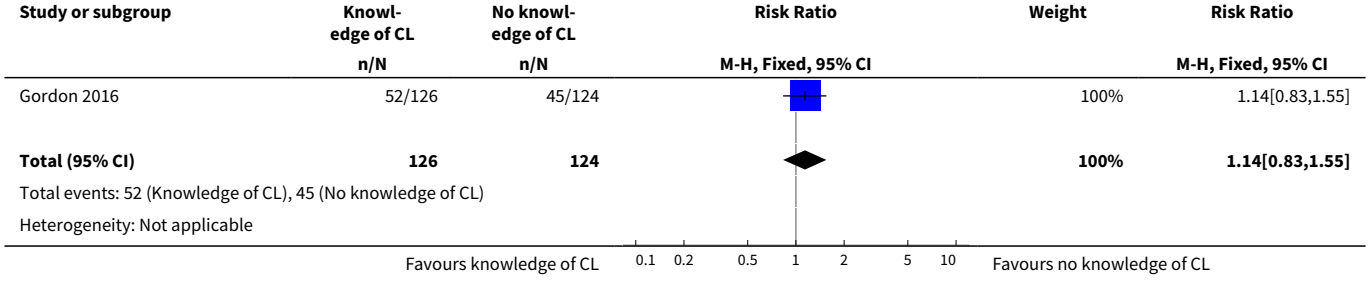
Analysis 1.9. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 9 Cervical cerclage.

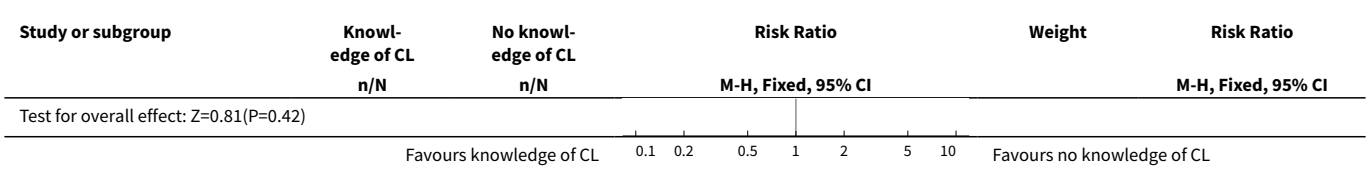


Analysis 1.10. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 10 Birthweight (g).



Analysis 1.11. Comparison 1 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic women with twins, Outcome 11 NICU admission.

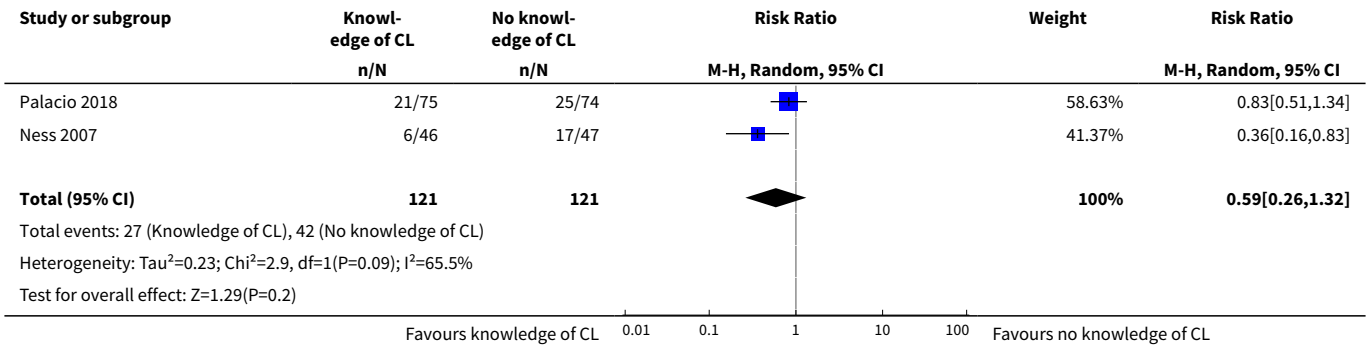




Comparison 2. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth < 37 weeks	2	242	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.32]
2 Preterm birth < 34 weeks	3	256	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.20]
3 Preterm birth < 28 weeks	2	137	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Gestational age at delivery (weeks)	3	290	Mean Difference (IV, Fixed, 95% CI)	0.64 [0.03, 1.25]
5 Birthweight < 2500 g	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.21, 2.44]
6 Perinatal death	2	138	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Maternal hospitalisation	1	93	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.85, 10.16]
8 Tocolysis	2	102	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.11, 6.58]
9 Steroids for fetal lung maturity	2	114	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.15, 19.64]

Analysis 2.1. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 1 Preterm birth < 37 weeks.



Analysis 2.2. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 2 Preterm birth < 34 weeks.

Study or subgroup	Knowledge of CL n/N	No knowledge of CL n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Palacio 2018	4/59	7/59		43.38%	0.57[0.18,1.85]
Ness 2007	3/49	6/48		37.57%	0.49[0.13,1.85]
Alfirevic 2007	2/21	3/20		19.05%	0.63[0.12,3.41]
Total (95% CI)	**129**	**127**		**100%**	**0.55[0.25,1.2]**
Total events: 9 (Knowledge of CL), 16 (No knowledge of CL)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					

Favours knowledge of CL — Favours no knowledge of CL

Analysis 2.3. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 3 Preterm birth < 28 weeks.

Study or subgroup	Knowledge of CL n/N	No knowledge of CL n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alfirevic 2007	0/21	0/20			Not estimable
Ness 2007	0/48	0/48			Not estimable
Total (95% CI)	**69**	**68**			**Not estimable**
Total events: 0 (Knowledge of CL), 0 (No knowledge of CL)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

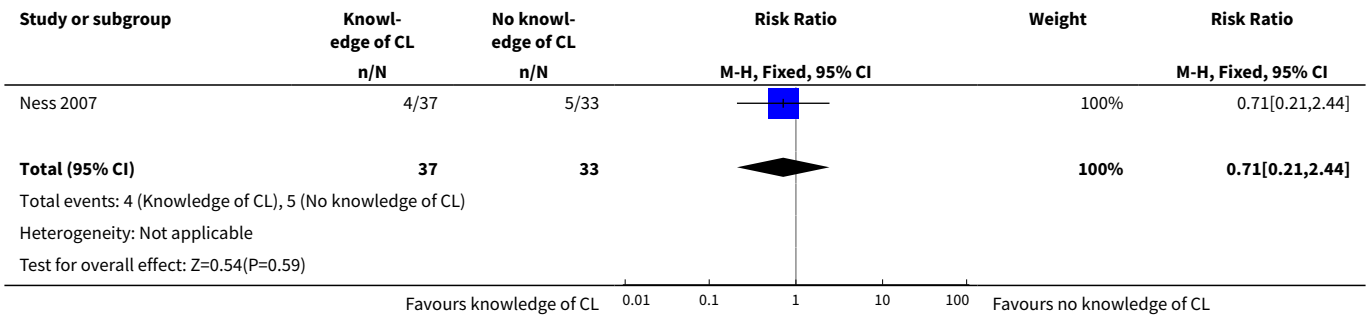
Favours knowledge of CL — Favours no knowledge of CL

Analysis 2.4. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 4 Gestational age at delivery (weeks).

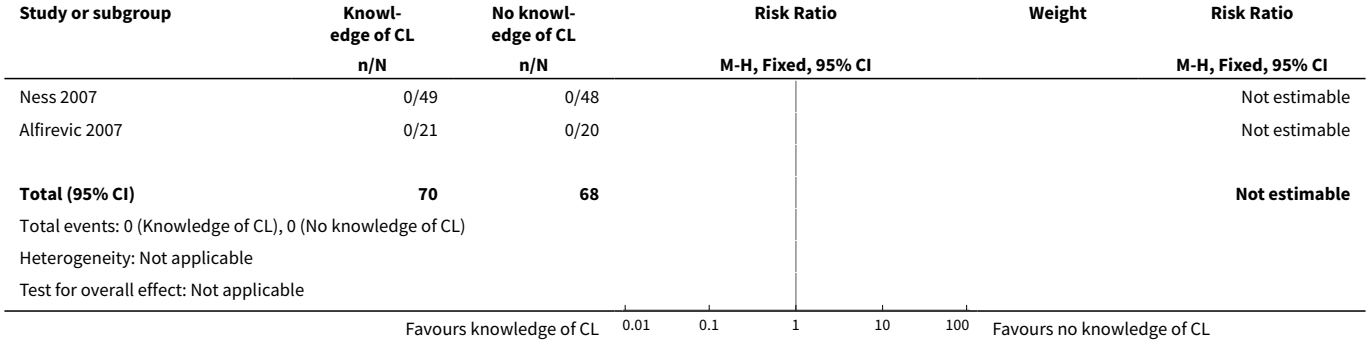
Study or subgroup	Knowledge of CL N	Knowledge of CL Mean(SD)	No knowledge of CL N	No knowledge of CL Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Palacio 2018	75	37.6 (2.6)	74	37.3 (2.7)		51.2%	0.3[-0.55,1.15]
Alfirevic 2007	21	37.9 (3)	20	37.6 (2.9)		11.38%	0.3[-1.51,2.11]
Ness 2007	51	38.3 (2.1)	49	37.1 (2.9)		37.42%	1.2[0.2,2.2]
Total ***	**147**		**143**			**100%**	**0.64[0.03,1.25]**
Heterogeneity: Tau^2=0; Chi^2=1.96, df=2(P=0.37); I^2=0%							
Test for overall effect: Z=2.05(P=0.04)							

Favours no knowledge of CL — Favours knowledge of CL

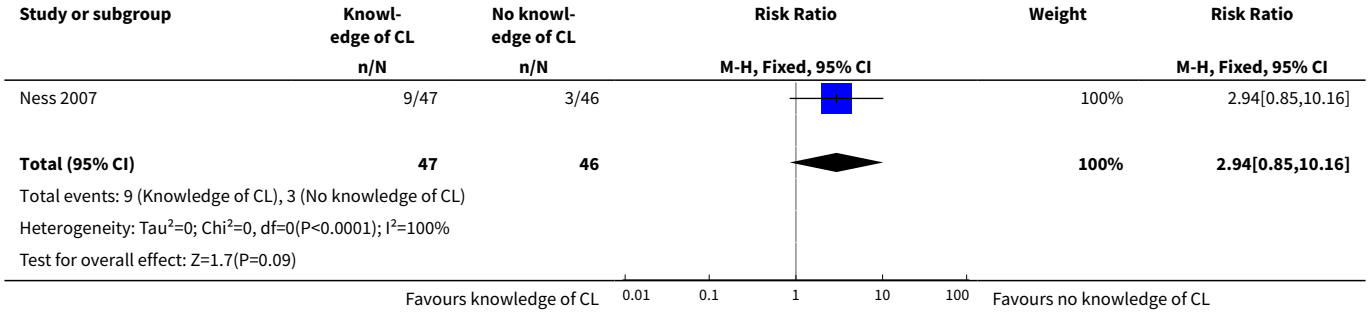
Analysis 2.5. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 5 Birthweight < 2500 g.



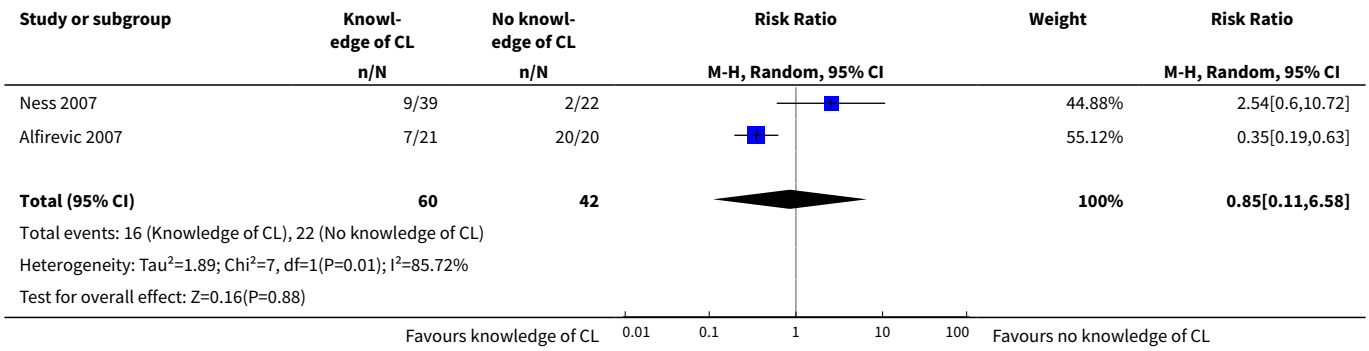
Analysis 2.6. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 6 Perinatal death.



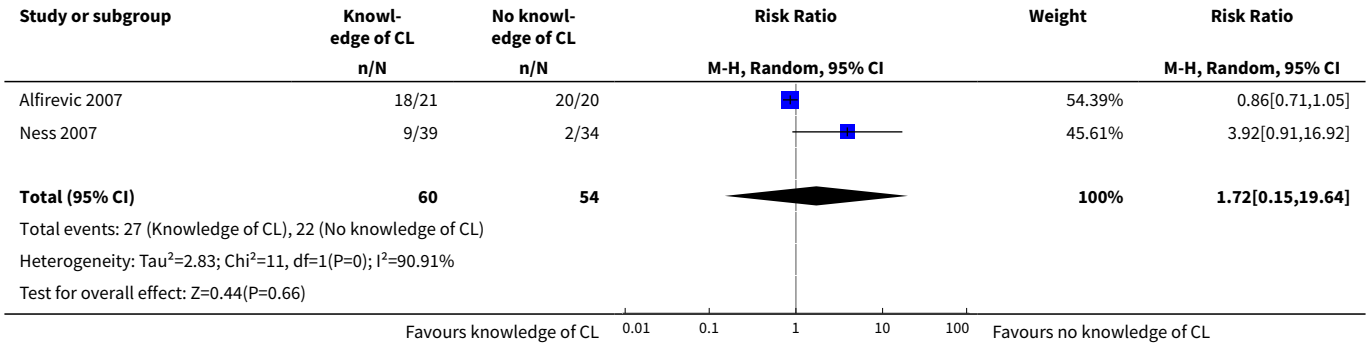
Analysis 2.7. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 7 Maternal hospitalisation.



Analysis 2.8. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 8 Tocolysis.



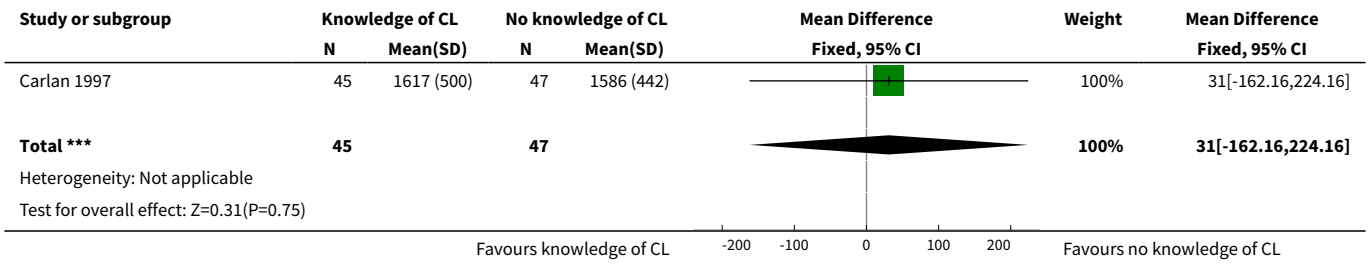
Analysis 2.9. Comparison 2 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with symptoms of PTL, Outcome 9 Steroids for fetal lung maturity.



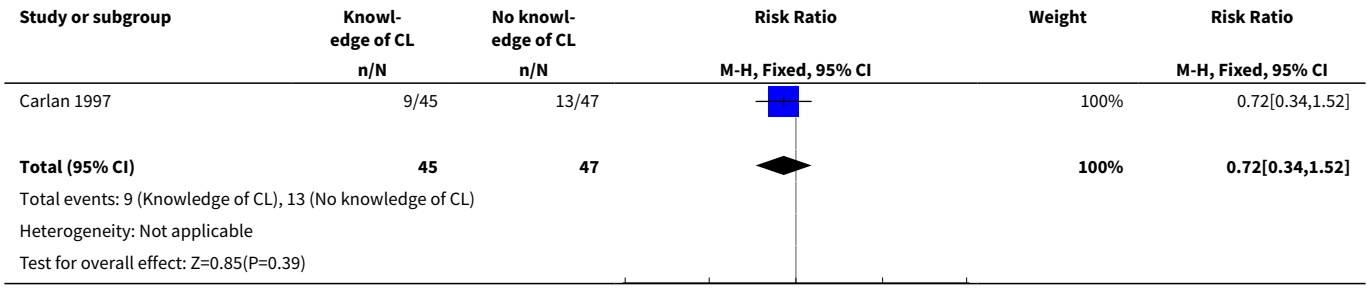
Comparison 3. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with PPROM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birthweight (g)	1	92	Mean Difference (IV, Fixed, 95% CI)	31.0 [-162.16, 224.16]
2 Chorioamnionitis	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.34, 1.52]
3 Endometritis	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.33, 5.88]
4 Neonatal infection	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.50, 2.78]

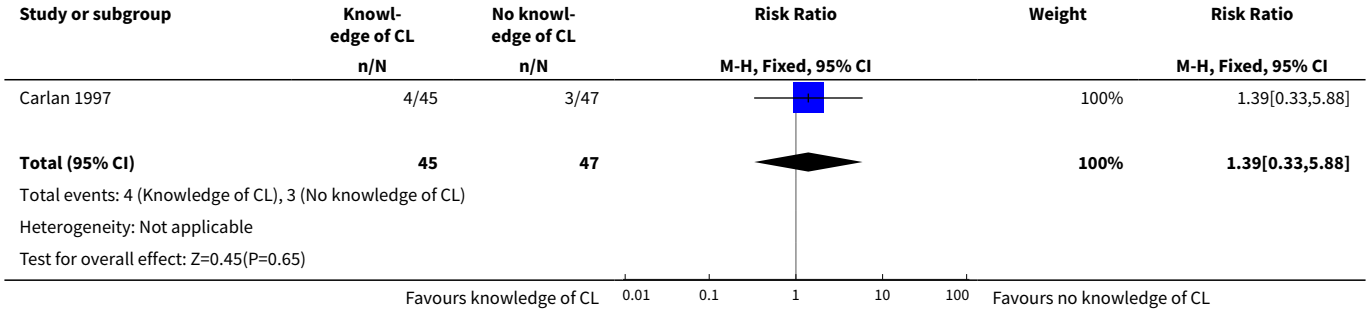
Analysis 3.1. Comparison 3 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with PPROM, Outcome 1 Birthweight (g).



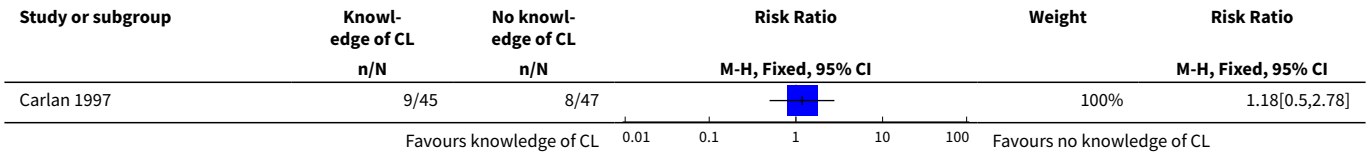
Analysis 3.2. Comparison 3 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with PPROM, Outcome 2 Chorioamnionitis.

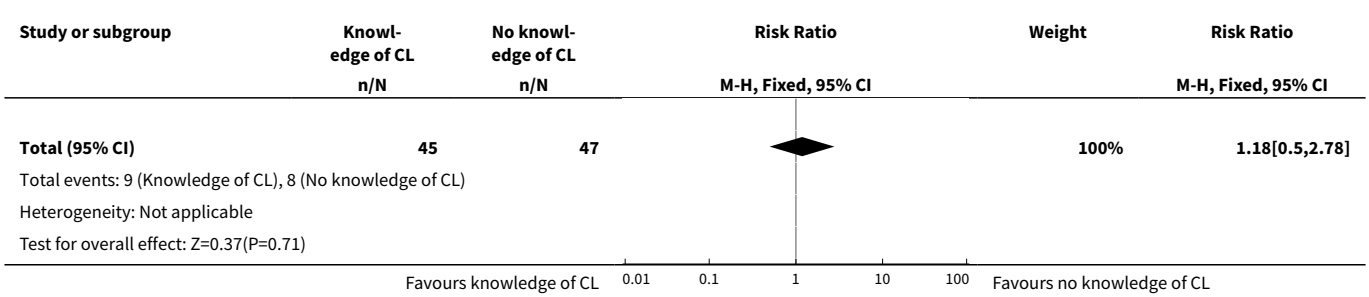


Analysis 3.3. Comparison 3 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with PPROM, Outcome 3 Endometritis.



Analysis 3.4. Comparison 3 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - singletons with PPROM, Outcome 4 Neonatal infection.

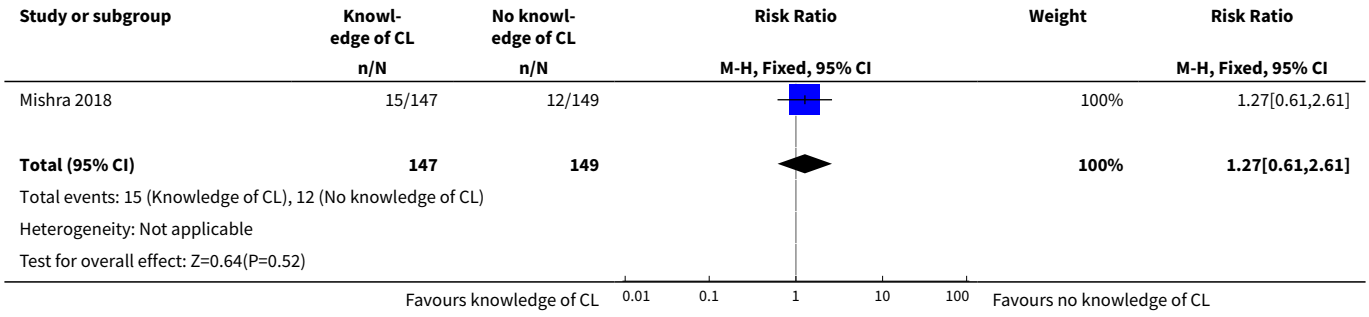




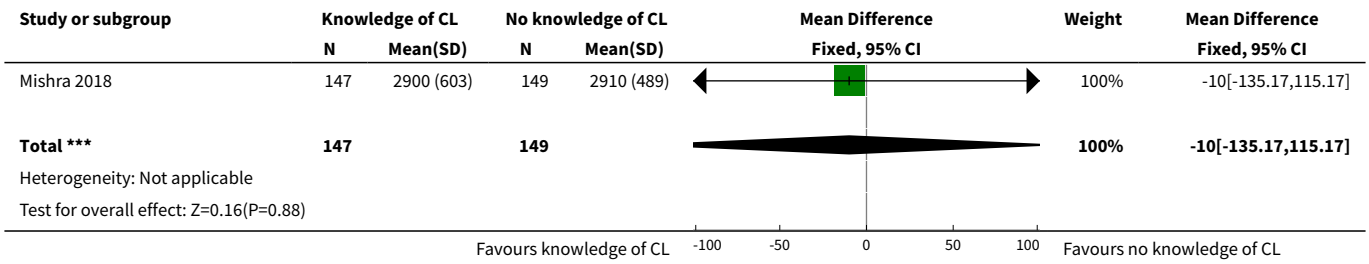
Comparison 4. Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth < 37 weeks	1	296	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.61, 2.61]
2 Birthweight (g)	1	296	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-135.17, 115.17]
3 Respiratory distress syndrome (RDS)	1	296	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.38, 10.90]
4 NICU admission	1	296	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 22.12]
5 Intraventricular haemorrhage (IVH)	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.53]
6 Neonatal death	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.19]

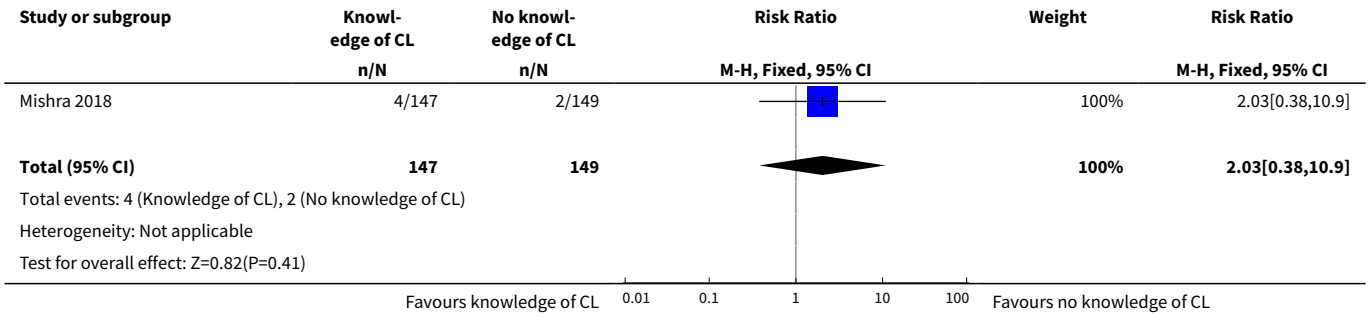
Analysis 4.1. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 1 Preterm birth < 37 weeks.



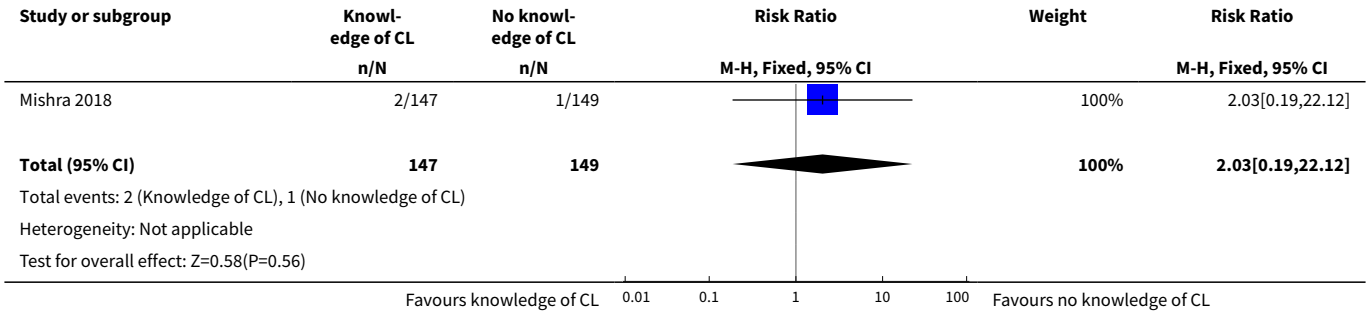
Analysis 4.2. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 2 Birthweight (g).



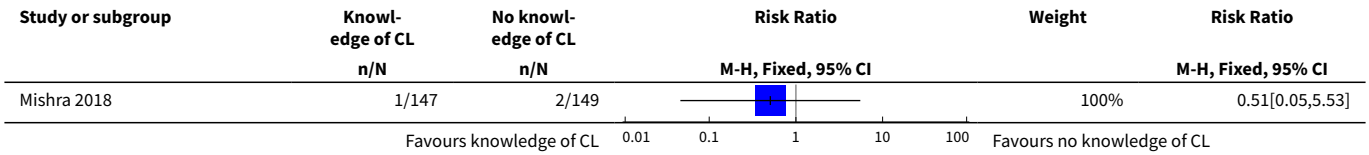
Analysis 4.3. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 3 Respiratory distress syndrome (RDS).

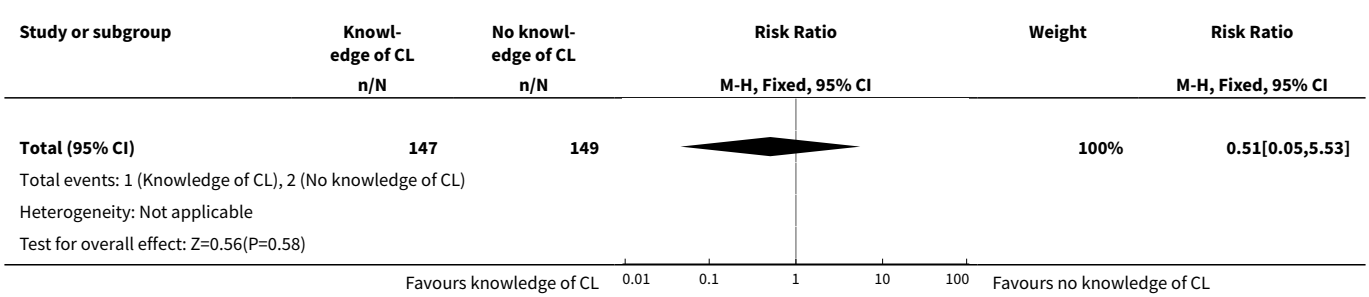


Analysis 4.4. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 4 NICU admission.

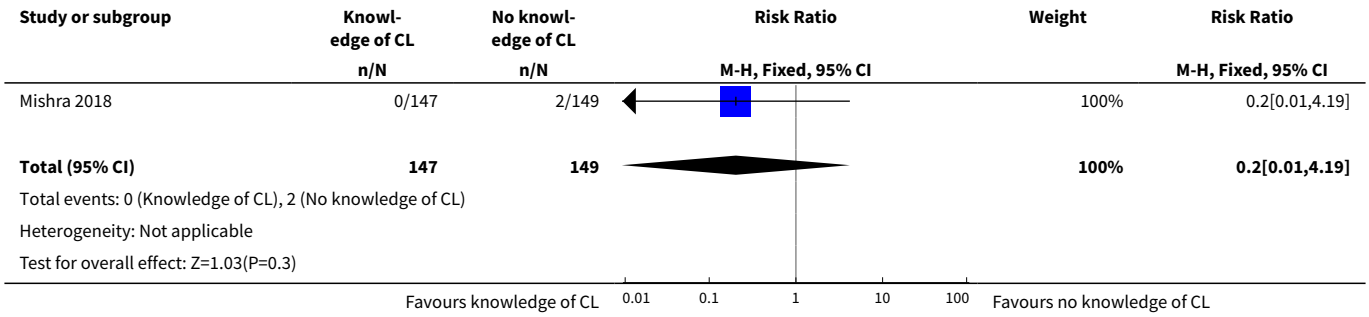


Analysis 4.5. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 5 Intraventricular haemorrhage (IVH).





Analysis 4.6. Comparison 4 Knowledge versus no knowledge of transvaginal ultrasound (TVU)-measured cervical length (CL) - asymptomatic singletons, Outcome 6 Neonatal death.



APPENDICES

Appendix 1. ICTRP and ClinicalTrials.gov - search methods

ICTRP

Each line was run separately

ultrasound AND preterm

sonography AND preterm

cervical AND length AND pregnancy

cervical AND length AND preterm

ClinicalTrials.gov

Advanced search

Interventional studies | Preterm Labor | ultrasound

Cervical length | Interventional studies | preterm

pregnancy | Interventional studies | cervical length

WHAT'S NEW

Date	Event	Description
30 August 2018	New citation required but conclusions have not changed	Conclusions remain unchanged.
30 August 2018	New search has been performed	Search updated and two new studies included (Mishra 2018; Vafaei 2017). A 'Summary of findings' table has been incorporated.

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 3, 2009

Date	Event	Description
28 January 2013	Amended	Information added on attrition bias for one study (Ness 2007).
26 September 2012	New search has been performed	Two studies identified from an updated search have been assessed for eligibility and both have been excluded. Methods have been updated.
26 September 2012	New citation required but conclusions have not changed	Review updated.
27 January 2012	Amended	Search updated. Two trial reports added to Studies awaiting classification (Burwick 2011; Simcox 2009).

CONTRIBUTIONS OF AUTHORS

Vincenzo Berghella devised the idea, applied for the review, wrote the draft of the review and approved the final edition. Gabriele Saccone edited and approved the final review, and performed review and analysis of pertinent and included studies. Both review authors were involved in the update of this review.

Contributions of editorial base

Zarko Alfirevic: Approved the review for publication.
Leanne Jones: Co-ordinated the editorial process. Advised on methodology, interpretation and content. Helped produce the 'Summary of findings' tables. Technically edited the review.

Denise Atherton: Updated standard methods, edited and copy edited the review. Co-ordinated peer review process.
Lynn Hampson: Designed and conducted all search strategies. Screened all trial reports, edited the Search methods section, search results and formatted all references in correct style.

Sarah Perry: Second screened all trial reports.

DECLARATIONS OF INTEREST

Vincenzo Berghella: is a co-author on one of the included trials (Ness 2007). VB was not involved in the assessment of eligibility or risk of bias for this trial; it was assessed by Gabriele Saccone.

Gabriele Saccone: is lead author on two ongoing trials (NCT02923973; NCT02928302). GS was not involved in the assessment of eligibility for these trials; they were assessed by the Cochrane Pregancy and Childbirth Group editorial staff.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

  NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS: 10/4001/02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A number of outcomes not prespecified in the original protocol were included in the first review, as listed below. We used the same outcomes in this revision.

1. Preterm birth (less than 36 weeks)
2. Preterm birth (less than 30 weeks)
3. Birthweight
4. Neonatal infection
5. Chorioamnionitis
6. Endometritis

We added a search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

We clarified the inclusion criteria, as follows:

Trials that did not measure the outcome of interest, as well as trials using manual digital cervical exam as control group were excluded.

INDEX TERMS

Medical Subject Headings (MeSH)

Cervical Length Measurement [*methods]; Cervix Uteri [*diagnostic imaging]; Pregnancy, Multiple; Pregnancy, Twin; Premature Birth [diagnostic imaging] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy