Cerclage for Short Cervix on Ultrasound in Singleton Gestations without Prior Spontaneous Preterm Birth: a Systematic Review and Meta-analysis of Trials using individual patient-level data

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ABSTRACT

Objective: The aim of this systematic review and meta-analysis was to quantify the efficacy of cervical cerclage in preventing preterm birth (PTB) in asymptomatic singleton pregnancies with a mid-trimester short transvaginal ultrasound cervical length (TVU CL) and without prior spontaneous PTB.

Methods: Electronic databases were searched from inception of each database until February 2017. No language restrictions were applied. We included all randomized controlled trials (RCTs) of asymptomatic singleton pregnancies without prior spontaneous PTB screened with TVU CL, found to have a midtrimester short CL <25mm, and then randomized to management with either cerclage (i.e. intervention group) or no cerclage (i.e. control group). We contacted corresponding authors of all the included trials to request access to the data and perform a meta-analysis of individual patient data. Data provided by the investigators were merged into a master database specifically constructed for the review. The primary outcome was PTB <35 weeks. The summary measures were reported as relative risk (RR) with 95% confidence interval (CI). The quality of the evidence was assessed using the GRADE approach.

Results: Five RCTs, including 419 asymptomatic singleton gestations with TVU CL <25mm and without prior SPTB, were analyzed. No statistically significant differences were found in PTB <35 (21.9% vs 27.7%; RR 0.88, 95% CI 0.63 to 1.23; I^2=0%; 5 studies, 419 participants),

<34, <32, <28, and <24 weeks, mean gestational age at delivery, preterm premature rupture of membranes, and neonatal outcomes, comparing women who were randomized in the cerclage group with those who were randomized in the control group, respectively. Planned subgroup analyses revealed a significant decrease in PTB <35 weeks in women with TVU CL <10mm (39.5% vs 58.0%; RR 0.68, 95% CI 0.47 to 0.98; I^2=0%; 5 studies, 126 participants), in women who received tocolytics (17.5% vs 25.7%; RR 0.61, 95% CI 0.38 to 0.98; I^2=0%; 5 studies, 154 participants), and in those who received antibiotics (18.3% vs 31.5%; RR 0.58, 95% CI 0.33 to 0.98; I^2=0%; 3 studies, 163 participants). The quality of evidence was downgraded two levels because of serious "imprecision" and serious "indirectness," and therefore was judged as low.

Conclusions: In women with singleton gestation, without prior spontaneous PTB but with TVU CL <25mm in the second trimester, cerclage does not prevent preterm delivery or improve neonatal outcome. Cerclage, in singletons without prior spontaneous PTB, seems to be possible efficacious at lower CLs, such as <10mm, and when tocolytics or antibiotics were used as additional therapy, requiring further studies in these subgroups. Given the low quality of evidence, further well-designed RCT is necessary to confirm the findings of this study.

INTRODUCTION

Preterm birth (PTB) is a major cause of perinatal morbidity and mortality.[1] Worldwide, about 15 million babies are born too soon every year, causing 1.1 million deaths, as well as short- and long-term disability in countless survivors.[2,3]

Few prognostic tests are available to predict PTB.[4,5] A short transvaginal ultrasound cervical length (TVU CL) has been shown to be a good predictor of spontaneous PTB, in both singletons and twins.[4-8]

Different strategies have been adopted for prevention of PTB,[9-24] including progesterone, cerclage, cervical pessary, as well as lifestyle modification, such as smoking cessation, diet, aerobic exercise, and nutritional supplements. The evidence supports the use of vaginal progesterone in singleton pregnancies with short cervix,[9] while cervical cerclage seems to be beneficial only in the subgroup of singleton gestations with both prior spontaneous PTB and TVU CL ≤25mm,[10] and not in singletons without prior PTB,[11] nor in multiple gestations.[24] Cervical pessary is relatively non-invasive, easy to use, does not require anesthesia, can be used in an outpatient clinic setting, and it is easily removed when necessary. However, data published are contradictory, and meta-analyses have shown no efficacy in prevention of PTB in both singleton,[13] and multiple pregnancies.[23]

Interestingly, only 235 women have been included in randomized controlled trials (RCTs) on cerclage for TVU CL <25mm for singleton pregnancies without prior spontaneous PTB,[11] while 504 for singleton pregnancies with prior spontaneous PTB.[10] Indeed, Berghella et al. in an individual patient data (IPD) meta-analysis of four RCTs found a non-significant 16% reduction in PTB <35 weeks in singletons without prior spontaneous PTB but with a TVU CL <25mm who were randomized to cerclage compared to no cerclage.[11]

Recently, Otsuki et al. reported data from a new RCT on cerclage in women with short TVU CL, including also singleton gestations without prior spontaneous PTB.[24] They showed that for women with TVU CL <25 mm between 16 and 26 weeks of gestation, cerclage might be considered to reduce the occurrence of threatened preterm labor.[25]

Our objective was to update and expand the previous IPD meta-analysis,[11] and to quantify the efficacy of cervical cerclage in preventing PTB and perinatal morbidity and mortality in asymptomatic singleton pregnancies with a mid-trimester sonographic short TVU CL and without prior spontaneous PTB.

METHODS

Search strategy

The review protocol was established by two investigators (VB, GS) prior to commencement and was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42016048269).

MEDLINE, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched for the following terms: ‘cerclage,’ ‘cervical cerclage,’ ‘salvage cerclage,’ ‘rescue cerclage,’ ‘emergency cerclage,’ ‘ultrasound-indicated cerclage,’ ‘short cervix,’ ‘cervical length,’ ‘ultrasound,’ and ‘randomized trial,’ from inception of each database until February 2017. All manuscripts were reviewed for pertinent references. No language restrictions were applied.

Study Selection

We included all RCTs of asymptomatic singleton pregnancies without prior spontaneous PTB screened with TVU CL, found to have a midtrimester CL <25mm, and then randomized to management with either cerclage (i.e. intervention group) or no cerclage (i.e. control group).. Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation), studies on multiple pregnancies and studies on symptomatic women were excluded. Trials evaluating history-indicated cerclage (placed for the sole indication of prior spontaneous PTB),[27] or ultrasound-indicated (placed for a short TVU CL) in women with also a prior spontaneous PTB,[10,11] or physical-exam indicated cerclage (placed for second trimester cervical dilatation detected on physical exam),[27] as well as studies on technical aspects of cerclage,[27] were also excluded. Therefore, eligible RCTs had to include women with singleton gestations, without prior spontaneous PTB, found to have upon TVU screening a short CL in the second trimester, who were randomized to cerclage versus no cerclage, and were followed for the primary outcome of PTB.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[29] Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5)

incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk" of bias.[29]

We contacted corresponding authors of all the included RCTs to request access to the data and perform a meta-analysis of IPD. Authors were asked to supply anonymized data (without identifiers) about patient baseline characteristics, experimental intervention, control intervention, co-interventions, and pre-specified outcome measures for every randomly assigned subject and were invited to become part of the collaborative group with joint authorship of the final publication. Data provided by the investigators were merged into a master database specifically constructed for the review. Data were checked for missing information, errors, and inconsistencies by cross-referencing the publications of the original trials. Quality and integrity of the randomization processes were assessed by reviewing the chronological randomization sequence and pattern of assignment, as well as the balance of baseline characteristics across treatment groups. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary.

Quality of evidence

For this review, the quality of the evidence was assessed using the GRADE approach in order to assess the quality of the body of evidence relating to the primary and secondary outcomes. GRADEpro Guideline Development Tool was used to import data from Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The 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.[29]

Outcomes

Primary and secondary outcomes were established a priori. The primary outcome was PTB <35 weeks. Secondary outcomes were: PTB <37, <34, <32, <28 and <24 weeks, mean gestational age at delivery in weeks, mean of latency in days (i.e. time from randomization to delivery), incidence of preterm premature rupture of membranes (PPROM), and neonatal outcomes including birth weight, low birth weight (LBW) (i.e. birth weight <2500 grams), very LBW (VLBW) (i.e. birth weight <1500 grams), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) grade 3 or 4, sepsis, necrotizing enterocolitis (NEC), admission to neonatal intensive care unit (NICU), mean of length of stay (LOS) in NICU in days, and neonatal death (i.e. death of a live-born baby within the first 28 days of life). We planned to assess the primary outcome (i.e. PTB <35 weeks) according to different TVU CL cutoffs (i.e. ≤20, ≤15, <10, <5 mm), according to race, according to type of cerclage, and according to additional therapy used.

Data analysis

The data analysis was completed independently by two authors (VB, GS) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. IPD were analyzed using the so-called two-stage approach. In this approach, the IPD are first analyzed separately in each study to produce study-specific estimates of relative treatment effect. A combined estimate is then obtained in the second step by

calculating a weighted average (inverse error-variance-based) of the individual estimates using methods analogous to meta-analyses of aggregate data. Between-study heterogeneity was explored using the I-squared, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. Meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of either a RR or a mean difference (MD) with 95% confidence interval (CI).

Potential publication biases were assessed statistically by using Begg's and Egger's tests.[30] Two-tailed p-value<0.05 was considered statistically significant.

Characteristics of the included women obtained in the merged database were analyzed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Data are shown as means ± standard deviation (SD), or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square or Fisher exact test. Comparisons between groups were performed with the use of the T-test to test group means with SD. Two sided p-values <0.05 were considered statistically significant.

All review stages were conducted independently by two reviewers (VB, GS). The two authors independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with a third reviewer (AC).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[31]

RESULTS

Study selection and population characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from reviewing of potentially relevant articles. Five RCTs,[25,32-35] including 419 asymptomatic singleton gestations with short mid-trimester TVU CL and without prior spontaneous PTB, were included in the meta-analysis.

The overall risk of bias of the included trials was low (Figure 2). All studies had a low risk of bias in "random sequence generation", "incomplete outcome data", and "selective reporting." Adequate methods for allocation of women were used. All randomized women were included in an intention-to-treat analysis. Given the intervention, double-blinding was not feasible and all trials were judged as high risk of bias in performance bias.

Publication bias, assessed using Begg's and Egger's tests, showed no significant bias (P=0.39 and P=0.51, respectively). The statistical heterogeneity between the studies was low with no inconsistency (I^2=0%) in the primary and most of the secondary outcomes.

Table 1 shows the characteristics of the included trials. All the included trials enrolled also women with prior spontaneous PTB which were excluded from the IPD. Multiple gestations were also excluded. Therefore, the IPD was used in order to include only singleton gestations without prior spontaneous PTB.

Out of the 419 women analyzed, 224 (53.5%) were included in the cerclage group (i.e. study group), and 195 (46.5%) in the control group. Only singleton gestations without prior spontaneous PTB and with short cervix <25mm were analyzed. Most of the included studies (4 out of the 5),[25,32,33,35] defined short cervix as TVU CL <25 mm; while To et al.[34] defined as TVU CL ≤15 mm. Three trials used only McDonald cerclage,[32,33,35] To et al.[34] only Shirodkar, while

Otsuki et al.[25] randomized women into three arms: McDonald cerclage, Shirodkar cerclage, or no cerclage. All studies used the transvaginal approach for cerclage. None of the 419 women received progesterone (Table 1).

In the Berghella et al. study,[35] indomethacin (100 mg perioperative loading dose per rectum followed by postoperative 50 mg orally every 6 hours for 48 hours) was left to the discretion of the obstetrician; while antibiotics were not used. In Althuisius et al.[33] all women in the cerclage group received perioperative antibiotics (amoxicillin/clavulanic acid 1 gr IV qid and metronidazole 500 mg IV tid for 24 hours followed by 6 days of amoxicillin/clavulanic acid 500 mg qid orally and metronidazole 500 mg tid orally) and indomethacin suppository (100 mg, two hours before and 6 hours after the operation). In Rust et al.[32] before randomization, all women were placed at inpatient bed rest for 48 to 72 hours and were treated identically with an amniocentesis, multiple urogenital cultures, and 48 to 72 hours of therapy with indomethacin (100 mg loading dose per rectum followed by 50 mg orally every 6 hours) and clindamycin (900 mg IV every 8 hours). In To et al.[34] no interventions, including tocolytics, antibiotics, and bed rest, were routinely recommended. In Otsuki et al.[25] all women randomized in the cerclage group received tocolytic agents (usually ritodrine 100mcg/min IV) until the next day after operation and no longer than two days; women in the cerclage group also received ampicillin 2g/day for two days. In this trial,[25] bed rest was recommended in both groups at least for 7 days and all patients were permitted to discharge from hospital after two weeks from admission or operation. Rust et al.[32] Althuisius et al.[33] Otsuki et al.[25] and Berghella et al.[35] routinely recommended some similar activity restriction for both women in the study and in the control group.

The women who received the cervical suture had it removed at 36 0/7 - 37 6/7 weeks of gestation unless spontaneous onset of labor, rupture of the membranes, or need for early delivery arose.

The gestational age at randomization was about 22 weeks (22.5 vs 22.2 weeks), and the mean TVU CL about 12 mm (12.6 vs 12.7 mm), in both groups (Table 2)

Synthesis of results

No statistically significant differences were found in PTB <35 weeks (Figure 3) and in the secondary outcomes (Table 3, Figure 4) comparing women who were randomized to the cerclage group with those who were randomized to the control group.

Planned subgroup revealed a significant decrease in PTB <35 weeks in women with TVU CL <10mm (39.5% vs 58.0%; RR 0.68, 95% CI 0.47 to 0.98), in white women, and in women who received tocolytics or antibiotics as additional therapy to cerclage (Table 4, Figure 5, Figure 6).

The quality of evidence was downgraded (Table 3) because of serious "imprecision." Outcomes were imprecise because studies included relatively few patients and few events and thus had wide CIs around the estimate of the effect and because the optimal information size was not reached. The quality of the evidence was also downgraded another one level because of serious "indirectness" because of the different study design.

COMMENT

Main findings

This IPD meta-analysis from five low risk of bias RCTs, including 419 women, showed that transvaginal cervical cerclage did not reduce the rate of PTB or improve neonatal outcome in asymptomatic singleton pregnancies with midtrimester TVU CL <25mm and without prior spontaneous PTB. Planned subgroup analyses revealed a significant decrease in PTB <35 weeks

in women with TVU CL <10mm, and when tocolytics or antibiotics were used as additional therapy.

The quality level of summary estimates was judged low as assessed by GRADE, indicating that the true effect may, or is even likely to, be substantially different from the estimate of the effect.

Comparison with existing literature

Our data supports earlier findings of a prior meta-analysis.[11] This prior review showed that cerclage did not prevent preterm delivery in the overall population of singletons without prior spontaneous PTB, but with short TVU CL.[11]

Strengths and limitations

Our study has several strengths. This meta-analysis included all RCTs published so far on the topic, studies of high quality and with a low risk of bias according to the Cochrane risk of bias tools. To our knowledge, no prior meta-analysis on this issue is as large, up-to-date or comprehensive. Statistical tests showed no significant potential publication biases. Intent-to-treat analysis was used. The statistical heterogeneity within the studies was very low. We also used patient-level data to explore for heterogeneity and maternal factors, reported in Table 2, and to perform subgroup analyses (Table 4).

Limitations of our study are inherent to the limitations of the included RCTs. The TVU CL cutoff for intervention was different in the RCT by To et al.[34] Different techniques for cerclage were used, but there is no definitive data proving superiority of one versus another technique, and the subgroup analysis on this issue failed to reveal any significant differences. Progesterone, which is currently recommended for women with short TVU CL,[36] was not used in any of the

included trials. The use of pericerclage tocolytics or antibiotics was not uniform in the included RCTs. Furthermore, most of the included RCTs routinely recommended bed rest, in both cerclage group and control group. So far there is no evidence supporting the use of bed rest at home or in hospital to prevent preterm delivery.[37] Grobman et al., in a secondary analysis of a RCT of 17-α hydroxyprogesterone caproate among nulliparous women with singleton gestations and TVU CL <30 mm by midtrimester ultrasonography, showed that activity restriction increased the risk of PTB <37 weeks.[38] In one trial,[25] women with genital tract infection were excluded, and the design of the study allowed rescue cerclage for all arms, when bulging membrane was noted. The high number of subgroup analyses and secondary outcomes may lead to high risk of false positive results. We also acknowledge that only one trial[25] was added in this meta-analysis compared to our prior review.[11] However, in this new review, IPD were used. An IPD has several distinct advantages over aggregate data meta-analysis (ADMA). IPD involves the synthesis of individual-level data from the individual trials, and therefore allows for the verification of published results. As IPD are available, an IPD meta-analysis allows for more flexibility regarding the inclusion and exclusion of individuals, and the choice of end points and subgroups, compared with ADMA. These subgroups showed potential benefit when the CL is <10mm and when tocolytics or antibiotics were used with cerclage. Given the low number of included trials, while no differences were found in patient characteristics available in the databases, unknown confounders cannot be ruled out.

Interpretation

Our findings provide evidence that cerclage does not prevent PTB in all singleton gestations without prior spontaneous PTB but with short TVU CL. In subgroup analysis of women who had TVU CL <10mm, or received additional therapy, such as tocolytics or antibiotics, cerclage may reduce PTB, and well-powered trials should be carried out in this group of patients. Notably, there is evidence in the literature that adjunctive perioperative tocolytics and/or antibiotics might increase the efficacy of the cervical cerclage.[39] Biologic plausibility would support these results, as pathways to PTB are several, and involve mechanical weakness to the cervix from prior surgical procedures[40] or other factors which could be treated with cerclage, infection which could be treated by antibiotics, and uterine contractions which could be treated by tocolytics.

Conclusions

In summary, based on this level-1 data, at least as used so far in these trials, there is not a significant association between cervical cerclage and a lower incidence of PTB in asymptomatic singleton gestations with short TVU CL and without prior spontaneous PTB. Cerclage seems to be possibly efficacious at lower CLs, such as <10mm, and when tocolytics or antibiotics were used as additional therapy, requiring further studies in these subgroups. Indeed, with a low number of included women in these subgroup analyses, the ability to discern differences in preterm delivery is impaired by type II error. We observed that with an a of 0.05 and 80% power, a sample size of 103 patients in each group, for a total of 206 singleton gestations without prior spontaneous PTB but short TVU CL <25mm, is required to detect a reduction in PTB <37 weeks from a 34% baseline risk of women given vaginal progesterone,[40] based on the RR of 0.54 with indomethacin, antibiotics, and cerclage versus no tocolysis, no antibiotics, and no cerclage. We are starting this new RCT.

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TABLES

Table 1. Characteristics of the included trials

	Rust 2001[32]	**Althuisius 2001**[33]	**To 2004**[34]	**Berghella 2004**[35]	**Otsuki 2016**[25]
Study location	USA	Netherlands	Multicenter**	USA	Japan
Sample size*	105 (51 vs 54)	9 (5 vs 4)	209 (106 vs 103)	21 (9 vs 12)	75 (53 vs 22)
GA at randomization (weeks)	16-24	14-27	22-24	14-24	16-26
Definition of short TVU CL	<25 mm	<25 mm	≤15 mm	<25 mm	<25 mm
Type of cerclage	McDonald	McDonald	Shirodkar	McDonald	McDonald (27/53) and Shirodkar (26/53)
Cerclage suture	Permanent Monofilament	Braided Tape	Braided Tape	Braided Tape	Braided Tape
Definition of prior spontaneous PTB (weeks)	16-36	17-33	16-32	16-34	16-36
Primary	PTB <34	PTB <34	PTB <33	PTB <35	GA at

outcome	weeks	weeks	weeks	weeks	delivery
Lost to follow-up	0%	2.8%	0.4%	0%	0%

**Data are presented as number in the cerclage group vs number in the control group. Data refer only to singleton pregnancies without prior spontaneous preterm birth*

***including UK, Brazil, South Africa, Slovenia, Greece, and Chile.*

GA, gestational age; TVU, transvaginal ultrasound; CL, cervical length; PTB, preterm birth

Table 2. Characteristics of the included women

	Cerclage **N = 224 (53.5%)**	**No cerclage** **N = 195 (46.5%)**	***P-value***
Age[25,32-35] **mean±SD**	29.6±6.3	29.7±6.5	0.72
Prior cone[33,35] **n (%)**	3/14 (21.4%)	4/16 (25.0%)	0.58
Race[32-35] **White n (%)** **Black n (%)** **Others n (%)***	 95/171 (55.5%) 57/171 (33.4%) 19/171 (11.1%)	 88/173 (50.9%) 68/173 (39.3%) 17/173 (9.8%)	0.75
Mullerian anomalies[33,35] **n (%)**	1/14 (7.1%)	0/16	0.44
Smoking[25,33,34,35] **n (%)**	18/173 (10.4%)	16/141 (11.3%)	0.70
GA at randomization[25,32-35] **mean±SD**	22.5±2.0	22.2±2.2	0.27
CL[25,32-35] **mean±SD**	12.6±6.4	12.7±6.3	0.93
Mode of delivery[25,33,34,35] **VD n (%)** **CD n (%)**	 135/173 (78.0%) 38/173 (22.0%)	 122/141 (86.5%) 19/141 (13.5%)	0.08

Not all the variables have been registered in every database; results therefore are accompanied with the number of cases in which the outcomes were registered (n) with the references of the included trials. Proportions are presented as percentage of n, rather than as percentages of the total population.

SD, standard deviation; GA, gestational age; CL, cervical Length; VD, vaginal delivery; CD, cesarean delivery

**Including Asian, Hispanic*

Table 3. Primary and secondary outcomes in all singleton pregnancies without prior spontaneous

	Singleton pregnancies without prior spontaneous PTB and with TVU CL ≤25 mm (n=419)					
Outcome	**Cerclage N = 224 (53.5%)**	**No cerclage N = 195 (46.5%)**	**RR or MD (95% CI)**	**I^2**	**Q-statistic**	**GRADE**
PTB <35 weeks[25,32-35]	49/224 (21.9%)	54/195 (27.7%)	0.88 (0.63 to 1.23)	0%	2.09	Low-quality of evidence
PTB <37 weeks[25,32-35]	81/224 (36.2%)	80/195 (41.0%)	0.93 (0.73 to 1.18)	57%	4.84	Low-quality of evidence
PTB <34 weeks[25,32-35]	45/224 (20.1%)	49/195 (25.1%)	0.89 (0.63 to 1.27)	0%	0.67	Low-quality of evidence
PTB <32 weeks[25,32-35]	38/224 (17.0%)	39/195 (20.0%)	0.96 (0.64 to 1.42)	0%	0.62	Low-quality of evidence

PTB <28 weeks[25,32-35]	26/224 (11.6%)	22/195 (11.3%)	1.15 (0.68 to 1.93)	0%	0.52	Low-quality of evidence
PTB <24 weeks[25,32-35]	5/224 (2.2%)	4/195 (2.0%)	1.14 (0.36 to 3.63)	0%	0.69	Low-quality of evidence
GA at delivery (weeks)[25,32-35]	35.81	35.59	0.22 (-0.58 to 1.02)	0%	2.02	Low-quality of evidence
Latency (days)[25,32-35]	86.68	83.41	3.27 (-3.22 to 9.76)	50%	8.14	Low-quality of evidence
PPROM[32,34,35]	34/166 (20.4%)	23/169 (13.6%)	1.52 (0.94 to 2.46)	0%	1.21	Low-quality of evidence
Birth weight (grams)[25,32-35]	2,635	2,540	94.65 (-146.23 to 335.53)	0%	0.41	Low-quality of

						evidence
LBW[25,32-35]	42/224 (18.7%)	49/195 (25.6%)	0.88 (0.44 to 1.74)	52%	9.41	Low-quality of evidence
VLBW[25,32-35]	22/224 (9.8%)	21/195 (10.8%)	0.97 (0.57 to 1.68)	0%	0.84	Low-quality of evidence
RDS[33,35]	2/14 (14.3%)	2/16 (12.5%)	1.33 (0.23 to 7.74)	0%	1.34	Low-quality of evidence
IVH[33,35]	1/14 (7.1%)	0/16	3.90 (0.18 to 85.93)	0%	1.27	Low-quality of evidence
Sepsis[33,35]	2/14 (14.3%)	2/16 (12.5%)	1.33 (0.23 to 7.74)	0%	0.67	Low-quality of evidence
NEC[33,35]	0/14	0/16	Not estimable	Not applicable	Not applicable	Low-quality

						of evidence
NICU[25,33,35]	3/67 (4.5%)	4/38 (10.5%)	0.80 (0.26 to 2.47)	31%	6.41	Low-quality of evidence
LOS in NICU (days)[33,35]	25,2	14,9	10.30 days (-27.35 to 47.95)	0%	2.34	Low-quality of evidence
Neonatal death[25,32,33,35]	7/118 (5.9%)	6/92 (6.5%)	1.08 (0.41 to 2.86)	0%	1.21	Low-quality of evidence

Data are presented as number (percentage) or as mean difference ± standard deviation.

Not all the variables have been registered in every database; results therefore are accompanied with the number of cases in which the outcomes were registered (n) with the references of the included trials. Proportions are presented as percentage of n, rather than as percentages of the total population.

PTB, preterm birth; TVU, transvaginal ultrasound; CL, cervical length; RR, relative risk; MD, mean difference; CI, confidence interval; GA, gestational age; PPROM, preterm premature rupture of membranes; LBW, low birth weight; VLBW, very low birth weight; RDS, respiratory

distress syndrome; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; LOS, length of stay;

Table 4. Primary and secondary outcomes in subgroup analyses

Only women with TVU CL ≤20 mm (n=349)				
Outcome	**Cerclage N = 188**	**No cerclage N = 161**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32-35]	47 (25.0%)	51 (31.7%)	0.79 (0.56 to 1.10)	0%
Only women with TVU CL ≤15 mm (n=305)				
Outcome	**Cerclage N = 159**	**No cerclage N = 146**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32-35]	43 (27.0%)	49 (33.6%)	0.81 (0.57 to 1.13)	0%
Only women with TVU CL <10 mm (n=126)				
Outcome	**Cerclage N = 76**	**No cerclage N = 50**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32-35]	30 (39.5%)	29 (58.0%)	**0.68 (0.47 to 0.98)**	0%
Only women with TVU CL <5 mm (n=48)				
Outcome	**Cerclage N = 27**	**No cerclage N = 21**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32-35]	15 (55.5%)	15 (71.4%)	0.79 (0.50 to 1.23)	0%

Only white women (n= 183)				
Outcome	**Cerclage** **N = 95**	**No cerclage** **N = 88**	**RR (95% CI)**	**I^2**
PTB <35 weeks[32-35]	21 (22.1%)	33 (37.5%)	**0.59 (0.37 to 0.94)**	0%
Only black women (n= 125)				
Outcome	**Cerclage** **N = 57**	**No cerclage** **N = 68**	**RR (95% CI)**	**I^2**
PTB <35 weeks[32-35]	18 (31.6%)	20 (29.4%)	1.07 (0.63 to 1.83)	0%
Shirodkar cerclage (n =257)				
Outcome	**Cerclage** **N = 132**	**No cerclage** **N = 125**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,34]	29 (22.0%)	32 (25.6%)	0.86 (0.55 to 1.33)	0%
McDonald cerclage (n =185)				
Outcome	**Cerclage** **N = 87**	**No cerclage** **N = 98**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32,33,35]	20 (23.0%)	29 (29.6%)	0.78 (0.48 to 1.27)	0%
Tocolytics and cerclage versus no tocolytics and no cerclage (n=254)				
Outcome	**Cerclage+Tocolytics** **N = 114**	**No cerclage and no tocolytics**	**RR (95% CI)**	**I^2**

		N = 140		
PTB <35 weeks[25,32-35]	20 (17.5%)	40 (25.7%)	**0.61 (0.38 to 0.98)**	0%
Tocolytics and cerclage versus tocolytics and no cerclage (n= 169)				
Outcome	**Cerclage+Tocolytics N = 114**	**Tocolytics and no cerclage N = 55**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32,33,35]	20 (17.5%)	18 (32.7%)	**0.54 (0.31 to 0.93)**	0%
Antibiotics and cerclage versus no antibiotics and no cerclage (n=249)				
Outcome	**Cerclage+Antibiotics N = 109**	**No cerclage and no antibiotics N = 140**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32-35]	20 (18.3%)	36 (25.7%)	0.71 (0.44 to 1.66)	0%
Antibiotics and cerclage versus antibiotics and no cerclage (n=163)				
Outcome	**Cerclage+Antibiotics N = 109**	**Antibiotics and no cerclage N = 54**	**RR (95% CI)**	**I^2**
PTB <35 weeks[25,32,33]	20 (18.3%)	17 (31.5%)	**0.58 (0.33 to 0.98)**	0%

Data are presented as number (percentage) or as mean difference ± standard deviation.

Not all the variables have been registered in every database; results therefore are accompanied with the number of cases in which the outcomes were registered (n) with the references of the included trials. Proportions are presented as percentage of n, rather than as percentages of the total population. Boldface data, statistically significant

PTB, preterm birth; TVU, transvaginal ultrasound; CL, cervical length; RR, relative risk; CI, confidence interval;

FIGURES

Figure 1. Flow diagram of studies identified in the systematic review. *(Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]). FFN, fetal fibronectin; PPROM, preterm premature rupture of membranes*

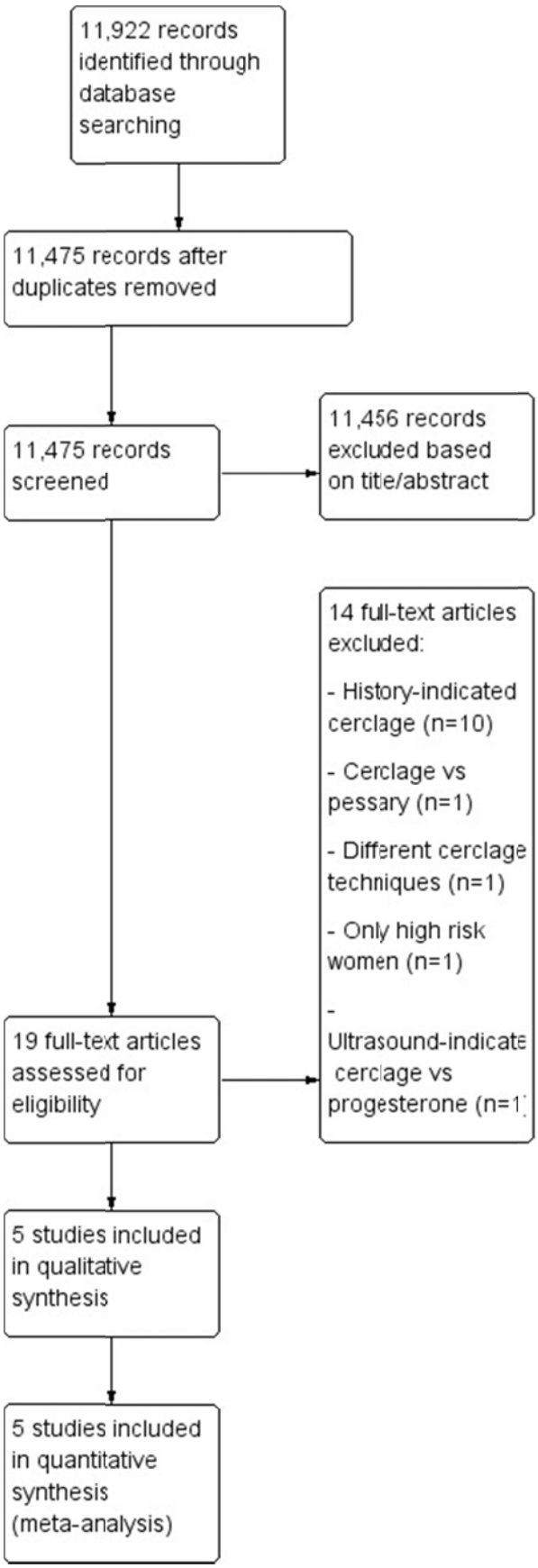

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

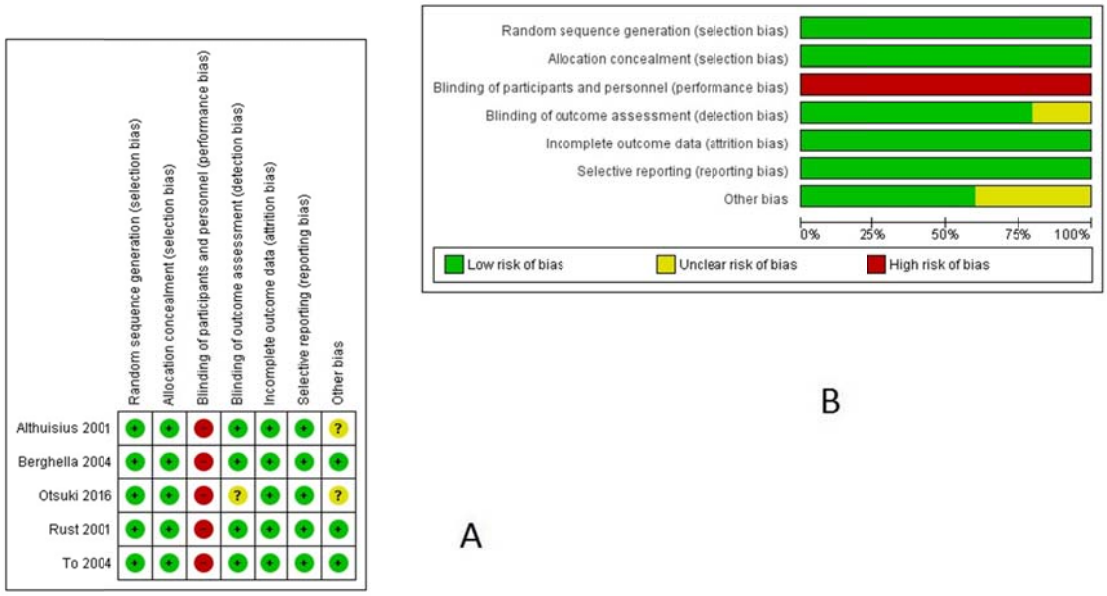

Figure 3. Forest plot for the risk of the primary outcome (i.e. incidence of preterm birth <35 weeks) in the overall population. *CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom; TVU CL, transvaginal ultrasound cervical length*

Figure 4. Incidence of preterm birth at different cutoffs comparing cerclage group (solid bars) and no cerclage group (striped bars). RR, relative risk; in parentheses: 95% confidence intervals.

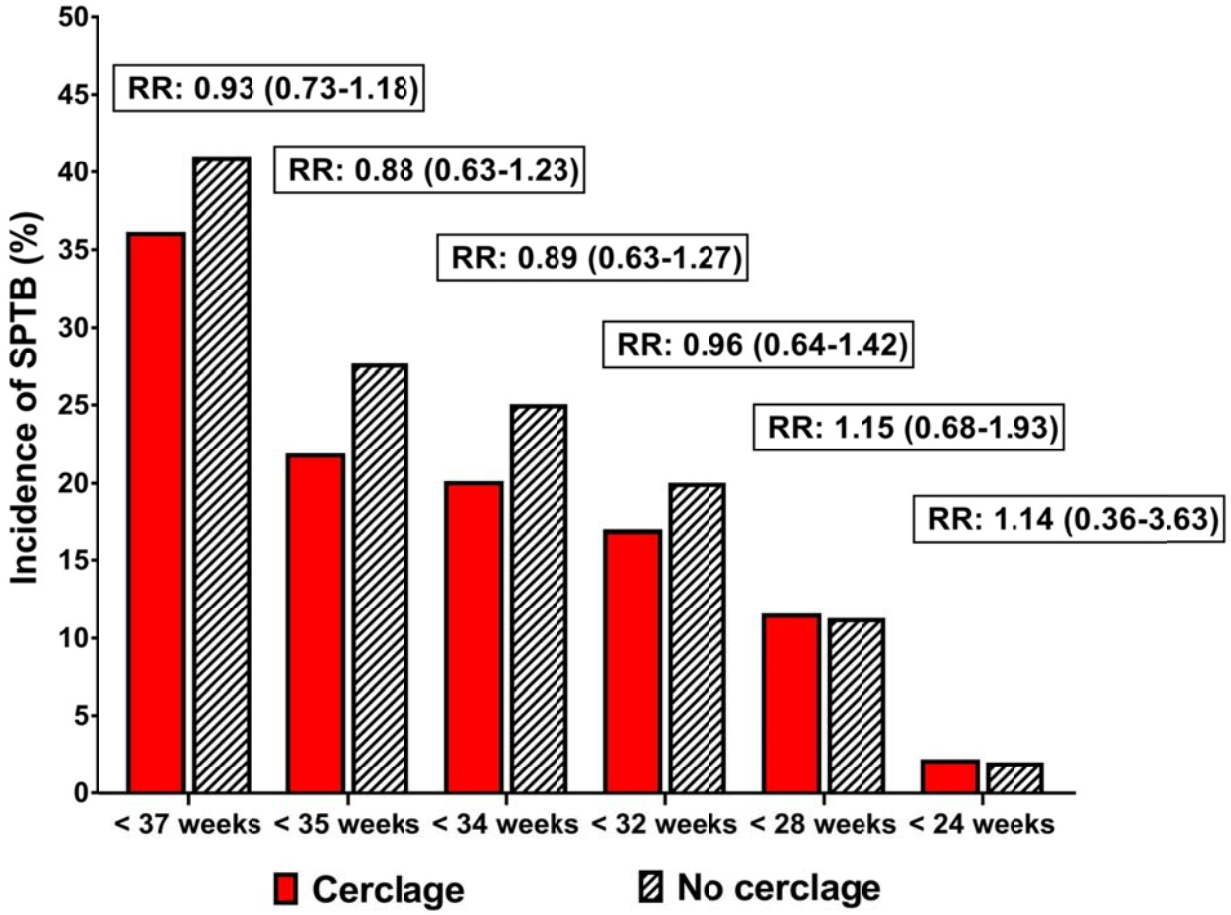

Figure 5. Incidence of preterm birth <35weeks by transvaginal ultrasound cervical length subgroups comparing cerclage group (solid bars) and no cerclage group (striped bars). RR, relative risk; in parentheses: 95% confidence intervals; *, statistically significant.

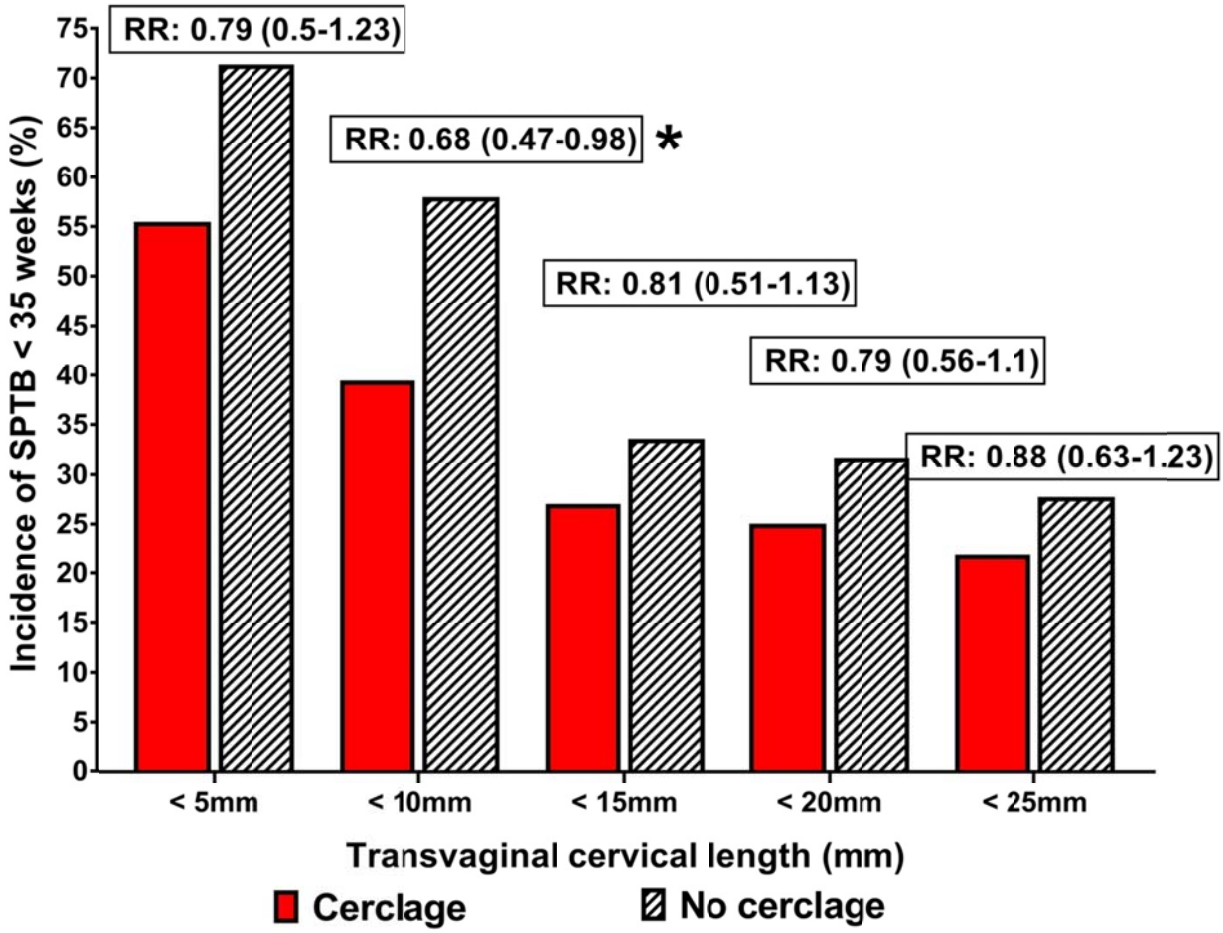

Figure 6. Incidence of preterm birth <35weeks by addition of tocolysis or not to cerclage (two left bars), and by addition of antibiotics or not to cerclage (two right bars) comparing cerclage group (solid bars) and no cerclage group (striped bars). RR, relative risk; in parentheses: 95% confidence intervals; *, statistically significant.