Cerclage for women with twin pregnancies: a systematic review and metaanalysis

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OBJECTIVE DATA: This study was conducted to estimate whether cerclage could extend the prolongation of pregnancy, reduce the risk of preterm birth, and improve perinatal outcomes in women with twin pregnancies.

STUDY ELIGIBILITY CRITERIA: We included randomized controlled trials and cohort studies comparing the efficacy of cerclage with no cerclage for women with twin pregnancies.

STUDY APPRAISAL AND SYNTHESIS METHODS: The following databases were searched for all published studies that compared cerclage placement with expectant management in twin pregnancies from inception to July 2018: Medline, EMBASE, Scopus, ClinicalTrials.gov, Web of Science, and Cochrane Library. Each report was reviewed for inclusion or exclusion standard, and data extraction was performed by 2 authors independently.

RESULTS: A total of 16 studies with 1211 women that met the inclusion criteria were included in the final analysis. Our outcomes indicated that cerclage placement for twin pregnancies with a cervical length of <15 mm was associated with significant prolongation of pregnancy by a mean difference of 3.89 weeks of gestation (95% confidence interval, 2.19−5.59; P=.000; I^2=0%) and a reduction of preterm birth at <37 weeks of gestation (risk ratio, 0.86; 95% confidence interval, 0.74−0.99; P=.040; I^2=0%), <34 weeks of gestation (risk ratio, 0.57; 95% confidence interval, 0.43−0.75; P=.000; I^2=0%) and <32 weeks of gestation (risk ratio, 0.61; 95% confidence interval, 0.41−0.90; P=.010; I^2=0%), compared with those pregnancies in the control group. For women with a dilated cervix of >10 mm, cerclage placement was associated with significant prolongation of pregnancy by a mean difference of 6.78 weeks of gestation (95% confidence interval, 5.32−8.24; P=.000; I^2=0%); a reduction of preterm birth at <34 weeks of gestation (risk ratio, 0.56; 95% confidence interval, 0.45−0.69; P=.000; I^2=28%), <32 weeks of gestation (risk ratio, 0.50; 95% confidence interval, 0.38−0.65; P=.000; I^2=14%), <28 weeks of gestation (risk ratio, 0.41; 95% confidence interval, 0.20−0.85; P=.030; I^2=80%), and <24 weeks of gestation (risk ratio, 0.35; 95% confidence interval, 0.18−0.67; P=.001; I^2=24%), and improvement of perinatal outcomes compared with those in the control group. However, for twin pregnancies with a normal cervical length (eg, cerclage for an indication for women with a history of preterm birth or twin alone), the efficacy of cerclage placement was less certain because of the limited data.

CONCLUSION: Our metaanalysis indicates that cerclage placement is beneficial for the reduction of preterm birth and the prolongation of pregnancy in twin pregnancies with a cervical length of <15 mm or dilated cervix of >10 mm. However, the benefit of history-indicated or twin alone−indicated cerclage is less certain in twin pregnancies with normal cervical length according to current literature. Further high-quality studies were needed to confirm the findings.

Key words: cervical cerclage, metaanalysis, preterm birth, twin pregnancy

The twin birth rate has risen over the last 3 decades with the use of assisted-reproductive technique,[1] which commonly is associated with increased risk for preterm birth (PTB).[2] It is reported that approximately 50% of twin pregnancies deliver preterm at <37 weeks of gestation and that approximately 14% deliver at <33 weeks of gestation.[3] To date, considerable efforts have been made to reduce the risk of PTB in twin pregnancies, with limited success.[4] Cervical cerclage is a significant surgical procedure for the prevention of PTB.[5] Emerging evidence indicates that the use of cerclage in singleton pregnancies with a short cervix could prolong the pregnancy period and reduce the rate of prematurity and neonatal morbidity and mortality.[5−7] However, most information on the benefit of cerclage is based on singleton gestations in this selected population, with only limited published data in twin pregnancies.[8]

Earlier metaanalyses presented no benefit of cerclage for women with twin pregnancies.[9,10] In 2014, a Cochrane review by Rafael et al[8] reported no significant differences in PTB at <34 weeks of gestation (risk ratio [RR], 1.16; 95% confidence interval [CI], 0.44−3.06) between the cerclage group and the control group. Saccone et al[11] performed an individual patient data metaanalysis and showed that women who received cerclage had a similar rate of PTB <34 weeks of gestation compared with those in the control group (RR, 2.19; 95% CI, 0.72−6.63). Fuchs and Senat[2] concluded that cervical cerclage in asymptomatic twins did not reduce the risk of PTB. However, available metaanalytic data remained of limited value in view of the few and small clinical studies that were included. Although published metaanalyses indicate the lack of efficacy of cerclage in twin pregnancies, data from

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AJOG at a Glance

Why was this study conducted?

The study was conducted to evaluate the efficacy of cerclage in preventing preterm birth and adverse perinatal outcomes.

Key findings

Cerclage was associated with a significant reduction in the risk of preterm birth and composite perinatal morbidity/death compared with that in placebo/no cerclage in twin pregnancies with more advanced cervical changes of preterm birth, such as a cervical length of <15 mm or dilated cervix.

What does this add to what is known?

This updated metaanalysis reaffirms that cerclage is effective in the prevention of preterm birth and improvement of perinatal outcomes in twin pregnancies with more advanced cervical changes of preterm birth, such as a cervical length of <15 mm or dilated cervix.

the US Standard Certificate of Live Birth indicated that roughly 10% of triplets and 1.3% of twins are still receiving cerclage.[12] Recently, several studies with larger samples reported that, in twin gestations with a short cervix, cerclage might reduce the rate of PTB compared with that in expectant management.[13–17] Some authors compared the efficacy of cerclage in twin pregnancies and singleton pregnancies and showed that women with twin pregnancies who received cerclage might show beneficial obstetric outcomes similar to those of women with singleton gestations.[18–22]

However, individual studies showed unreliable results on the benefits of cerclage in twin pregnancies. Thus, updated systematic review and meta-analysis are needed because more recent studies that demonstrate the efficacy of cerclage in twin pregnancies have been published. In the present metaanalysis, we aimed to identify all available evidence, thus far to obtain a powerful indication regarding the efficacy of cerclage in women with twin pregnancies on the prevention of PTB, prolongation of pregnancy, and improvement of perinatal outcomes.

Materials and Methods

The metaanalysis was carried out according to the Metaanalysis of Observational Studies in Epidemiology (MOOSE) guidelines during the study design.[23]

Search strategy

To assemble all the relevant literatures, the following exploded medical subjects heading terms were used for the initial literature search: "cerclage" or "cervical stitch" or "cervical suture" or "cervical ligation" or "shirodkar suture" or "shirodkar operation" or "shirodkar stitch" or "shirodkar procedure" or "McDonald suture" or "McDonald operation" or "McDonald stitch" or "McDonald procedure" AND "twin" or "multiple" in electronic databases of Medicine, EMBASE, Clinicaltrials.gov, the Cochrane library, and Google Scholar for trials from their inception until July 2018. The reference lists of retrieved trials and other relevant publications including case reports, reviews, and metaanalyses were examined to identify articles that were not found by electronic searches. No restrictions for language or geographic location were applied. In addition, we contacted experts in the area to obtain additional data. The electronic search and the eligibility of the studies were assessed independently by 2 of the authors (C.L. and J.S). Disagreement regarding potential relevance was solved by discussion with a third reviewer (K.H).

Study selection

We included studies (randomized controlled trials [RCTs] or cohort studies) in which women with twin pregnancies were assigned to a cerclage group for the prevention of PTB or to a control group. With regard to the type of intervention, cerclage was performed during pregnancy despite the indications; with regard to the control, all participants received no treatment as usual without progesterone or cervical pessary; with regard to the outcomes, a study should report at least 1 of the outcomes. A study was excluded from the metaanalysis for the following reasons: (1) if a study reported the use of cerclage in singleton or triplet pregnancies; (2) if a study was an editorial, a letter to the editor, a review, or a study that involved animal experiments; (3) if different studies were involved in the same trial and showed an overlap between the results; (4) if the necessary data were extrapolated from the reported outcomes; (5) if the results of singleton, twins, and/or higher order pregnancies were not stratified; and (6) if the outcomes of interest were not described.

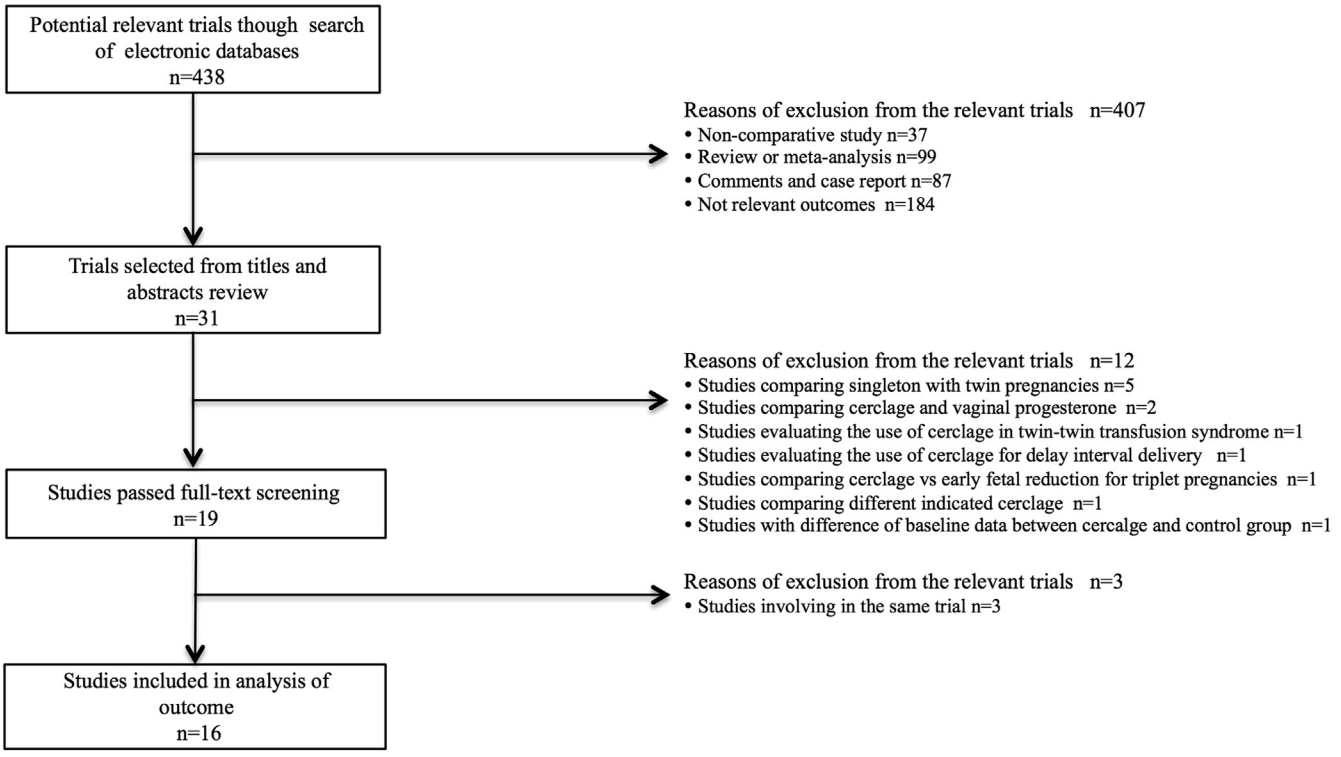
Data extraction

All included studies that met inclusion and exclusion criterion based on the title and abstract information were screened and extracted by 2 reviewers independently. The extracted information included study design, publication date, participant number, age, gestational age, and interventions and outcomes of interest for each study. At any stages, if disagreement between the 2 reviewers occurred, a final decision was made by discussion with a third author. In addition, to ensure completeness and accuracy of the extracted studies, authors were contacted through e-mail or phone, if necessary.[14,20]

Our primary outcomes were the incidence of PTB at <24, <28, <32, <34, and <37 weeks of gestation. The secondary outcomes, if available, were the following neonatal outcomes: neonatal death, fetal death, perinatal death, and neonatal morbidities such as respiratory distress syndrome (RDS), grade III/IV intraventricular hemorrhage, grade III or IV necrotizing enterocolitis that required surgery, neonatal sepsis, and retinopathy of prematurity that required laser treatment.

Prespecified subgroup analysis was performed according to the types of

FIGURE 1
Flow disgram of studies identifed in the metaanalysis



Flowchart of search results and process for identification, selection, and inclusion of articles.

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cerclage indications (eg, ultrasound-indicated, physical examination–indicated, history-indicated, and twin only–indicated cerclage). To further investigate the potential effect of cervical length (CL) on the efficacy of ultrasound-indicated cerclage, a subgroup analysis by CL cut-offs were carried out. In addition, to reduce the heterogeneity, a subgroup analysis was performed based on the type of study (RCT vs cohort studies).

Study quality

The quality of the included studies was assessed according to a risk of bias approach. The Cochrane handbook for systematic reviews of interventions was used to assess RCTs with the following possible measure: low, unclear, or high risk of bias.[24] The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias of the cohort studies.[25] The scale was developed to assess the quality of case-control and cohort studies and contained 3 parameters of quality that included (1) selection, (2) comparability, and (3) exposure/outcome assessment. Studies that achieved $\geq$7 points were considered to be high quality.

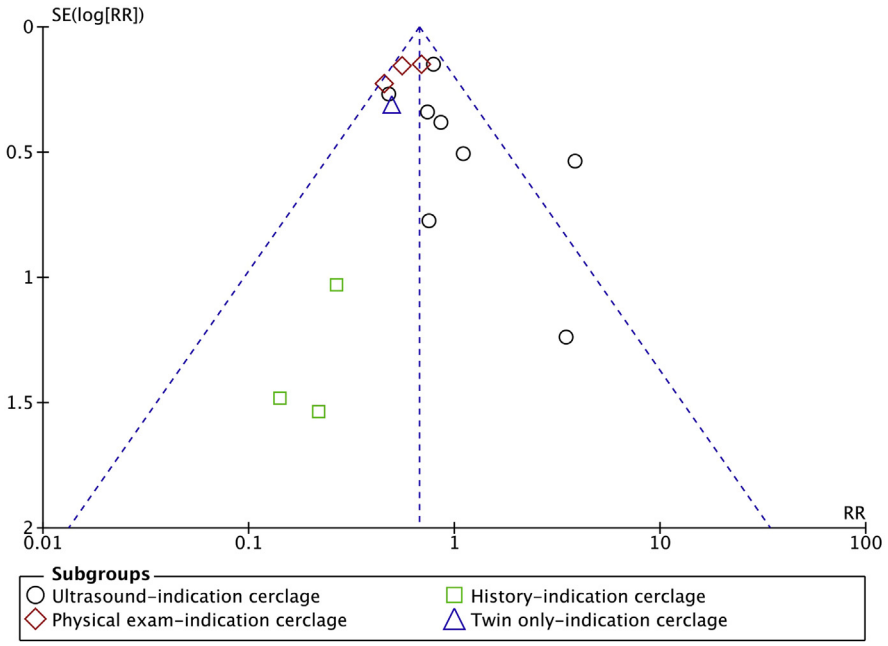
Statistical analysis

We analyzed the data from all included studies using Review Manager software (RevMan, version 5.2; Nordic Cochrane Centre, Copenhagen, Denmark). The weighted mean difference and RR with 95% CI were applied to compare continuous and dichotomous variables, respectively. Heterogeneity among the outcomes of combined trials was determined with the use of the chi^2 and I^2 tests. A probability value of $<$.05 and an I^2 value of $>$50% were suggestive of statistical heterogeneity. Data were pooled and analyzed with the use of either the fixed-effects or random-effects model according to the results of the calculation of heterogeneity. A fixed effects model was used if there was no or low heterogeneity (I^2 $<$50%); otherwise, the random-effects model was used. A probability value of $<$.05 was considered to be statistically significant. For data that could not be incorporated to the metaanalysis, a narrative overview was presented. Funnel plots were used to assess the potential for publication bias. Sensitivity analysis was performed to evaluate the robustness of the results by rejecting the study with the higher statistical heterogeneity.

Results

A total of 438 records were identified with the use of our search strategy for electronic databases and manual citation searches. After screening the title and abstract, 407 studies were excluded, and the remaining 31 records with full-text were further assessed. Five studies that compared the clinical outcome of cerclage between singleton and twin pregnancies[18–21,26] and 2 studies that compared the clinical outcomes between

FIGURE 2
Funnel plot for the assessment of publication bias



Funnel plot to evaluate the presence of publication bias.

RR, risk ratio; *SE*, standard error.

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cerclage and vaginal progesterone were further excluded.[27,28] Five studies were further excluded for the following reasons: 1 study evaluated the benefit of cerclage for twin-twin transfusion syndrome[29]; 1 study evaluated the use of cerclage after the loss of first fetus for delayed interval delivery[30]; 1 study compared the early fetal reduction to twin vs cervical cerclage for triplet pregnancies[31]; 1 study compared the outcomes of ultrasound-indicated cerclage and physical examination-indicated cerclage in twin pregnancies,[32] and 1 study by Roman et al[33] that had a significant difference in the baseline data between the cerclage and control group might result in high bias. Then, 1 study by Althuisius et al[34] referred to the same trial and other studies by the same authors[35–37]; thus, the outcomes were combined. Finally, 16 studies were eligible for systematic review after critical evaluation.[13–17,34,38–47] The procedure of study selection is presented in Figure 1. The symmetric plot demonstrated no published bias (Figure 2), which was further confirmed with the use of Begg's and Egger's tests (P=.58 and P=.72, respectively).

The detailed characteristics of each study are presented in Table 1. Eight articles evaluated the effectiveness of ultrasound-indicated cerclage[13,16,34,38–42,48]; 2 articles evaluated physical examination-indicated cerclage[17,43]; 3 articles evaluated the use of history-indicated cerclage,[44-46] and 2 articles evaluated twin only–indication cerclage in twin pregnancies.[14,47] An article by Han et al[15] consisted of 3 indicated cerclages. Of the 16 studies, 5 studies were RCTs[34,40,42,45,47]; 3 were perspective cohort studies,[14,41,46] and the remaining 8 were retrospective cohort studies.[13,15–17,38,39,43,44] A total of 597 women underwent difference indicated cerclage and 526 women underwent expectant treatment. The majority of studies reported history-indicated and twin only–indicated cerclage performed at 12–16 weeks of pregnancy. Ultrasound-indicated and physical examination–indicated cerclage were completed at 16–24 weeks of pregnancy. Patients in the control group were advised to take bed rest, bathroom privileges, and ultrasound examination.

Five RCTs were analyzed with the use of the Cochrane risk-of-bias tool.[34,40,42,45,47] Of the 5 included RCTs, 3 trials were classified as having unclear sequence generation and unclear allocation concealment.[40,45,47] All studies reported high risk of blinding participants and personnel and unclear risk of blinding outcomes. The outcome data and selective outcome reporting were unclear in 1 study,[47] and the other risk of bias was unclear in the same study. According to our NOS, the overall quality of the cohort studies was good. Of the 11 cohort studies,[13–17,38,39,41,43,44,46] 4 studies had an NOS score of 9[16,17,38,39]; 4 studies had an NOS score of 8[13,15,43,44]; 2 studies had an NOS score of 7,[41,46] and 1 study had an NOS score of 6[14] (Appendix).

A total of 9 studies (3 RCTs[34,40,42] and 6 cohort studies[13,15,16,38,39,41]) with 471 women evaluated the efficacy of ultrasound-indicated cerclage in twin pregnancies with short cervix (CL, <25 mm). The pooled outcomes from RCTs tended to indicate that cerclage placement was not beneficial for women with twin pregnancies as compared with that in the control group, as demonstrated by the occurrence rate of PTB at <34 weeks of gestation (RR, 2.42; 95% CI, 1.12–5.21; P=.020; I^2=36%) and the occurrence rate of RDS (RR, 5.09; 95% CI, 1.75–14.78; P=.003; I^2=0%). However, the pooled outcomes from cohort studies tended to show that cerclage placement is beneficial for women with twin pregnancies as compared with that in the control group, as demonstrated by the occurrence rate of PTB at <34 weeks of gestation (RR, 0.73; 95% CI, 0.59–0.90; P=.003; I^2=0%), and <32 weeks of gestation (RR, 0.68; 95% CI, 0.51–0.92; P=.010; I^2=0%; Tables 2 and 3). The difference noted between RCTs and cohort studies precluded a definite conclusion on the efficacy of ultrasound-indicated cerclage in twin pregnancies with a CL of <25 mm.

Subgroup analyses from 3 cohort studies revealed that, in women with CL of 15–25 mm, cerclage placement had

TABLE 1
Characteristics of studies included in this metaanalysis

Study	Year	Type of study	Country	Participants	Main outcomes	Cervical length or dilated cervix at screening, cm	Gestation weeks of cerclage placement, wk	Gestational age at delivery, wk
Ultrasound-indicated cerclage								
Adams et al[13]	2018	Retrospective cohort study	United States	Exp:43/Con:39	Preterm birth at <37, 34, 32, 28, and 24 weeks of gestation; neonatal outcomes[a]	Exp:1.6±1.2[b]/ Con:1.3±1.0[b]	20.8±1.9[b]	Exp:34.4±4.2[b]/ Con:32.9±5.7[b]
Han et al[15]	2018	Retrospective cohort study	United States	Exp:36/Con:20	Preterm birth at <36, 34, and 32 weeks of gestation; chorioamnionitis, birthweight, and perinatal death	Exp:1.46/Con:1.55	NR	NR
Houlihan et al[38]	2016	Retrospective cohort study	United Kingdom	Exp:40/Con:40	Preterm birth at <34, 32, 30, and 28 weeks of gestation; neonatal outcomes[a]	Exp:1.2 (0.5-2.3)[c]/ Con:1.2 (0.5-2.4)[c]	21.9 (16.1-24.9)[c]	Exp:36.0 (32.9-37.4)[c]/Con:31.6 (27.1-36.7)[c]
Roman et al[16]	2015	Retrospective cohort study	United States	Exp:57/Con:83	Preterm birth at <37, 34, 32, 30, and 28 weeks of gestation; neonatal outcomes[a]	Exp:1.5±0.6[b]/Con: 1.6±0.7[b]	19.5±1.8	Exp:32.1±5.1[b]/ Con: 32.6±4.6[b]
Roman et al[39]	2005	Retrospective cohort study	United States	Exp:19/Con:12	Preterm birth at <34, 32, 30, and 28 weeks of gestation; preterm premature rupture of membranes; neonatal outcomes[a]	Exp:1.5 (0.3-2.5)[c]/ Con:1.5 (0.2-2.3)[c]	20.8 (15.7-23.6)[c]	Exp:34.0 (21.3-38.9)[c]/Con:34.4 (23.1-38.0)[c]
Berghella et al[40]	2004	Prospective randomized controlled trials	United States	Exp:3/Con:1	Preterm birth at <34, 32, 30, 28 and 24 weeks of gestation; preterm premature rupture of membranes; neonatal outcomes[a]	Exp:1.6±0.9[b]/ Con:1.7±0.8[b]	19.6±2.4[b]	Exp:21±1[b]/ Con:34±0[b]
Newman et al[41]	2002	Prospective cohort study	United States	Exp:21/Con:12	Preterm birth at <34 weeks of gestation; preterm premature rupture of membranes	Exp:<2.5/ Con:<2.5	22.3±3.1[b]	Exp:33.5±3.6[b]/ Con:32.8±3.9[b]
Althuisius et al[34]	2001	Prospective randomized controlled trials	Australia	Exp:8/Con:9	Preterm birth at <34 weeks of gestation; neonatal morbidity	Exp:<2.5/ Con:<2.5	16–24	Exp:37.9±1.3[b]/ Con:32.4±6.5[b]
Rust et al[42]	2000	Prospective randomized controlled trials	United States	Exp:13/Con:15	Preterm birth at <37, 34, 32, and 28 weeks of gestation; neonatal morbidity	Exp:<2.5/ Con:<2.5	16–24	Exp:29.8±5.1/ Con:33.9±4.4[b]

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(continued)

TABLE 1
Characteristics of studies included in this metaanalysis *(continued)*

Study	Year	Type of study	Country	Participants	Main outcomes	Cervical length or dilated cervix at screening, cm	Gestation weeks of cerclage placement, wk	Gestational age at delivery, wk
Physical examination–indicated cerclage								
Han et al[15]	2018	Retrospective cohort study	United States	Exp:96/Con:39	Preterm birth at <36, 34, and 32 weeks of gestation; chorioamnionitis, birthweight, and perinatal death	Exp:0.9/Con:1.1	NR	NR
Abbasi et al[43]	2017	Retrospective cohort study	Canada	Exp:27/Con:9	Preterm birth at <34, 32, 28 and 24 weeks of gestation; neonatal morbidity	Exp:2.6±1.3[b] ≤2 (12); 3-4, (0); >4 (2)/Con: 3.0±1.5[b] ≤2 (3); 3-4 (4); >4 (2)	21.4±2.6[b]	Exp:28.9±6.1[b]/ Con:24.3±2.6[b]
Roman et al[17]	2016	Retrospective cohort study	United States	Exp:38/Con:38	Preterm birth at <34, 32, 28 and 24 weeks of gestation; perinatal death and neonatal outcomes[a]	Exp:2.0±1.1[b] >2 (24)/ Con:2.1±0.9[b] >2 (24).	20.7±1.6[b]	Exp:31.2±5.6[b]/ Con:24.3±4.2[b]
History-indicated cerclage								
Han et al[15]	2018	Retrospective cohort study	United States	Exp:36/Con:20	Preterm birth at <36, 34, and 32 weeks of gestation; chorioamnionitis, birthweight, and perinatal death	History of preterm birth at with normal cervical length	NR	NR
Matsui et al[44]	2017	Retrospective cohort study	Japan	Exp:16/Con:46	Preterm birth at <36, 35, and 34 weeks of gestation	History of preterm birth at with normal cervical length; Symptom of threatened abortion	NR	NR
MRC/RCOG Working Party on Cervical Cerclage[45]	1993	Prospective randomized controlled trials	United Kingdom	Exp:12/Con:16	Preterm birth at <37 and 33 weeks of gestation; neonatal outcomes[a]	History of Preterm birth at with normal cervical length	NR	Exp:34.9±6.2[b]/ Con:34.2±4.7[b]
Eskandar et al[46]	2007	Prospective cohort study	Saudi Arabia	Exp:76/Con:100	Preterm birth at <37 weeks of gestation	History of preterm birth at with normal cervical length	NR	NR

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(continued)

TABLE 1
Characteristics of studies included in this metaanalysis *(continued)*

Study	Year	Type of study	Country	Participants	Main outcomes	Cervical length or dilated cervix at screening, cm	Gestation weeks of cerclage placement, wk	Gestational age at delivery, wk
Twin only–indication cerclage								
Chavan and Jassawalla[14]	2016	Prospective cohort study	India	Exp:50/Con:50	Preterm birth at <37, 34 weeks of gestation; neonatal outcomes[a]	Normal cervical length	16–22	NR
Dor et al[47]	1982	Prospective randomized controlled trials	Israel	Exp:22/Con:23	Preterm birth at <37 weeks of gestation; neonatal outcomes[a]	Normal cervical length	At 13	Exp:29.8±5.1[b]/ Con:33.9±4.4[b]

Con, Women without cerclage; *Exp*, women treated with difference-indicated cerclage; *NR*, not reported.

[a] Included at least 1 of the following items: respiratory distress syndrome, intraventricular hemorrhage grade 3 and 4, necrotizing enterocolitis grade 3 and 4 that requires surgery, proven sepsis, or retinopathy of prematurity that requires laser treatment; [b] Data are given as mean±standard deviation; [c] Data is given as number (range).

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no effect on the prolongation of pregnancy (mean difference, 1.40 weeks of gestation; 95% CI, −1.17 to −3.97; *P*=.290) and the prevention of PTB at any pregnancy weeks of gestation.[13,15,16] For a CL of <15 mm, cerclage placement was associated with a significant prolongation of pregnancy by mean difference of 3.89 weeks of gestation (95% CI, 2.19−5.59; *P*=.000; I^2=0%) and significant reduction of PTB at <37, <34, and <32 weeks of gestation as compared with that in the control group (Table 4).

A total of 3 cohort studies with 244 women evaluated the efficacy of physical examination−indicated cerclage in twin pregnancies with a cervix that was dilated >10 mm.[15,17,43] The pooled outcomes showed cerclage placement was associated with a significant prolongation of pregnancy by a mean difference of 6.78 weeks of gestation (95% CI, 5.32−8.24; *P*=.000; I^2=0%) and significant reduction of PTB rate at <34, <32, <28, and <24 weeks of gestation and achieved a significant improvement in perinatal outcomes, which included perinatal death, stillbirth, neonatal death, RDS, grade III or IV necrotizing enterocolitis, grade III/IV intraventricular hemorrhage, and retinopathy of prematurity, when compared with patients without cerclage (Table 3).

A total of 4 studies (1 RCT[45] and 3 cohort studies[15,44,46]) with 348 women evaluated the efficacy of history-indicated cerclage in twin pregnancies. Data from RCT[45] and cohort studies[15,44,46] demonstrated that cerclage placement did not reduce the occurrence rate of PTB at <37, <34, <32, and <28 weeks of gestation (Table 2) and was not associated with an improvement in perinatal outcomes, which included perinatal death, stillbirth, neonatal death, and RDS when compared with women without cerclage (Table 3).

Only 2 studies (1 RCT[47] and 1 cohort study[14]) with 145 women evaluated the efficacy of twin only−indicated cerclage in twin pregnancies with normal CL. Pooled analysis of the outcomes was not feasible. Thus, a narrative overview was presented. An RCT by Dor et al[47] reported that cerclage placement was not associated with a reduction of PTB in

TABLE 2
Incidence of preterm birth <37, 34, 32, 28, and 24 weeks and pregnancy prolongation between women with cerclage and with no cerclage

Clinical outcomes	No. of trials	Intervention, n/N	Control, n/N	Statistical method	I^2, %	Effect estimate	*P* value
Ultrasound-indicated cerclage							
Randomized controlled trial							
PTB<37 week	3[34,40,42]	22/24	19/25	Risk ratio (M-H, Fixed, 95%)	0	1.18 (0.91–1.53)	.200
PTB<34 week	3[34,40,42]	15/24	6/25	Risk ratio (M-H, Fixed, 95%)	36	2.42 (1.12–5.21)	.020
PTB<32 week	3[34,40,42]	11/24	4/25	Risk ratio (M-H, Fixed, 95%)	0	2.48 (0.96–6.37)	.060
PTB<28 week	3[34,40,42]	7/24	2/25	Risk ratio (M-H, Fixed, 95%)	0	2.62 (0.72–9.51)	.140
Pregnancy prolongation	1[9]	31	30	Mean difference (IV, Fixed 95%)	—	−0.60 (−4.03–2.83)	.730
Cohort study							
PTB<37 week	3[13,15,16]	102/136	118/142	Risk ratio (M-H, Fixed, 95%)	0	0.94 (0.83–1.06)	.310
PTB<34 week	6[13,15,16,38,39,41]	83/216	114/206	Risk ratio (M-H, Fixed, 95%)	0	0.73 (0.59–0.90)	.003
PTB<32 week	5[13,15,16,38,39]	49/195	77/194	Risk ratio (M-H, Fixed, 95%)	8	0.68 (0.51–0.92)	.010
PTB<28 week	4[13,16,38,39]	22/159	40/174	Risk ratio (M-H, Fixed, 95%)	13	0.64 (0.40–1.02)	.060
PTB<24 week	3[13,16,38]	8/140	12/162	Risk ratio (M-H, Random, 95%)	63	0.55 (0.08–3.64)	.540
Pregnancy prolongation	2[13,16]	100	122	Risk ratio (M-H, Fixed, 95%)	0	2.53 (1.25–3.81)	.001
Physical examination–indicated cerclage							
Randomized controlled trial	No report						
Cohort study							
PTB<37 week	3[15,17,43]	111/119	64/64	Risk ratio (M-H, Fixed, 95%)	0	0.95 (0.89–1.01)	.120
PTB<34 week	3[15,17,43]	57/119	58/64	Risk ratio (M-H, Fixed, 95%)	28	0.56 (0.45–0.69)	.000
PTB<32 week	3[15,17,43]	42/119	51/64	Risk ratio (M-H, Fixed, 95%)	14	0.50 (0.38–0.65)	.000
PTB<28 week	3[15,17,43]	29/119	46/64	Risk ratio (M-H, Random, 95%)	80	0.41 (0.20–0.85)	.030
PTB<24 week	3[15,17,43]	13/119	23/64	Risk ratio (M-H, Fixed, 95%)	24	0.35 (0.18–0.67)	.001
Pregnancy prolongation	2[17,43]	65	47	Mean difference (IV, Fixed, 95%)	0	6.78 (5.32–8.24)	.000

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(continued)

TABLE 2
Incidence of preterm birth <37, 34, 32, 28, and 24 weeks and pregnancy prolongation between women with cerclage and with no cerclage *(continued)*

Clinical outcomes	No. of trials	Intervention, n/N	Control, n/N	Statistical method	I^2, %	Effect estimate	*P* value
History-indicated cerclage							
Randomized controlled trial							
PTB<37 week	1[45]	8/12	8/16	Risk ratio (M-H, Fixed, 95%)	—	1.33 (0.71–2.51)	.370
PTB<34 week	1[45]	1/12	5/16	Risk ratio (M-H, Fixed, 95%)	—	0.27 (0.04–1.99)	.200
PTB<32 week	1[45]	1/12	4/16	Risk ratio (M-H, Fixed, 95%)	—	0.33 (0.04–2.61)	.300
PTB<28 week	1[45]	1/12	1/16	Risk ratio (M-H, Fixed, 95%)	—	1.33 (0.09–19.23)	.830
Cohort study							
PTB<37 week	3[15,44,46]	53/124	56/148	Risk ratio (M-H, Fixed, 95%)	40	0.94 (0.48–1.86)	.870
PTB<34 week	2[15,44]	2/48	4/48	Risk ratio (M-H, Fixed, 95%)	0	0.34 (0.10–1.17)	.090
PTB<32 week	1[15]	0/6	1/2	Risk ratio (M-H, Fixed, 95%)	—	0.14 (0.01–2.60)	.190
PTB<28 week	1[46]	12/76	8/100	Risk ratio (M-H, Fixed, 95%)	—	1.97 (0.85–4.95)	.110
Twin only—indicated cerclage							
Randomized controlled trial							
PTB<37 week	1[47]	10/22	11/23	Risk ratio (M-H, Fixed, 95%)	—	0.95 (0.51–1.78)	.870
PTB<28 week	1[47]	1/22	2/23	Risk ratio (M-H, Fixed, 95%)	—	0.52 (0.05–5.36)	.590
Cohort study							
PTB<37 week	1[14]	34/50	46/50	Risk ratio (M-H, Fixed, 95%)	—	0.74 (0.60–0.91)	.004
PTB<34 week	1[14]	11/50	22/50	Risk ratio (M-H, Fixed, 95%)	—	0.50 (0.27–0.92)	.030

IV, Inverse Variance; *M-H*, Mantel-Haenszel; *PTB*, preterm birth.

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TABLE 3
Perinatal outcomes between women with cerclage and with no cerclage

Clinical outcomes	No. of trials	Intervention, n/N	Control, n/N	Statistical method	I^2, %	Effect estimate	*P* value
Ultrasound-indicated cerclage							
Randomized controlled trial							
Perinatal death	3[9,35,42]	11/48	3/50	Risk ratio (M-H, Fixed, 95%)	0	2.66 (0.83—8.54)	.100
Neonatal death	1[9]	6/6	0/2	Risk ratio (M-H, Fixed, 95%)	—	5.57 (0.44—70.55)	.180
Respiratory distress syndrome	3[9,35,42]	15/48	3/50	Risk ratio (M-H, Fixed, 95%)	0	5.09 (1.75—14.78)	.003
Necrotizing enterocolitis	3[9,35,42]	0/48	0/50	Risk ratio (M-H, Fixed, 95%)	—	—	/
Intraventricular hemorrhage	3[9,35,42]	3/48	3/50	Risk ratio (M-H, Random, 95%)	53	1.20 (0.08—17.29)	.890
Birthweight <1500 g	3[9,35,42]	25/48	7/50	Risk ratio (M-H, Fixed, 95%)	0	3.35 (1.63—6.92)	.001
Birthweight <2500 g	3[9,35,42]	42/48	29/50	Risk ratio (M-H, Fixed, 95%)	15	1.46 (1.13—1.88)	.004
Cohort study							
Perinatal death	2[13,16]	25/200	30/244	Risk ratio (M-H, Random, 95%)	80	1.05 (0.65—1.71)	.830
Stillbirth	2[13,16]	12/200	12/244	Risk ratio (M-H, Random, 95%)	52	0.99 (0.12—6.99)	.920
Neonatal death	1[13]	5/86	8/76	Risk ratio (M-H, Random, 95%)	—	0.55 (0.19—1.62)	.280
Respiratory distress syndrome	1[13]	14/86	12/76	Risk ratio (M-H, Fixed, 95%)	—	1.03 (0.51—2.09)	.930
Necrotizing enterocolitis	1[13]	2/86	1/76	Risk ratio (M-H, Fixed, 95%)	—	1.77 (0.16—19.11)	.640
Intraventricular hemorrhage	1[13]	3/86	2/76	Risk ratio (M-H, Fixed, 95%)	—	1.33 (0.23—7.72)	.750
Retinopathy of prematurity	1[13]	6/86	1/76	Risk ratio (M-H, Fixed, 95%)	—	5.3 (0.65—43.06)	.120
Birthweight <1500 g	2[16,41]	41/156	71/190	Risk ratio (M-H, Random, 95%)	61	0.77 (0.56—1.05)	.090
Physical examination—cerclage							
Randomized controlled trial	No report						
Cohort study							
Perinatal death	1[17]	21/76	45/76	Risk ratio (M-H, Fixed, 95%)	0	0.47 (0.31—0.70)	.000
Stillbirth	2[17,43]	35/130	42/94	Risk ratio (M-H, Fixed, 95%)	0	0.62 (0.43—0.90)	.010
Neonatal death	2[17,43]	3/95	11/52	Risk ratio (M-H, Random, 95%)	75	0.14 (0.03—0.59)	.007
Respiratory distress syndrome	2[17,43]	32/95	46/52	Risk ratio (M-H, Random, 95%)	64	0.45 (0.34—0.59)	.000
Necrotizing enterocolitis	2[17,43]	9/95	15/52	Risk ratio (M-H, Fixed, 95%)	0	0.32 (0.15—0.71)	.005
Intraventricular hemorrhage	2[17,43]	6/95	19/52	Risk ratio (M-H, Random, 95%)	63	0.15 (0.05—0.42)	.000
Retinopathy of prematurity	1[17]	1/54	9/42	Risk ratio (M-H, Fixed, 95%)	0	0.09 (0.01—0.66)	.020
Birthweight <1500 g	1[17]	33/76	70/76	Risk ratio (M-H, Fixed, 95%)	—	0.47 (0.36—0.61)	.000

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(continued)

TABLE 3
Perinatal outcomes between women with cerclage and with no cerclage *(continued)*

Clinical outcomes	No. of trials	Intervention, n/N	Control, n/N	Statistical method	I^2, %	Effect estimate	*P* value
History-indicated cerclage							
Randomized controlled trial							
Perinatal death	1[45]	2/24	2/32	Risk ratio (M-H, Fixed, 95%)	—	1.33 (0.20–8.80)	.770
Stillbirth	1[45]	0/24	2/32	Risk ratio (M-H, Fixed, 95%)	—	0.26 (0.01–5.26)	.380
Cohort study	No report						
Twin only–indicated cerclage							
Randomized controlled trial	No report						
Cohort study	No report						

M-H, Mantel-Haenszel.

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twin pregnancies. A cohort study with a low quality (NOS 6) by Chavan and Jassawalla[14] showed cerclage placement could reduce the rate of PTB but did not change the outcomes of perinatal death and neonatal complications. Given the few numbers of included studies and the lower quality, the result should be noted with extreme caution.

Comment

Main findings

Our metaanalysis demonstrated that cerclage placement was beneficial for the reduction of PTB and the prolongation of pregnancy in twin pregnancies with a CL <15 mm or dilated cervix >10 mm. However, for twin pregnancies with a CL 15–25 mm or a normal CL (eg, a history of PTB or twin only as a indication of cerclage), cerclage placement did not seem to be beneficial (Figure 3). The outcomes demonstrated that cerclage placement was effective for twin pregnancies with more advanced cervical changes. It is reasonable because cerclage itself presented both detriment and benefit: for twin pregnancies with low-risk of PTB (eg, normal cervix), cerclage may be less harmful than beneficial; for twin pregnancies with high-risk of PTB (eg, cervical dilation at presentation), cerclage may be more beneficial than harmful.

Discussion and comparison with existing literature

A shorter CL is defined as a CL <25 mm between 18 and 22 weeks of gestation and has been demonstrated as 1 of the best predictors for PTB.[49] This definition of CL is fully applicable for singleton pregnancies and is used in the treatment recommendations, but it does not entirely apply to twin pregnancies, presumably because of different mechanisms that lead to cervical shortening.[49] It has been reported that a CL <25 mm at 24 weeks of gestation was at approximately the 9th percentile for CL measurement in singletons, although the percentage was approximately 18% in twin gestation.[50,51] According to a study of 214 asymptomatic twin pregnancies by Souka et al,[52] the rate of PTB ≤32 weeks of gestation increased

TABLE 4
The incidence of preterm birth by subgroup analysis according to the different cervical lengths

Clinical outcomes	No. of trials	Intervention, n/N	Control, n/N	Statistical method	I^2, %	Effect estimate	*P* value
Preterm birth <37 weeks of gestation							
Cervical length							
<25 mm	3[13,15,16]	102/136	118/142	Risk ratio (M-H, Fixed, 95%)	0	0.94 (0.83–1.06)	.310
16–24 mm	3[13,15,16]	42/57	48/67	Risk ratio (M-H, Fixed, 95%)	25	1.18 (0.95–1.46)	.140
≤15 mm	3[13,15,16]	60/79	67/75	Risk ratio (M-H, Fixed, 95%)	0	0.86 (0.74–0.99)	.040
Preterm birth <34 weeks of gestation							
<25 mm	6[13,15,16,38,39,41]	83/216	114/206	Risk ratio (M-H, Fixed, 95%)	0	0.73 (0.59–0.90)	.003
16–24 mm	3[13,15,16]	18/57	26/67	Risk ratio (M-H, Fixed, 95%)	10	0.91 (0.59–1.40)	.670
≤15 mm	3[13,15,16]	34/79	58/75	Risk ratio (M-H, Fixed, 95%)	0	0.57 (0.43–0.75)	.000
Preterm birth <32 weeks of gestation							
<25 mm	5[13,15,16,38,39]	49/195	77/194	Risk ratio (M-H, Fixed, 95%)	8	0.68 (0.51–0.92)	.010
16–24 mm	3[13,15,16]	18/57	28/67	Risk ratio (M-H, Fixed, 95%)	48	0.83 (0.54–1.27)	.380
15 mm or less	3[13,15,16]	24/79	39/75	Risk ratio (M-H, Fixed, 95%)	0	0.61 (0.41–0.90)	.010
Preterm birth <28 weeks of gestation							
<25 mm	4[13,16,38,39]	22/159	40/174	Risk ratio (M-H, Fixed, 95%)	13	0.64 (0.40–1.02)	.060
16–24 mm	2[13,16]	11/41	19/62	Risk ratio (M-H, Fixed, 95%)	0	0.86 (0.46–1.62)	.640
≤15 mm	2[13,16]	9/70	11/60	Risk ratio (M-H, Fixed, 95%)	0	0.69 (0.31–1.55)	.370
Preterm birth <24 weeks of gestation							
<25 mm	3[13,16,38]	8/140	12/162	Risk ratio (M-H, Random, 95%)	63	0.55 (0.08–3.64)	.540
16–24 mm	2[13,16]	4/41	3/62	Risk ratio (M-H, Fixed, 95%)	0	2.04 (0.49–8.47)	.320
≤15 mm	2[13,16]	4/59	6/60	Risk ratio (M-H, Random, 95%)	76	0.56 (0.02–16.52)	.740
Pregnancy prolongation							
<25 mm	2[13,16]	100	122	Mean difference (IV, Fixed 95%)	0	2.53 (1.25–3.81)	.001
16–24 mm	1[16]	25	44	Mean difference (IV, Fixed 95%)	/	1.40 (−1.17–3.97)	.290
≤15 mm	2[13,16]	59	60	Mean difference (IV, Fixed 95%)	0	3.89 (2.19–5.59)	.000

IV, Inverse Variance; *M-H*, Mantel-Haenszel.

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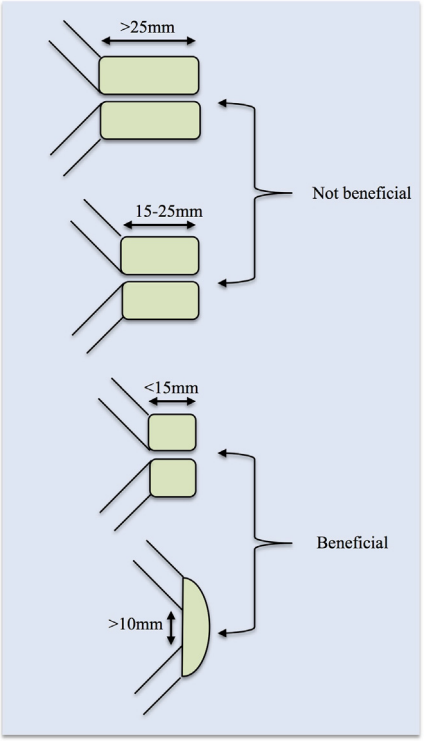
exponentially with decreasing CL at 23 weeks of gestation, from 6.7% at CL >25 mm to 31% at CL 16−25 mm and 66% at CL <15 mm. These data indicated that CL measurement also played a significant role in the prediction of PTB in twins. A cut-off value of CL <25 mm commonly is considered as the best indication for the performance of cerclage in singleton. However, in twin pregnancies, previous studies that evaluated the efficacy of cerclage according to CL <25 mm presented contradictory results.[9,10] Recently, some studies highlighted the potential benefit of cerclage placement in twin pregnancies with a CL <15 mm, with seemingly even greater effects with shorter CLs.[13−17] In the present metaanalysis, the pooled data that was based on earlier RCTs published before 2004 indicated cerclage placement for twin pregnancies with a shorter CL <25 mm did not appear to be beneficial, which is in line with published metaanalyses.[8,9,53] However, the data from recent cohort studies presented a different point, that cerclage placement might be associated with a reduction of PTB and pregnancy prolongation. These outcomes indicated that some viewpoint was changing with the development of theory and practice, which promoted further studies to confirm the findings. Subgroup analysis according to the cut-off of CL indicated that cerclage placement for twin pregnancies with a CL <15 mm reduced the rate of PTB and prolonged pregnancy. For CL 15−25 mm, there is no benefit from cerclage placement. It is believed that the majority of twin pregnancies with CL <15 mm were exposed to a higher risk of spontaneous preterm labor or premature ruptured membranes at any time. A CL <15 mm might present higher sensitivity and specificity to distinguish between women who truly will deliver and those who will not. Thus, for women in twin pregnancies with a CL <15 mm, the beneficial effect of cerclage is superior to no cerclage.

For twin pregnancies with a cervix that is dilated >10 mm, our metaanalysis also showed more beneficial effect from cerclage placement that obtained with expectant management. Although all included studies reported a potential benefit of cerclage in twins, the selection and timing to place cerclage remained inconsistent according to the included studies. For example, Roman et al[17] performed a cerclage at 16−24 weeks of gestation in twin pregnancies with cervical dilation ranging from 1−4 cm. They also stratified women into those with cervical dilation <2 or >2 cm; the outcomes showed no significant differences in obstetric outcomes between the cerclage and control groups. Abbasi et al[43] performed a cerclage at <26 weeks of gestation in 12 sets of twins with cervical dilation 1−2 cm, 9 sets of twins with cervical dilation 3-4 cm, and 2 sets of twins with cervical dilation >4 cm. Thus, the decision to place this cerclage should be individualized according to the gestational age and the risks of severe PTB. Society of Obstetricians and Gynecologist in Canada guidelines suggest that this cerclage may be considered when the cervix is dilated <4 cm without contractions at <24 week of gestation in singleton pregnancy. Further research is required to confirm whether the recommendation could be applied in twins.[53]

According to our experiences, women who are treated with physical examination−indicated cerclage expectantly may have been perceived to be at higher risk of PTB or imminent delivery. A cerclage placement may provide an opportunity to avoid the potential risk of PTB. Thus, restriction of the criteria for cerclage to twin pregnancies with a high-risk of preterm labor may present significant favorable outcomes.

The efficacy of history-indicated or twin only−indicated cerclage placement, as a prophylactic treatment in unselected twin pregnancies, is less certain because of the limited data. According to Society of Obstetricians and Gynecologist in Canada and Royal College of Obstetricians and Gynecologists guidelines that involve singleton pregnancies, a prophylactic cerclage should be considered at 12−14 weeks of gestation in women with a history of ≥3 previous pregnancy losses.[53−55] However, in the twin pregnancies, these observations were not reported because few data were available.

FIGURE 3
Summary of main outcomes in the metaanalysis



The primary outcomes from the meta-analysis.

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Several studies by Ananth et al,[56] Facco et al,[57] and Schaaf et al[58] reported that previous PTB of a singleton pregnancy was associated with an increased risk of PTB in subsequent twin pregnancies. However, limited studies specifically evaluated the issue of prophylactic cerclage for the indications of a high-risk history of PTB have presented not only any harm but also fail to show any benefit. Further studies are necessary to assess whether twin alone or a history of ≥1 previous PTBs could be considered as an indication for cerclage placement.

Strengths and limitations

As is often the case with a metaanalysis, our study presents several important limitations that could bias the final results. First, because the pooled effect estimates were derived mainly from cohort trials with a small sample size, susceptibility to a confounding factor is a

concern, which was inadequate to draw a strong conclusion. Second, a major limitation was clinical heterogeneity caused by non-standardized treatment protocols and outcome measures. For example, the CL or dilation and intervention at a different pregnancy phase might have an effect on outcomes. Third, the majority of included studies lacked the data of neonatal outcomes, especially for long-term neurodevelopmental outcomes among the surviving neonates. Fourth, it was difficult to evaluate the use of cerclage with other modalities (eg, progesterone or pessary) in twin pregnancies and to compare the outcome of cerclage in monochorionic or dichorionic twin pregnancies because none of the included trials reported these comparisons.

The strength of this study is that we conducted a wide search to find relevant studies and synthesized the results of smaller existing studies on the use of cerclage in twins. In addition, we pooled the outcomes according to the different indications, which could reduce the bias. Although the quality of the study methods and reportage of these studies varied widely, the results of the meta-analysis were consistent with the primary findings.

Conclusion and implications

Our metaanalysis indicates that cerclage placement is beneficial for the reduction of PTB and the prolongation of pregnancy in twin pregnancies with a CL of <15 mm or dilated cervix of >10 mm. However, the benefit of history-indicated or twin only—indicated cerclage placement is less certain according to current literature. We must point out that the outcomes should be applied with caution because of the insufficiency of strong supporting evidence. There is a definite need for high-quality trials of appropriate size and duration to identify the best candidates for cerclage. ■

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APPENDIX

The bias assessment of included studies

Study	Selection	Comparability	Outcome	Total			
Newcastle-Ottawa Scale for nonrandomized studies							
Adams et al 2018	4	1	3	8			
Han et al 2018	4	2	2	8			
Houlihan et al 2016	4	2	3	9			
Matsui et al 2017	3	2	3	8			
Roman et al 2016	4	2	3	9			
Roman et al 2015	4	2	3	9			
Abbasi et al 2017	4	1	2	8			
Roman et al 2005	4	2	3	9			
Chavan and Jassawalla 2016	3	0	3	6			
Eskandar et al 2007	4	0	3	7			
Newman et al 2002	3	1	3	7			
Cochrane risk of bias for randomized studies	Other bias	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes data	Incomplete outcome data	Selective reporting
Berghella et al 2004	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Althuisius et al 2001	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Rust et al 2000	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
MRC/RCOG 1993	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Dor et al 1982	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

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