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CERVICAL PESSARY TO PREVENT PRETERM BIRTH IN ASYMPTOMATIC HIGH-RISK WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

OBJECTIVE: To evaluate the efficacy and safety of cervical pessary to prevent preterm birth and adverse perinatal outcomes in asymptomatic high-risk women.

DATA SOURCES: MEDLINE, EMBASE, POPLINE, CINAHL, and LILACS (from their inception to October 31, 2019), Cochrane databases, Google Scholar, bibliographies, and conference proceedings.

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Condensation: Cervical pessary does not prevent preterm birth or improve perinatal outcome in asymptomatic women with singleton or twin gestations at risk for preterm delivery

Disclosure: The authors declare no conflicts of interest.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials that compared cervical pessary with standard care (no pessary) or alternative interventions in asymptomatic women at high risk for preterm birth.

STUDY APPRAISAL AND SYNTHESIS METHODS: The systematic review was conducted according to the Cochrane Handbook guidelines. The primary outcome was spontaneous preterm birth <34 weeks of gestation. Secondary outcomes included adverse pregnancy, maternal and perinatal outcomes. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated. Quality of evidence was assessed using the GRADE methodology.

RESULTS: Twelve studies (4687 women and 7167 fetuses/infants) met the inclusion criteria: 8 evaluated pessary vs no pessary in women with a short cervix, 2 assessed pessary vs no pessary in unselected multiple gestations, and 2 compared pessary vs vaginal progesterone in women with a short cervix. There were no significant differences between the pessary and no pessary groups in the risk of spontaneous preterm birth <34 weeks of gestation among singleton gestations with a cervical length ≤25 mm (RR 0.80, 95% CI 0.43–1.49; 6 trials, 1982 women; low-quality evidence), unselected twin gestations (RR 1.05, 95% CI 0.79–1.41; 1 trial, 1177 women; moderate-quality evidence), twin gestations with a cervical length <38 mm (RR 0.75, 95% CI 0.41–1.36; 3 trials, 1128 women; low-quality evidence), and twin gestations with a cervical length ≤25 mm (RR 0.72, 95% CI 0.25–2.06; 2 trials, 348 women; low-quality evidence). Overall, no significant differences were observed between the pessary and no pessary groups in preterm birth <37, <32, and <28 weeks of gestation, and most adverse pregnancy, maternal, and perinatal outcomes (low- to moderate-quality evidence for most outcomes). There were no significant differences in the risk of spontaneous preterm birth <34 weeks of gestation between pessary and vaginal progesterone in singleton gestations with a cervical length ≤25 mm (RR 0.99, 95% CI 0.54–1.83; 1 trial, 246 women; low-quality evidence) and twin gestations with a cervical length <38 mm (RR 0.73, 95% CI 0.46–1.18; 1 trial, 297 women; very low-quality evidence). Vaginal discharge was significantly more frequent in the pessary group than in the no pessary and vaginal progesterone groups (RRs ~2.20; high-quality evidence).

CONCLUSION: Current evidence does not support the use of cervical pessary to prevent preterm birth or improve perinatal outcomes in singleton or twin gestations with a short cervix and in unselected twin gestations.

Keywords

prematurity; preterm delivery; multiple gestation; twin gestation; short cervix; transvaginal ultrasound; cervical length; neonatal morbidity; neonatal mortality

INTRODUCTION

Complications of preterm birth are the leading cause of death among children younger than 5 years worldwide, accounting for approximately 18% of all deaths, and 35% of deaths among newborns.[1] In 2014, preterm birth affected 10.6% of livebirths globally, equating to about 14.84 million liveborn preterm neonates.[2] In the United States, the rate of preterm birth has been rising since 2014, and increased significantly from 9.93% in 2017 to 10.02% in 2018.[3]

Preterm neonates who survive are at greater risk of experiencing short-term complications such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, intraventricular hemorrhage, periventricular leukomalacia, and retinopathy of prematurity, than neonates born at term.[4–8] Furthermore, children born preterm have lower cognitive, motor, and academic performance scores, and are more likely to be diagnosed with cerebral palsy, visual and hearing impairments, attention deficit hyperactivity disorder, and behavioral problems than children born at term.[9–15] Systematic reviews of observational studies and recent large longitudinal follow-up studies strongly suggest that preterm birth is associated with a significantly higher risk of developing chronic diseases in adulthood such as metabolic syndrome,[16] diabetes,[17] lung function impairment,[18] venous thromboembolism,[19] sleep-disordered breathing,[20] ischemic heart disease,[16,21,22] and chronic kidney disease.[23]

Importantly, in a recent nationwide cohort study of more than 4 million people, preterm birth was associated with a significantly increased mortality at all attained ages from birth to 45 years.[24] This outcome could not be attributed to sociodemographic factors, or shared genetic/environmental factors in families, but rather to the consequences of preterm birth.[19,20,22–24]

The burden of preterm birth on health services and other sectors of the economy, for families and caregivers, and more broadly, for society, is substantial.[4,25] Moreover, preterm birth has a major impact on the quality of life of parents and families.[4,26]

Preterm labor is a syndrome[27–33] associated with multiple etiologic processes such as infection/inflammation,[34–44] vascular disorders,[45,46] decidual senescence,[47–51] uterine overdistention,[52–55] decline in progesterone action,[56–60] cervical disease, [61–65] breakdown of maternal-fetal tolerance,[66–68] premature activation of fetal immune system,[67,69] and maternal stress,[31,70,71] among others. Genetic and environmental factors contribute to each etiology of the preterm labor syndrome.[72–79] A logical consequence of the complexity of the preterm labor syndrome is that there is not a single biomarker to identify the patient at risk, or a single intervention to prevent all, or even most cases.[80,81]

In recent years, several interventions have been proposed for the prevention of preterm birth in asymptomatic high-risk women, including progestogens (17α-alpha-hydroxyprogesterone caproate,[82–99] vaginal progesterone,[84,85,88,90–93,96,99–112] and oral progesterone[99,113]), omega−3 long-chain polyunsaturated fatty acids supplementation,[114–117] cervical cerclage,[90,91,96,99,118–128] and cervical pessary.[90,91,96,99,129–132] High-quality evidence indicates that vaginal progesterone is effective for preventing preterm birth and improving neonatal outcomes in asymptomatic women with a singleton gestation and a midtrimester sonographic short cervix, regardless of the history of spontaneous preterm birth, without any demonstrable deleterious effects on childhood neurodevelopment or maternal health.[107,109] Cervical cerclage has been shown to be effective in reducing the risk of preterm birth and adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth, and a midtrimester sonographic short cervix.[118] The efficacy of the administration of 17α-alpha-hydroxyprogesterone caproate, oral progesterone,

and omega−3 long-chain polyunsaturated fatty acids to prevent preterm birth remains inconclusive.[113,117,133]

Several systematic reviews regarding the efficacy of cervical pessary for preventing preterm birth in women at high risk have reported conflicting results;[134–143] consequently, a thorough examination of the currently available evidence on the efficacy of this intervention is justified. We performed a systematic review and meta-analysis of aggregate data to evaluate the efficacy and safety of cervical pessary for the prevention of preterm birth and perinatal morbidity and mortality in asymptomatic high-risk women.

MATERIAL AND METHODS

This systematic review was conducted following the guidelines outlined in the last edition of the Cochrane Handbook for Systematic Reviews of Interventions[144] and reported in accordance with the PRISMA statement.[145] The study protocol was registered with PROSPERO, number CRD42019141531. Two of the authors (A.C.-A. and R.R.) independently retrieved and reviewed studies for eligibility and assessed their risk of bias. Any disagreements encountered in the review process were resolved through discussion between the two reviewers.

Search strategy

Identification of relevant articles was undertaken through searches in MEDLINE, EMBASE, POPLINE, LILACS, CINAHL, the Cochrane Central Register of Controlled Trials, clinical trial registries (all from their inception to October 31, 2019), and Google Scholar, using a combination of keywords and text words related to *cervical pessary* and *preterm birth*. We reviewed proceedings of congresses and scientific meetings on obstetrics, maternal-fetal medicine, and ultrasound in obstetrics, reference lists of retrieved articles, previously published systematic reviews, and review articles for any additional relevant studies. We also contacted investigators in the field to locate unpublished studies. There were no language restrictions.

Eligibility criteria

We included randomized controlled trials comparing cervical pessary with standard care (no pessary) or alternative interventions (such as vaginal progesterone or cervical cerclage) in asymptomatic women at high risk for preterm birth (such as those with a midtrimester sonographic short cervix, history of preterm birth, multiple gestation, and uterine anomalies or excisional cervical procedures) with the aim of preventing preterm birth and/or adverse perinatal outcomes. Trials were excluded if they: (1) were quasi-randomized; (2) assessed cervical pessary in women with arrested preterm labor or placenta previa; or (3) did not report clinical outcomes. Studies published only as abstracts were excluded if additional information on methodological issues and results could not be obtained. Trials with planned co-interventions were eligible for inclusion provided that the co-interventions were permitted equally in each trial arm.

Outcome measures

The prespecified primary outcome was spontaneous preterm birth <34 weeks of gestation. Secondary outcomes included spontaneous preterm birth <37, <32 and <28 weeks of gestation, any preterm birth <37, <34, <32, and <28 weeks of gestation, mean gestational age at delivery, chorioamnionitis, preterm prelabor rupture of membranes (PPROM), vaginal discharge, vaginal infection, vaginal bleeding, pelvic discomfort, use of tocolytic agents, cesarean delivery, maternal death, fetal death, neonatal death, perinatal death, birthweight <1500 and <2500 g, Apgar score <7 at 5 minutes, RDS, necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia, any composite adverse neonatal or perinatal outcome, admission to the neonatal intensive care unit (NICU), use of mechanical ventilation, and long-term neurodevelopmental and health outcomes in children.

Data extraction

Using a specially developed data extraction form, one investigator (A.C.-A.) extracted the relevant data from eligible studies, which were then verified independently by another investigator (R.R.). Information was extracted on study characteristics (randomization procedure, concealment allocation method, blinding of clinicians, women and outcome assessors, follow-up period, completeness of outcome data for each outcome, including attrition and exclusions from the analysis, and intention-to-treat analysis), participants (inclusion and exclusion criteria, number of women in randomized groups, baseline characteristics, and country and date of recruitment), details of intervention (type of cervical pessary, gestational age at trial entry, scheduled gestational age for pessary removal, frequency of and reasons for early pessary removal, interventions used in the control group, compliance, and use of co-interventions) and outcomes (definition of outcomes, number of outcome events and/or mean ± SD for each outcome).

Risk of bias assessment

The risk of bias in each study was assessed through the use of the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2),[146,147] which considers the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For each domain, the tool comprises a series of “signaling questions” aiming to elicit information about features of the trial that are relevant to risk of bias. Once the signaling questions were answered, the next step was to reach a risk-of-bias judgement and assign one of three levels to each domain: “low risk of bias”, “some concerns”, or “high risk of bias”. Finally, an overall risk of bias judgement was reached for each study as follows: “low risk of bias” (the study is judged to be at low risk of bias for all domains), “some concerns” (the study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain), and “high risk of bias” (the study is judged to be at high risk of bias in at least one domain or to have some concerns for multiple domains in a way that substantially lowers confidence in the result).

Data synthesis

The data synthesis was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[148] Outcomes were analyzed on an intent-to-treat basis. The denominator for pregnancy and maternal outcomes was the number of women, whereas for perinatal and child outcomes we used the number of fetuses/neonates and children, respectively. Analyses were undertaken separately for singleton gestations with a midtrimester sonographic cervical length ≤25 mm, unselected multiple gestations, twin gestations with a midtrimester sonographic cervical length <38 mm, and twin gestations with a midtrimester sonographic cervical length ≤25 mm.

A random-effects model was used to calculate the pooled relative risk (RR) for dichotomous outcomes and the mean difference for continuous outcomes with corresponding 95% confidence intervals (CIs). We chose a random-effects model, anticipating heterogeneity between the results of the relevant studies. When the RR was statistically significant, we calculated the number needed to treat (NNT) with 95% CI for an additional beneficial outcome or an additional harmful outcome of cervical pessary.[149]

For perinatal outcomes of multiple gestations, we estimated pooled RRs with 95% CIs assuming independence between fetuses/neonates by using data reported in the studies at the fetal/neonatal level. However, because of the potential of non-independence of outcomes in fetuses/neonates from multiple gestations, we also planned estimating pooled adjusted RRs with 95% CIs by using an estimate of the intracluster correlation coefficient (ICC) derived from the trial, or from similar trials, as recommended by the Cochrane Handbook.[150] Given that ICCs for perinatal outcomes were not reported in the included studies, we used those that had recently been estimated from randomized controlled trials in women with a twin gestation, which had similar aims and inclusion/exclusion criteria to those of trials included in our systematic review.[151] We considered the adjusted RRs as the main estimates of the pessary's effect on perinatal outcomes in multiple gestations.

Heterogeneity of treatment effect was assessed with the I^2 statistic.[152] In addition, forest plots were visually inspected for evidence of heterogeneity. If there was evidence of statistical heterogeneity ($I^2 \geq 30\%$), we planned to explore the possible sources using sensitivity and subgroup analyses, to search for evidence of bias or methodological differences among trials. We also addressed heterogeneity by calculating 95% prediction intervals for meta-analyses that contained at least three studies, which provide a predicted range for the true effect size in future studies.[153–155]

In singleton gestations with a cervical length ≤25 mm, we performed subgroup analyses for the primary outcome according to concomitant use of vaginal progesterone (yes vs no), cervical length (≤10 mm vs 11–25 mm), and obstetric history (no previous preterm birth vs at least 1 previous preterm birth). In twin gestations with a cervical length ≤25 mm, we performed a subgroup analysis according to cervical length (≤10 mm vs 11–25 mm). An interaction P value ≥0.05 was considered to indicate that the effect of treatment did not differ significantly between subgroups.[156–158]. We also planned to assess publication and related biases if at least 10 studies were included in a meta-analysis; however, these analyses were not performed given the limited number of trials included in the review. Prespecified

sensitivity analyses to explore the impact of risk of bias on results were not performed because most trials were judged to be at low risk of bias.

Quality of evidence

The quality of evidence for primary and secondary outcomes was assessed using the GRADE approach, which takes into account five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[159] The GRADE approach categorizes the certainty of the evidence into four levels: (1) high: we are very confident that the true effect lies close to that of the estimate of the effect, and further research is unlikely to change our confidence in the estimate of the effect; (2) moderate: we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) low: our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect; and (4) very low: we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

Statistical analyses were performed using Review Manager (Version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect (Version 3.2.8; StatsDirect Ltd, Cheshire, United Kingdom). The quality of evidence was assessed using GRADEpro GDT (GRADEpro Guideline Development Tool [Software]; McMaster University, Hamilton, Canada).

RESULTS

Selection, characteristics and risk of bias of studies

Figure 1 summarizes the process of identification and selection of studies. Twelve studies,[160–171] which included 4687 women and 7167 fetuses/infants, met the inclusion criteria: 8 evaluated pessary vs no pessary in women with a short cervix (6 in singleton gestations[160–165] and 2 in twin gestations[169,170]), 2 assessed pessary vs no pessary in unselected multiple gestations (1 in twin gestations[168] and another in both twin and triplet gestations[167]), and 2 compared pessary vs vaginal progesterone in women with a short cervix (1 in singleton gestations[166] and another in twin gestations[171]). The study by Liem et al[167] did not report outcome data separately for twin and triplet gestations. Data on child neurodevelopmental outcomes for that trial were reported in two additional publications.[172,173] We obtained additional unpublished data for the two largest trials in singleton[162] and twin gestations.[168]

The main characteristics of the studies included in the systematic review are shown in Table 1. Ten trials were specifically designed to evaluate the use of cervical pessary in women with a short cervix (defined as cervical length ≤25 mm,[160,162–166,169] <25 mm,[161] ≤30 mm,[170] and <38 mm[171]). The remaining two studies[167,168] tested the effect of cervical pessary in women with unselected multiple gestations but also reported results for subgroups of women with a short cervix (defined as cervical length <38 mm[167] and ≤25 mm[168]).

Cervical length at trial entry was measured in all women enrolled in the trial by Nicolaides et al,[168] and in 76.4% of women in the trial by Liem et al[167] (81.4% in the

pessary group vs 71.5% in the no pessary group, $P = 0.0009$). The mean or median gestational age at trial entry was 23.5 weeks in one study,[162] between 21–22 weeks in 8 studies,[160,161,164–166,168–170] 19.6 weeks in one study,[163] and about 17.4 weeks in two studies.[167,171] Among studies in singleton gestations, the mean or median cervical length at randomization was about 20 mm in six studies [160–163,165,166] and 12 mm in the remaining study.[164] Among studies in multiple gestations, the mean or median cervical length at randomization was about 20 mm in two studies,[169,170] about 32 mm in two studies,[168,171] and 44 mm in one study.[167]

Ten studies used the Arabin pessary[160–164,166–169,171] and two the Bioteque cup pessary.[165,170] Pessary removal was scheduled for 37 weeks of gestation in nine studies,[160–166,168,169] and 36 weeks of gestation in the remaining three studies.[167,170,171] The main indications for early pessary removal included preterm labor not responding to tocolytic therapy, active vaginal bleeding, PPROM, severe patient discomfort, and patient request (Supplemental Table 1). The frequency of pessary removal before schedule ranged from 0.5%[160] to 51.7%[165] in singleton gestations, and from 2.9%[169] to 69.6%[170] in multiple gestations (Supplemental Table 2).

Vaginal progesterone was concomitantly used in six of the 10 studies that compared pessary vs no pessary.[162–165,168,170] The proportion of patients who received vaginal progesterone simultaneously with a pessary was ≥86% in three studies,[163–165] 45.4% in one study,[162] 6.5% in another,[170] and 0.2% in the remaining study.[168] The primary outcome was spontaneous preterm birth <34 weeks of gestation in six trials, [160,162,164,166,168,169] any preterm birth <34 weeks of gestation in three trials,[161,170,171] any preterm birth <37 weeks of gestation in two trials,[163,165] and a composite adverse perinatal outcome in one trial.[167]

Among the 10 studies that compared pessary vs no pessary, seven (four in singleton gestations[161–163,165] and three in multiple gestations[167,168,170]) reported that there were no significant differences between the study groups in the risk of preterm birth and adverse perinatal outcomes. Two studies performed in singleton gestations with a short cervix showed that pessary use was associated with a significant decrease in the risk of preterm birth and adverse perinatal outcomes.[160,164] The remaining study, performed in twin gestations with a short cervix, reported that pessary significantly reduced the risk of spontaneous preterm birth <34 weeks but had no effect on neonatal morbidity and mortality.[169] The two trials that compared pessary and vaginal progesterone in singleton[166] and twin[171] gestations with a short cervix did not report significant differences in the frequency of the primary outcome between the study groups.

Ten studies[160–169] were deemed to be at low risk of bias for all domains of the RoB 2 tool (Figure 2). Two studies were judged as having “some concerns” in the domain of bias arising from the randomization process.[170,171] In the study of Berghella et al,[170] there was an excess in statistically or marginally significant differences in baseline characteristics between intervention groups, whereas in the study by Dang et al[171] there was imbalance in some key prognostic factors – this is unlikely to be due to chance. The between-group difference is large enough to result in bias in the intervention effect size estimate. The study by Dang et al[171] was also considered to have “some concerns” in the domain of

bias in selection of the reported result because we detected serious discrepancies between the trial report and the protocol posted in clinicaltrials.gov,[174] which strongly suggest that a subgroup analysis according to cervical length was not prespecified but was conducted post-hoc.[175] In addition, it is implausible that no woman enrolled in this trial had a cervical length <18 mm, which suggests that there was a bias in the execution of this study. Overall, this trial was judged to be at high risk of bias.

Pessary vs no pessary in singleton gestations with a cervical length ≤25 mm

Six studies, with a total of 1982 women, compared pessary vs no pessary in singleton gestations with a cervical length ≤25 mm.[160–165] The placement of a pessary was not associated with a significant reduction in the risk of spontaneous preterm birth <34 weeks (11.3% vs 15.0%; RR 0.80, 95% CI 0.43–1.49; P=0.48; I^2=81%; low-quality evidence; 95% prediction interval of the RR, 0.13–5.00) (Figure 3). There were no significant differences between the pessary and no pessary groups in the risk of spontaneous preterm birth <37, <32, and <28 weeks of gestation, and any preterm birth <37, <34, <32, and <28 weeks of gestation (RRs from 0.71–1.21; low- to moderate-quality evidence for most outcomes) (Table 2). The mean gestational age at delivery did not significantly differ between the study groups (mean difference 0.87 weeks, 95% CI −0.52 to 2.26; P=0.22; 5 studies,[1–5] 1864 women; I^2=93%; low-quality evidence).

The use of pessary was associated with an increased risk of both vaginal discharge (RR 2.15, 95% CI 1.67–2.78; NNT for harm 3, 95% CI 2–3; 95% prediction interval of the RR, 1.04–4.45) and pelvic discomfort (RR 3.28, 95% CI 1.96–5.50; NNT for harm 16, 95% CI 11–26; 95% prediction interval of the RR, 1.96–5.49) (high-quality evidence for both outcomes). One study,[160] reported that pessary significantly reduced the frequency of tocolytic agents use (RR 0.63, 95% CI 0.50–0.81; NNT for benefit 5, 95% CI 3–10; moderate-quality evidence). There were no significant differences between the pessary and no pessary groups in other pregnancy and maternal outcomes, as well as in adverse perinatal outcomes (low-quality evidence for most outcomes).

Subgroup analyses of the effect of pessary on spontaneous preterm birth <34 weeks among singleton gestations with a cervical length ≤25 mm according to prespecified variables are presented in Table 3. Overall, there was no evidence of a different effect related to concomitant use of vaginal progesterone (P for interaction=0.70), history of preterm birth (P for interaction=0.24), and cervical length (P for interaction=0.68). The frequency of spontaneous preterm birth <34 weeks was comparable in women who received a pessary plus vaginal progesterone and those who received only vaginal progesterone (15.2% vs 16.1%; RR 0.91, 95% CI 0.47–1.76). In addition, pessary was associated with a non-significant reduction in the risk of spontaneous preterm birth <34 weeks of gestation in women with at least 1 previous preterm birth (RR 0.53, 95% CI 0.23–1.20) and women with a cervical length ≤10 mm (RR 0.58, 95% CI 0.10–3.23).

Pessary vs no pessary in unselected multiple gestations

Two studies (1985 women and 3988 fetuses/infants) evaluated pessary vs no pessary in unselected multiple gestations: one in twin gestations (1177 women and 2354 fetuses/

infants)[168] and the other in both twin (790 women and 1580 fetuses/infants) and triplet (18 women and 54 fetuses/infants) gestations.[167] The frequencies of spontaneous preterm birth and any preterm birth <34, <37, <32, and <28 weeks of gestation did not significantly differ between the study groups (most RRs from 0.92–1.07; high-quality evidence for preterm birth <37 weeks, moderate-quality evidence for preterm birth <34 and <32 weeks, and low- to moderate-quality evidence por preterm birth <28 weeks) (Table 4).

The risk of both vaginal discharge (RR 2.96, 95% CI 2.46–3.57; NNT for harm 4, 95% CI 4–5) and cesarean delivery (RR 1.13, 95% CI 1.06–1.21; NNT for harm 13, 95% CI 8–29) was significantly higher in the pessary group than in the no pessary group (high-quality evidence for both outcomes). There were no significant differences between the pessary and no pessary groups in adverse perinatal outcomes (moderate-quality evidence for most outcomes).

Pessary vs no pessary in twin gestations with a cervical length <38 mm

Four studies (1261 women and 2524 fetuses/infants) provided data for this comparison: Liem et al[167] (133 women [131 with a twin gestation and 2 with a triplet gestation] with a cervical length <38 mm and 268 fetuses/infants); Nicolaides et al[168] (948 women with a cervical length <38 mm and 1896 fetuses/infants); Goya et al[169] (134 women with a cervical length ≤25 mm and 268 fetuses/infants); and Berghella et al[170] (46 women with a cervical length ≤30 mm and 92 fetuses/infants).

For the purpose of this meta-analysis, the two triplet gestations (1 each in the pessary and no pessary groups) in the study by Liem et al[167] were considered as twin gestations. There was no significant difference between the pessary and no pessary groups in the risk of spontaneous preterm birth <34 weeks (RR 0.75, 95% CI 0.41–1.36; I^2=69%; low-quality evidence; 95% prediction interval of the RR, 0.11–5.37). No significant differences were observed between the two study groups in mean gestational age at delivery and frequencies of preterm birth <37, <34, <32, and <28 weeks of gestation (low- to moderate-quality evidence for most outcomes).

The placement of a pessary was associated with a significant reduction in the use of tocolytic agents (RR 0.69, 95% CI 0.49–0.98; NNT for benefit 8, 95% CI 4–59), and a significant increase in the risk of vaginal discharge (RR 1.93, 95% CI 1.66–2.23; NNT for harm 4, 95% CI 3–5; 95% prediction interval of the RR, 1.67–2.24) (high-quality evidence for both outcomes). There were no significant differences between the study groups in other adverse pregnancy, maternal, and perinatal outcomes (low- to moderate-quality evidence for most outcomes).

Pessary vs no pessary in twin gestations with a cervical length ≤25 mm

Two studies (348 women and 696 fetuses/infants) reported data for this comparison: Nicolaides et al[168] (214 women and 428 fetuses/infants); and Goya et al[169] (134 women and 268 fetuses/infants). There were no significant differences between the pessary and no pessary groups in the risk of spontaneous preterm birth and any preterm birth <34, <37, <32, and <28 weeks of gestation, adverse pregnancy and perinatal outcomes, and most adverse maternal outcomes (low-quality evidence for most outcomes).

Both vaginal discharge (RR 1.86, 95% CI 1.51–2.28; NNT for harm 3, 95% CI 2–5; high-quality evidence) and vaginal infection (RR 1.96, 95% CI 1.01–3.79; NNT for harm 8, 95% CI 4–147; moderate-quality evidence) were significantly more frequent in the pessary group than in the no pessary group. A subgroup analysis performed with data from 1 study[168] showed that the effect of pessary on spontaneous preterm birth <34 weeks of gestation did not significantly differ between women with a cervical length ≤10 mm (RR 0.92, 95% CI 0.53–1.57) and those with a cervical length between 11–25 mm (RR 1.29, 95% CI 0.77–2,16) (*P* for interaction=0.37).

Pessary vs vaginal progesterone in singleton gestations with a cervical length ≤25 mm

A randomized, non-inferiority trial at low risk of bias compared the efficacy of pessary and vaginal progesterone (200 mg/day) in 254 women with a singleton gestation and a cervical length ≤25 mm at 19–22 weeks of gestation.[166] The frequency of spontaneous preterm birth <34 weeks was very similar in the pessary and vaginal progesterone groups (14.2% vs 14.3; RR 0.99, 95% CI 0.54–1.83; low-quality evidence).

Pessary was not non-inferior to vaginal progesterone because the range of risk difference (−8.9% to 8.6%) fell outside the predefined margin (4%). There were no significant differences between the study groups in spontaneous preterm birth <37 weeks (RR 1.02, 95% CI 0.63–1.65) and <28 weeks (RR 1.05, 95% CI 0.44–2.49), perinatal death (RR 1.89, 95% CI 0.48–7.38), and composite adverse neonatal outcome (RR 1.13, 95% CI 0.66–1.94) (low-quality evidence for all). The risks of vaginal discharge (RR 1.22, 95% CI 1.07–1.40) and vaginal discomfort (RR 8.02, 95% CI 2.94–21.92) were significantly higher in the pessary group than in the vaginal progesterone group (high-quality evidence for both).

Pessary vs vaginal progesterone in twin gestations with a cervical length <38 mm

A trial at high risk of bias evaluated the efficacy and safety of pessary vs vaginal progesterone (400 mg/day) in 300 women with a twin gestation and a cervical length <38 mm at 16–22 weeks of gestation.[171] In that trial, no woman had a cervical length <18 mm, and 94% of women conceived after fertilization in vitro, which compromises its external validity. There was no significant difference between the pessary and vaginal progesterone groups in the risk of the primary outcome of preterm birth <34 weeks (16.2% vs 22.1%; RR 0.73, 95% CI 0.46–1.18; very low-quality evidence). The use of pessary significantly reduced the risk of preterm birth <37 weeks (RR 0.81, 95% CI 0.66–0.99), birthweight <2500 g (RR 0.80, 95% CI 0.69–0.92), composite adverse perinatal outcome (RR 0.70, 95% CI 0.43–0.93), RDS (RR 0.63, 95% CI 0.37–0.94), neonatal sepsis (RR 0.52, 95% CI 0.27–0.90), and admission to the NICU (RR 0.59, 95% CI 0.35–0.82) (low-quality evidence for all). The risk of vaginal discharge was significantly higher in the pessary group than in the vaginal progesterone group (RR 2.91, 95% CI 2.15–3.94; low-quality evidence).

In a subgroup analysis among women with a cervical length between 18 and 28 mm (N=82), which appears to be post-hoc, pessary was associated with a significant decrease in the risk of preterm birth <34 weeks of gestation (RR, 0.47, 95% CI 0.24–0.90) and several adverse neonatal outcomes.

Effect of pessary on long-term neurodevelopmental and health outcomes

Thus far, only 1 study has evaluated the effects of pessary on infants' long-term neurodevelopmental and health outcomes.[167] In 2019, a follow-up study of the trial that compared pessary and no pessary in unselected multiple gestations[167] reported the long-term neurodevelopmental and health outcomes of 514 surviving infants at 4 years of age (32.9% of surviving infants at the end of trial).[173] There were no significant between-group differences in the risk of developmental delay (odds ratio [OR] 1.54, 95% CI 0.83–2.85), behavioral problems (OR 1.37, 95% CI 0.66–2.82), and physical problems (OR 1.28, 95% CI 0.57–2.91). The frequency of an abnormal childhood outcome (a composite of the 3 above outcomes) was 22.8% in the pessary group vs 15.9% in the no pessary group (OR 1.58, 95% CI 0.94–2.65). There were also no significant differences in these outcome measures between the pessary (N=85) and no pessary (N=34) groups in the subgroup of children whose mothers had a cervical length <38 mm.

Previously, another follow-up study[172] from the same trial[167] reported that, among 173 surviving children born to mothers with a cervical length <38 mm, the frequency of neurodevelopmental disability at 3 years of corrected age did not differ significantly between the study groups (OR 1.43, 95% CI 0.38–5.40).

COMMENT

Principal findings of the study

The pooled evidence of this systematic review shows that, to date, (1) cervical pessary is not an effective intervention for reducing preterm birth and adverse perinatal outcomes in asymptomatic women with a singleton or twin gestation and a midtrimester sonographic cervical length ≤25 mm, a twin gestation and a midtrimester sonographic cervical length <38 mm, or unselected twin gestations; (2) among women with a singleton gestation and a cervical length ≤25 mm who receive vaginal progesterone, there is no added benefit of placing a cervical pessary; (3) there is insufficient evidence to determine whether cervical pessary is at least as effective as vaginal progesterone in preventing preterm birth and improving perinatal outcomes in women with a singleton or twin gestation and a sonographic short cervix in the midtrimester; (4) cervical pessary appears to be safe for women although it increases the frequency of vaginal discharge; and (5) at least until 4 years of age, there are no significant differences in neurodevelopmental and health outcomes between children born to mothers who received a pessary and those born to mothers who did not receive a pessary.

There was substantial between-trial heterogeneity in about one-half of the meta-analyses performed in the population of women with a singleton or twin gestation and a short cervix. If heterogeneity is identified among a group of trials considered suitable for meta-analysis, one of the available options is to not do the meta-analysis.[148] Nevertheless, we agree with the view that any degree of statistical heterogeneity would be acceptable,[176] and we considered that, even in the presence of substantial heterogeneity, an estimate of the average effect of cervical pessary across studies and the statistical significance of this effect would be worth reporting to clinicians. Then, despite the small number of trials included in the

meta-analyses, we explored the sources of heterogeneity as thoroughly as possible and were unable to identify plausible explanations. We used random effects models to incorporate heterogeneity among studies that cannot readily be explained by other factors. This approach provides the most useful and conservative estimate for informing practice in the presence of unexplained heterogeneity. In addition, we also calculated 95% prediction intervals as an alternative way of expressing the amount of heterogeneity in a meta-analysis.

Explaining conflicting results among trials that compared pessary vs no pessary

Several reasons have been proposed to explain the conflicting results among trials comparing pessary vs no pessary.[136,138,177–179] First, a high frequency of early pessary removal could explain the negative results of some trials and vice versa. This explanation would not apply to the study by Liem et al,[167] which showed beneficial effects of pessary in the subgroup of women with a cervical length <38 mm despite a high frequency of early pessary removal before 32 weeks of gestation in the overall population (19.7%). It would also not apply to the study by Hui et al[161] in which pessary had no beneficial effects despite a low frequency of early pessary removal (3.8%). Second, unsupervised training with inadequate placement of the pessary could explain the negative results of some trials. This explanation would not apply to the trial by Liem et al[167] because no specific training about placement of the pessary was provided, and there was a beneficial effect of this intervention in the subgroup of women with a cervical length <38 mm. On the other hand, the trials by Dugoff et al[165] and Berghella et al[170] reported negative results despite pessary insertion training that consisted of a didactic session and a hands-on session, and all staff were required to demonstrate competence in pessary placement on a live model. Finally, it has been repeatedly claimed that pessaries have the advantage that they are operator-independent, non-invasive, and easy to place and remove when required.[129–131,138,160,164,167,169]

Third, the concomitant administration of vaginal progesterone to participants could have attenuated benefits from the pessary. The subgroup analysis according to concomitant administration of vaginal progesterone in singleton gestations with a cervical length ≤25 mm suggested that the response to pessary did not significantly differ between women who received vaginal progesterone and those who did not (*P* for interaction=0.70). Nevertheless, this point of view could be feasible, since pessary was associated with a 30% non-significant reduction in the risk of spontaneous preterm birth <34 weeks of gestation among women who did not concomitantly receive vaginal progesterone, whereas the reduction was only 9% among women who concomitantly received vaginal progesterone (Table 3). Fourth, suboptimal serial cervical length monitoring at follow-up to detect cervical shortening could account for negative results in some trials. This explanation would not apply to the trials by Nicolaides et al,[162,168] Hui et al,[161] and Karbasian et al,[163] which reported negative results even though cervical length was routinely measured every 4 weeks until 34 weeks of gestation. Finally, it has been suggested that a pessary might be beneficial when placed earlier in pregnancy. This explanation would not apply to the studies by Goya et al,[160,169] and Saccone et al[164] in which pessary was placed at a mean gestational age of ~22.3 weeks and had beneficial effects.

Cervical pessary plus vaginal progesterone vs vaginal progesterone alone in women with a short cervix

Based on results from some non-randomized studies, it has been suggested that the combined use of cervical pessary and vaginal progesterone could be superior to vaginal progesterone alone for the prevention of preterm birth in asymptomatic women with a singleton or twin gestation and a short cervix.[180–182] By contrast, in the present meta-analysis, a prespecified subgroup analysis including a total of 825 women with a singleton gestation and a cervical length ≤25 mm, showed only a slight difference in the frequency of spontaneous preterm birth <34 weeks of gestation between women who concomitantly used cervical pessary and vaginal progesterone and those who used only vaginal progesterone (15.2% vs 16.1%; P=0.78). Remarkably, the frequency of spontaneous preterm birth <34 weeks of gestation in women who received only vaginal progesterone was very similar to that observed in women who received vaginal progesterone (15%) in the individual patient data meta-analysis by Romero et al[107] that compared vaginal progesterone vs placebo in singleton gestations with a cervical length ≤25 mm. In addition, the trial by Karbasian et al,[163] which was specifically designed to compare the combined use of cervical pessary and vaginal progesterone vs vaginal progesterone alone in singleton gestations with a cervical length ≤25 mm, did not find any significant differences in the risk of preterm birth and adverse perinatal outcomes between the study groups. In summary, thus far, the combined use of cervical pessary and vaginal progesterone is not superior to using vaginal progesterone alone for preventing preterm birth and adverse perinatal outcomes in patients with a singleton gestation and a short cervix.

Quality of evidence

Overall, the quality of evidence according to the GRADE methodology was judged as moderate to low for most outcomes, which means that our confidence in the effect estimate is moderate at best and the true effect may be different from the estimate of the effect. Thereby, further research may change the effect estimates, which is supported by the wide 95% prediction intervals of the RRs for the primary outcome in singleton gestations with a cervical length ≤25 mm (0.13 to 5.00) and twin gestations with a cervical length <38 mm (0.11 to 5.37). However, it should be noted that the prediction interval can be imprecise if the number of studies in the meta-analysis is small.[155]

Strengths and limitations

The reliability and robustness of our systematic review are supported by (1) the rigorous methodology used in its conduction and the strict adherence to the guidelines included in the new edition of the Cochrane Handbook for Systematic Reviews of Interventions;[144] (2) the risk of bias assessment of trials included in the review, which was based on the updated RoB 2 tool;[146,147] (3) the exploration of potential sources of heterogeneity; (4) the calculation of 95% prediction intervals that estimate where the true effects are to be expected for similar ongoing or planned trials; (5) the performance of subgroup analyses in an attempt to identify specific groups of women in whom pessary could be beneficial; (6) the assessment of the potential effect of the use of concomitant co-interventions, such as vaginal progesterone, on the efficacy of cervical pessary; (7) the assessment of the efficacy of cervical pessary in 4

groups of asymptomatic women considered at high risk for preterm birth; (8) the inclusion of additional unpublished data from the two largest trials; and (9) the overall low risk of bias of most trials included in the review.

Our review is subject to some potential limitations: (1) as previously discussed, we were unable to provide explanations for the substantial statistical heterogeneity found in several of the meta-analyses performed; (2) only a few trials reported data for the prespecified subgroup analyses according to cervical length and obstetric history. As a result, our analysis has limitations in its power to estimate the effects of cervical pessary within these subgroups; (3) the number of trials that compared cervical pessary vs vaginal progesterone in patients with a short cervix is still small for us to draw definitive conclusions; (4) several trials did not report results for some outcome measures that were assessed in our systematic review. It is possible that, if these results were reported more consistently, the effect sizes might be somewhat different; (5) the performance of multiple analyses could increase the risk of type I error in our systematic review. However, the likelihood of type I errors in our meta-analyses is low because we found only a few statistically significant results, most of which appear to be real differences between the pessary and no pessary groups; and (6) a considerable number of results were based on a single study and some secondary outcomes had a limited statistical power.

Recently, the main results of the STOPPIT-2 trial were published in abstract form.[183] In this study, women with a twin gestation and a midtrimester cervical length ≤35 mm were randomized either to Arabin pessary (N=250) or to standard care (no pessary) (N=253). There were no significant differences between the pessary and no pessary groups in the frequency of spontaneous preterm birth <34 weeks of gestation (18.4% vs 20.6%, P=0.54) and a composite of adverse perinatal outcomes (11.5% vs 12.7%, P=0.48). The inclusion of the results of this trial in the meta-analyses on the effect of pessary in twin gestations with a cervical length <38 mm reaffirms our conclusion that this intervention is not effective for reducing spontaneous preterm birth <34 weeks (pooled RR 0.81, 95% CI 0.57–1.15) and adverse perinatal outcomes (pooled adjusted RR 0.92, 95% CI 0.64–1.32) in this high-risk population.

Implications for practice and research

Current evidence does not support the use of cervical pessary to prevent preterm birth or improve perinatal outcomes in singleton or twin gestations with a short cervix and in unselected twin gestations. In addition, among patients with a singleton gestation and a short cervix who receive vaginal progesterone, a cervical pessary should not be placed given that the device does not offer any additional benefits over administration of vaginal progesterone alone in reducing preterm birth and adverse perinatal outcomes.

Further research is required before conclusive advice can be provided regarding the benefits of placing a cervical pessary in women at high risk for preterm birth. We identified 22 planned, ongoing, or completed trials of pessary placement for the prevention of preterm birth in asymptomatic high-risk women in the main clinical trial registry databases. The results of these trials could significantly change the results of our review because the quality level of the summary estimates was moderate to low as assessed by GRADE.

Moreover, these trials will provide information as to whether cervical pessary is effective for preventing preterm birth in women with a singleton gestation and a short cervix who do not concomitantly use vaginal progesterone, or in the subgroups of women with a singleton gestation, short cervix, and at least 1 previous preterm birth or a cervical length ≤10 mm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a Glance

Why was the study conducted?

To determine whether the placement of a cervical pessary in asymptomatic women at risk for preterm delivery (with singleton or multiple gestations) prevents preterm birth and improves perinatal outcomes.

Key findings

- The placement of a cervical pessary did not reduce the risk of preterm birth (<37, <34, <32, and <28 weeks of gestation) or adverse perinatal outcomes in women with:
  - Singleton gestations and a cervical length ≤25 mm
  - Unselected twin gestations
  - Twin gestations and a cervical length <38 mm
  - Twin gestations and a cervical length ≤25 mm
- There were no significant differences in the risk of spontaneous preterm birth <34 weeks of gestation between pessary and vaginal progesterone in women with a singleton gestation and a cervical length ≤25 mm, and women with a twin gestation and a cervical length <38 mm

What does this study add to what is known?

This systematic review and meta-analysis does not support the use of cervical pessary to prevent preterm birth in asymptomatic women with singleton or twin gestations at risk for preterm delivery.

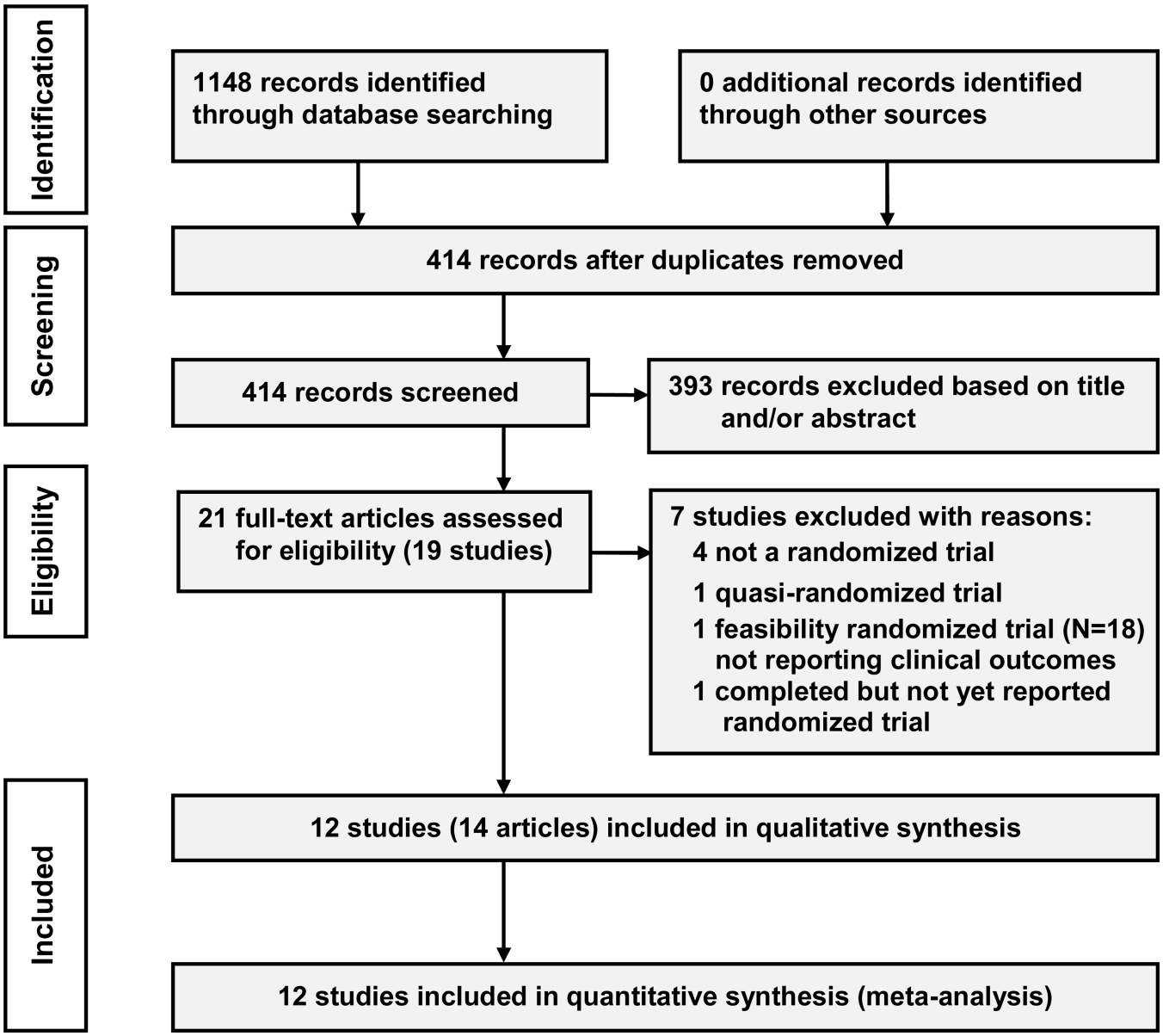

Figure 1:
Summary of evidence search and selection

Figure 2:
Risk of bias in each included study

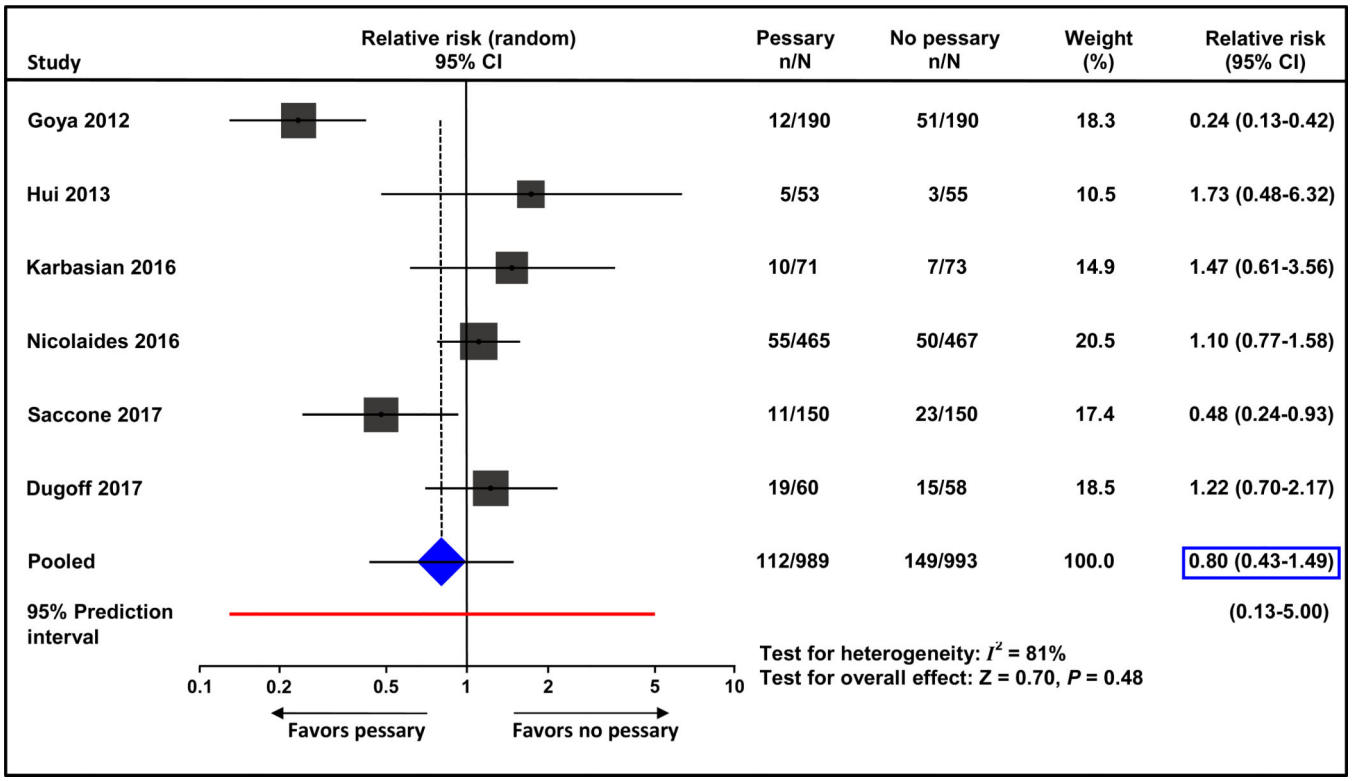

Figure 3:

Effect of cervical pessary on spontaneous preterm birth <34 weeks of gestation in singleton gestations with a cervical length ≤25 mm

CI, confidence interval

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TABLE 1

Characteristics of studies included in the systematic review

First author, reference, year (country)	Participants	Interventions (sample size)	GA at trial entry, wk	Cervical length at trial entry, mm	Concomitant use of vaginal progesterone	Primary outcome	Main findings
Singleton gestations							
Goya,[160] 2012 (Spain)	Women with a singleton gestation and a cervical length ≤25 mm	• Arabin pessary (n = 190) • No pessary (n = 190)	20–23; mean, 22.3	19.0 ± 4.8	Pessary group: 0% No pessary group: 0%	Spontaneous PTB < 34 wk	Cervical pessary significantly reduced PTB and adverse perinatal outcomes
Hui,[161] 2013 (China)	Women with a singleton gestation and a cervical length <25 mm	• Arabin pessary (n = 53) • No pessary (n = 55)	20–24; mean, 21.9	20.1 ± 0.5	Pessary group: 0% No pessary group: 0%	PTB <34 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Nicoiaides,[162] 2016 (Muiticountry[a])	Women with a singleton gestation and a cervical length ≤25 mm	• Arabin pessary (n = 465) • No pessary (n = 467)	20–24; median, 23.5	20.0 (14.0—22.0)[b]	Pessary group: 44% No pessary group: 47%	Spontaneous PTB < 34 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Karbasian,[163] 2016 (Iran)	Women with a singleton gestation and a cervical length ≤25 mm	• Arabin pessary plus vaginal progesterone 400 mg/d (n = 71) • Vaginal progesterone 400 mg/d (n = 73)	18–22; mean, 19.6	22.0 ± 1.7	Pessary group: 100% No pessary group: 100%	PTB <37 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Saccone,[164] 20 1 7 (Itaiy)	Women with a singleton gestation, no previous spontaneous PTB, and a cervical length ≤25 mm	• Arabin pessary (n = 150) • No pessary (n = 150)	18–23; mean, 22.4	12.0 ± 5.8	Pessary group: 89% No pessary group: 83%	Spontaneous PTB < 34 wk	Pessary significantly reduced PTB and adverse perinatal outcomes
Dugoff,[165] 2018 (United States)	Women with a singleton gestation, no previous spontaneous PTB, and a cervical length ≤25 mm	• Bioteque cup pessary (n = 60) • No pessary (n = 58)	18–23; mean, 21.1	Pessary group: 17.6 (10.9—22.0)[b] No pessary group: 19.0 (11.2—22.9)[b]	Pessary group: 84% No pessary group: 91%	PTB <37 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Cruz-Meiguizo,[166] 2018 (Spain)	Women with a singleton gestation and a cervical length ≤25 mm	• Arabin pessary (n = 125) • Vaginal progesterone 200 mg/d (n = 118)	19–22; mean, 21.3	20.9 ± 4.2	Pessary group: 5% Progesterone group: 100%	Spontaneous PTB < 34 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Multiple gestations							
Liem,[167] 2013 (Netherlands)	Women with a multiple gestation (97.8% twins and 2.2% triplets)	• Arabin pessary (n = 401) • No pessary (n = 407)	12–20, mean 17.0	43.9 ± 8.3	Pessary group: 0% No pessary group: 0%	Composite adverse perinatal outcome[c]	There were no significant differences between the study groups in PTB and adverse perinatal outcomes

First author, reference, year (country)	Participants	Interventions (sample size)	GA at trial entry, wk	Cervical length at trial entry, mm	Concomitant use of vaginal progesterone	Primary outcome	Main findings
Nicolaides,[168] 2016 (Multicountry)[d]	Women with a twin gestation	• Arabin pessary (n = 588) • No pessary (n = 589)	20–24; median, 22.7	32.0 (27.0—37.0)[b]	Pessary group: 0% No pessary group: 0.3%	Spontaneous PTB <34 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Goya,[169] 2016 (Spain)	Women with a twin gestation and a cervical length ≤25 mm	• Arabin pessary (n = 68) • No pessary (n = 66)	20–23; mean, 22.3	19.4 ± 3.6	Pessary group: 0% No pessary group: 0%	Spontaneous PTB < 34 wk	Cervical pessary significantly reduced PTB. There was no effect on adverse neonatal outcomes
Berghella,[170] 2017 (United States)	Women with a diamniotic twin gestation and a cervical length ≤30 mm	• Bioteque cup pessary (n = 23) • No pessary (n = 23)	18–27; median, 21.1	Pessary group: 16.7 (10.7—27.8)[b] No pessary group: 22.9 (15.9—25.6)[b]	Pessary group: 4% No pessary group: 9%	PTB <34 wk	There were no significant differences between the study groups in PTB and adverse perinatal outcomes
Dang,[171] 2019 (Vietnam)	Women with a twin gestation and a cervical length <38 mm	• Arabin pessary (n = 148) • Vaginal progesterone 400 mg/d (n = 149)	16–22, mean, 17.8	31.3 ± 4.3	Pessary group: 1% Progesterone group: 100%	PTB <34 wk	There were no significant differences between the study groups in PTB <34 wk. Pessary significantly reduced PTB <37 wk and adverse perinatal outcomes

GA, gestational age; *PTB,* preterm birth.

[a]England, Slovenia, Portugal, Chile, Australia, Italy, Albania, Germany, and Belgium

[b]Median (interquartile range)

[c]Occurrence of any of the following events: stillbirth, periventricular leukomalacia of grade 2 orworse, severe respiratory distress syndrome of grade 2 or worse, bronchopulmonary dysplasia, intraventricular hemorrhage of grade 2B or worse, necrotizing enterocolitis, proven sepsis, and neonatal death within 6 weeks after the expected term date

[d]United Kingdom, Spain, Germany, Austria, Slovenia, Portugal, Italy, Belgium, Albania, China, Brazil, and Chile.

Conde-Agudelo. Cervical pessary to prevent preterm birth in asymptomatic high-risk women. Am J Obstet Gynecol 2020.

TABLE 2.

Effect of cervical pessary on pregnancy, maternal, and perinatal outcomes in singleton gestations with a cervical length ≤25 mm

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Quality of evidence
Pregnancy/maternal outcomes							
Spontaneous preterm birth <37 weeks	4[160,162,164,165]	196/865 (22.7%)	282/865 (32.6%)	0.71 (0.41–1.24)	0.23	91	Low
Spontaneous preterm birth <32 weeks	1[162]	41/465 (8.8%)	34/467 (7.3%)	1.21 (0.78–1.87)	0.39	NA	Low
Spontaneous preterm birth <28 weeks	4[160,162,164,165]	44/865 (5.1%)	52/865 (6.0%)	0.76 (0.37–1.54)	0.44	65	Low
Preterm birth <37 weeks	5[160–162,164,165]	197/799 (24.7%)	205/803 (25.5%)	0.95 (0.75–1.19)	0.64	31	High
Preterm birth <34 weeks	6[160–165]	123/989 (12.4%)	159/993 (16.0%)	0.82 (0.46–1.45)	0.50	81	Low
Preterm birth <32 weeks	3[162–164]	62/686 (9.0%)	56/690 (8.1%)	1.11 (0.78–1.58)	0.57	2	Moderate
Preterm birth <28 weeks	4[161,162,164,165]	46/728 (6.3%)	41/730 (5.6%)	1.08 (0.71–1.65)	0.72	5	Moderate
Chorioamnionitis	5[160,162–165]	18/936 (1.9%)	17/938 (1.8%)	1.04 (0.54–2.00)	0.90	0	Low
PPROM	6[160–165]	103/989 (10.4%)	103/993 (10.4%)	0.90 (0.57–1.42)	0.65	52	Low
Vaginal discharge	5[160–162,164,165]	594/891 (66.7%)	257/895 (28.7%)	2.15 (1.67–2.78)	<0.00001	81	High
Vaginal infection	2[161,162]	138/458 (30.1%)	116/405 (28.6%)	1.04 (0.85–1.28)	0.68	0	Moderate
Vaginal bleeding	2[160,161]	8/243 (3.3%)	9/245 (3.7%)	0.87 (0.35–2.21)	0.78	0	Low
Pelvic discomfort	3[161,162,164]	59/641 (9.2%)	18/647 (2.8%)	3.28 (1.96–5.50)	<0.00001	0	High
Use of tocolytic agents	1[160]	64/190 (33.7%)	101/190 (53.2%)	0.63 (0.50–0.81)	0.0002	NA	Moderate
Cesarean delivery	4[160,162,164,165]	198/865 (22.9%)	192/865 (22.2%)	1.01 (0.81–1.25)	0.96	27	High
Maternal death	3[160,162,164]	0/805 (0.0%)	0/807 (0.0%)	Not estimable	NA	NA	Low
Perinatal outcomes							
Fetal death	6[160–165]	12/989 (1.2%)	12/993 (1.2%)	1.01 (0.44–2.31)	0.98	0	Low
Neonatal death	6[160–165]	13/989 (1.3%)	16/993 (1.6%)	0.83 (0.40–1.72)	0.61	0	Low
Perinatal death	6[160–165]	25/989 (2.5%)	28/993 (2.8%)	0.88 (0.51–1.53)	0.66	1	Moderate
Birthweight <1500 g	3[160,162,164]	58/805 (7.2%)	69/807 (8.6%)	0.71 (0.30–1.68)	0.44	81	Low
Birthweight <2500 g	4[160,162–164]	158/876 (18.0%)	200/880 (22.7%)	0.73 (0.39–1.35)	0.31	88	Low
Apgar score <7 at 5 min	1[162]	27/465 (5.8%)	29/467 (6.2%)	0.94 (0.56–1.55)	0.80	NA	Moderate
Respiratory distress syndrome	5[160–162,164,165]	62/918 (6.8%)	90/920 (9.8%)	0.72 (0.36–1.43)	0.35	73	Low

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Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Quality of evidence
Necrotizing enterocolitis	4[160,162,164,165]	11/865 (1.3%)	10/865 (1.2%)	1.15 (0.47–2.79)	0.76	0	Low
Intraventricular hemorrhage	5[160–162,164,165]	17/918 (1.9%)	14/920 (1.5%)	1.16 (0.48–2.80)	0.73	21	Low
Neonatal sepsis	5[160–162,164,165]	49/918 (5.3%)	56/920 (6.1%)	0.80 (0.46–1.40)	0.44	43	Low
Retinopathy of prematurity	4[160,162,164,165]	8/865 (0.9%)	16/865 (1.8%)	0.51 (0.10–2.59)	0.42	56	Very low
Bronchopulmonary dysplasia	2[164,165]	13/210 (6.2%)	17/208 (8.2%)	0.76 (0.38–1.53)	0.44	0	Low
Any composite adverse neonatal outcome	4[160,162,164,165]	69/865 (8.0%)	114/865 (13.2%)	0.59 (0.28–1.27)	0.18	83	Low
Admission to NICU	4[161–164]	81/739 (11.0%)	82/745 (11.0%)	1.01 (0.64–1.58)	0.97	53	Low
Mechanical ventilation	1[162]	40/465 (8.6%)	33/467 (7.1%)	1.22 (0.78–1.90)	0.38	NA	Moderate

Data are n/N.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

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TABLE 3.

Subgroup analyses of effect of cervical pessary on spontaneous preterm birth <34 weeks in singleton gestations with a cervical length ≤25 mm

Subgroup	No of trials	Pessary	No pessary	Relative risk (95% CI)	I^2, %	Interaction *P* value
Concomitant use of vaginal progesterone						0.70
No	4[160–162,164]	31/521 (6.0%)	67/518 (12.9%)	0.70 (0.23–2.14)	78	
Yes	3[162–164]	62/408 (15.2%)	67/417 (16.1%)	0.91 (0.47–1.76)	67	
Obstetric history						0.24
No previous preterm birth	3[162,164,165]	78/605 (12.9%)	72/591 (12.2%)	0.97 (0.54–1.76)	71	
≥1 previous preterm birth	1[162]	7/70 (10.0%)	16/84 (19.0%)	0.53 (0.23–1.20)	NA	
Cervical length						0.68
≤10 mm	2[162,164]	28/111 (25.2%)	25/83 (30.1%)	0.58 (0.10–3.23)	85	
11–25 mm	2[162,164]	38/504 (7.5%)	48/534 (9.0%)	0.84 (0.56–1.27)	0	

Data are n/N.

CI, confidence interval; *NA*, not applicable.

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TABLE 4.

Effect of cervical pessary on pregnancy, maternal, and perinatal outcomes in unselected multiple gestations

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Pregnancy/maternal outcomes								
Spontaneous preterm birth <34 weeks	1[168]	80/588 (13.6%)	76/589 (12.9%)	1.05 (0.79–1.41)	0.72	NA	NA	Moderate
Spontaneous preterm birth <37 weeks	1[168]	205/588 (34.9%)	197/589 (33.4%)	1.04 (0.89–1.22)	0.61	NA	NA	High
Spontaneous preterm birth <32 weeks	1[168]	42/588 (7.1%)	45/589 (7.6%)	0.93 (0.62–1.40)	0.74	NA	NA	Moderate
Spontaneous preterm birth <28 weeks	1[168]	19/588 (3.2%)	13/589 (2.2%)	1.46 (0.73–2.94)	0.28	NA	NA	Low
Preterm birth <37 weeks	2[167,168]	546/989 (55.2%)	560/996 (56.2%)	0.98 (0.91–1.06)	0.65	0	NA	High
Preterm birth <34 weeks	1[168]	98/588 (16.7%)	92/589 (15.6%)	1.07 (0.82–1.38)	0.63	NA	NA	Moderate
Preterm birth <32 weeks	2[167,168]	93/989 (9.4%)	102/996 (10.2%)	0.92 (0.70–1.20)	0.53	0	NA	Moderate
Preterm birth <28 weeks	2[167,168]	35/989 (3.5%)	36/996 (3.6%)	0.98 (0.60–1.59)	0.93	10	NA	Moderate
Chorioamnionitis	2[167,168]	16/989 (1.6%)	15/996 (1.5%)	1.06 (0.52–2.14)	0.88	0	NA	Low
PPROM	2[167,168]	143/989 (14.5%)	125/996 (12.6%)	1.15 (0.92–1.44)	0.21	0	NA	Moderate
Vaginal discharge	2[167,168]	342/966 (35.4%)	115/970 (11.9%)	2.96 (2.46–3.57)[b]	<0.0001	96	NA	High
Vaginal infection	1[168]	116/555 (20.9%)	86/511 (16.8%)	1.24 (0.97–1.60)	0.09	NA	NA	Moderate
Pelvic discomfort	1[168]	33/565 (5.8%)	29/563 (5.2%)	1.13 (0.70–1.84)	0.61	NA	NA	Moderate
Use of tocolytic agents	1[167]	74/401 (18.5%)	92/407 (22.6%)	0.82 (0.62–1.07)	0.15	NA	NA	Moderate
Cesarean delivery	2[167,168]	632/989 (63.9%)	559/996 (56.1%)	1.13 (1.06–1.21)	0.0004	0	NA	High
Maternal death	2[167,168]	1/989 (0.1%)	0/996 (0.0%)	3.04 (0.12–74.52)	0.49	NA	NA	Low
Perinatal outcomes								
Fetal death	2[167,168]	22/1987 (1.1%)	32/2001 (1.6%)	0.69 (0.40–1.19)	0.18	0	0.69 (0.34–1.39)	Moderate
Neonatal death	2[167,168]	40/1987 (2.0%)	42/2001 (2.1%)	0.96 (0.62–1.48)	0.85	0	0.93 (0.54–1.61)	Moderate
Perinatal death	2[167,168]	62/1987 (3.1%)	74/2001 (3.7%)	0.84 (0.61–1.18)	0.32	0	0.87 (0.57–1.33)	Moderate
Birthweight <1500 g	2[167,168]	182/1987 (9.2%)	182/2001 (9.1%)	1.01 (0.83–1.23)	0.94	0	1.00 (0.77–1.29)	Moderate
Birthweight <2500 g	2[167,168]	1106/1987 (55.7%)	1136/2001 (56.8%)	0.98 (0.93–1.04)	0.48	0	0.98 (0.92–1.05)	High
Respiratory distress syndrome	2[167,168]	145/1958 (7.4%)	129/1969 (6.6%)	1.13 (0.90–1.41)	0.31	0	1.14 (0.85–1.53)	Moderate

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Necrotizing enterocolitis	2[167,168]	16/1958 (0.8%)	13/1969 (0.7%)	1.24 (0.60–2.57)	0.56	0	1.28 (0.58–2.81)	Low
Intraventricular hemorrhage	2[167,168]	26/1958 (1.3%)	22/1969 (1.1%)	1.19 (0.67–2.09)	0.55	0	1.19 (0.62–2.31)	Moderate
Neonatal sepsis	21[67,168]	85/1958 (4.3%)	91/1969 (4.6%)	0.94 (0.70–1.25)	0.67	0	0.94 (0.67–1.32)	Moderate
Retinopathy of prematurity	1[168]	12/1147 (1.0%)	3/1146 (0.3%)	4.00 (1.13–14.12)	0.03	NA	3.50 (0.73–16.77)	Low
Bronchopulmonary dysplasia	1[167]	2/811 (0.2%)	9/823 (1.1%)	0.23 (0.05–1.04)	0.06	NA	0.17 (0.02–1.40)	Low
Periventricular leukomalacia	1[167]	0/811 (0.0%)	5/823 (0.6%)	0.09 (0.01–1.67)	0.11	NA	0.11 (0.01–2.09)	Low
Any composite adverse neonatal/perinatal outcome	2[167,168]	196/1958 (10.0%)	192/1969 (9.8%)	1.03 (0.85–1.24)	0.79	0	1.03 (0.81–1.32)	Moderate
Admission to NICU	2[167,168]	457/1987 (23.0%)	466/2001 (23.3%)	0.96 (0.77–1.18)	0.67	60	0.98 (0.82–1.18)	Moderate
Mechanical ventilation	1[168]	114/1147 (9.9%)	97/1146 (8.5%)	1.17 (0.91–1.52)	0.22	NA	1.16 (0.82–1.64)	Moderate

Data are n/N.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

[a]Taking into account the non-independence of perinatal outcomes between twins/triplets.

[b]RR was estimated using fixed effect model because the estimate obtained using random-effects model was unrealistic.

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TABLE 5.

Effect of cervical pessary on pregnancy, maternal, and perinatal outcomes in twin gestations with a cervical length <38 mm

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Pregnancy/maternal outcomes								
Spontaneous preterm birth <34 weeks	3[168–170]	87/577 (15.1%)	99/551 (18.0%)	0.75 (0.41–1.36)	0.34	69	NA	Low
Spontaneous preterm birth <37 weeks	3[168–170]	196/577 (34.0%)	201/551 (36.5%)	0.79 (0.48–1.30)	0.35	74	NA	Low
Spontaneous preterm birth <32 weeks	1[168]	38/486 (7.8%)	42/462 (9.1%)	0.86 (0.57–1.31)	0.48	NA	NA	Moderate
Spontaneous preterm birth <28 weeks	3[168–170]	25/577 (4.3%)	26/551 (4.7%)	0.90 (0.49–1.68)	0.75	18	NA	Moderate
Preterm birth <37 weeks	3[167,168,170]	338/587 (57.6%)	320/540 (59.3%)	0.95 (0.85–1.06)	0.37	18	NA	High
Preterm birth <34 weeks	3[168–170]	104/577 (18.0%)	112/551 (20.3%)	0.80 (0.45–1.42)	0.44	72	NA	Low
Preterm birth <32 weeks	2[167,168]	57/564 (10.1%)	63/517 (12.2%)	0.72 (0.38–1.34)	0.30	62	NA	Low
Preterm birth <28 weeks	3[167,168,170]	24/587 (4.1%)	27/540 (5.0%)	0.71 (0.28–1.82)	0.47	59	NA	Low
Chorioamnionitis	2[169,170]	4/91 (4.4%)	3/89 (3.4%)	1.30 (0.29–5.76)	0.73	0	NA	Low
PPROM	3[168–170]	89/577 (15.4%)	83/551 (15.1%)	0.76 (0.34–1.72)	0.52	49	NA	Low
Vaginal discharge	3[168–170]	285/557 (51.2%)	140/531 (26.4%)	1.93 (1.66–2.23)	<0.0001	0	NA	High
Vaginal infection	1[168]	91/458 (19.9%)	70/400 (17.5%)	1.14 (0.86–1.50)	0.38	NA	NA	Moderate
Pelvic discomfort	1[168]	29/466 (6.2%)	26/442 (5.9%)	1.06 (0.63–1.77)	0.83	NA	NA	Moderate
Use of tocolytic agents	2[167,169]	38/146 (26.0%)	47/121 (38.8%)	0.69 (0.49–0.98)	0.04	0	NA	High
Cesarean delivery	3[168–170]	388/577 (67.2%)	329/551 (59.7%)	1.08 (0.92–1.28)	0.34	24	NA	Moderate
Perinatal outcomes								
Fetal death	3[167–169]	15/1265 (1.2%)	20/1167 (1.7%)	0.71 (0.36–1.38)	0.31	0	0.70 (0.30–1.64)	Low
Neonatal death	4[167–170]	20/1311 (1.5%)	32/1213 (2.6%)	0.56 (0.13–2.35)	0.43	80	0.55 (0.14–2.12)	Low
Perinatal death	3[167–169]	31/1265 (2.5%)	49/1167 (4.2%)	0.42 (0.13–1.31)	0.13	71	0.50 (0.20–1.25)	Low
Birthweight <1500 g	2[168,169]	100/1104 (9.1%)	98/1053 (9.3%)	0.97 (0.72–1.30)	0.84	0	0.97 (0.68–1.38)	Moderate
Birthweight <2500 g	2[168,169]	596/1104 (54.0%)	611/1053 (58.0%)	0.87 (0.68–1.11)	0.26	64	0.89 (0.70–1.12)	Moderate
Respiratory distress syndrome	4[167–170]	123/1286 (9.6%)	102/1183 (8.6%)	1.13 (0.88–1.45)	0.34	0	1.14 (0.82–1.56)	Moderate
Necrotizing enterocolitis	4[167–170]	9/1286 (0.7%)	9/1183 (0.8%)	1.00 (0.40–2.48)	0.99	0	1.00 (0.38–2.63)	Low

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Intraventricular hemorrhage	4[167–170]	19/1286 (1.5%)	21/1183 (1.8%)	0.57 (0.12–2.65)	0.48	54	0.60 (0.15–2.31)	Low
Neonatal sepsis	4[167–170]	74/1286 (5.8%)	62/1183 (5.2%)	1.05 (0.62–1.77)	0.86	19	1.08 (0.57–2.06)	Moderate
Retinopathy of prematurity	3[168–170]	12/1129 (1.1%)	3/1072 (0.3%)	3.40 (1.04–11.09)	0.04	0	3.25 (0.80–13.22)	Low
Bronchopulmonary dysplasia	2[167,170]	4/203 (2.0%)	7/157 (4.5%)	0.59 (0.16–2.20)	0.43	10	0.77 (0.19–3.02)	Low
Periventricular leukomalacia	1[167]	0/157 (0.0%)	1/111 (0.9%)	0.24 (0.01–5.75)	0.38	NA	0.24 (0.01–5.71)	Low
Any composite adverse neonatal/perinatal outcome	4[167–170]	145/1286 (11.3%)	139/1183 (11.7%)	0.86 (0.50–1.49)	0.58	77	0.90 (0.54–1.53)	Low
Admission to NICU	|[168]	301/972 (31.0%)	276/924 (29.9%)	1.05 (0.87–1.28)	0.60	NA	1.04 (0.86–1.24)	High
Mechanical ventilation	1[168]	102/972 (10.5%)	83/924 (9.0%)	1.17 (0.89–1.54)	0.27	NA	1.18 (0.81–1.70)	Moderate

Data are n/N.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

[a]Taking into account the non-independence of perinatal outcomes between twins.

TABLE 6.

Effect of cervical pessary on pregnancy, maternal, and perinatal outcomes in twin gestations with a cervical length ≤25 mm

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Pregnancy/maternal outcomes								
Spontaneous preterm birth <34 weeks	2[168,169]	44/174 (25.3%)	54/174 (31.0%)	0.72 (0.25–2.06)	0.54	87	NA	Low
Spontaneous preterm birth <37 weeks	2[168,169]	102/174 (58.6%)	98/174 (56.3%)	1.01 (0.85–1.20)	0.88	0	NA	High
Spontaneous preterm birth <32 weeks	1[168]	24/106 (22.6%)	22/108 (20.4%)	1.11 (0.67–1.86)	0.69	NA	NA	Low
Spontaneous preterm birth <28 weeks	2[168,169]	18/174 (10.3%)	17/174 (9.8%)	0.93 (0.23–3.71)	0.91	75	NA	Low
Preterm birth <37 weeks	1[168]	72/106 (67.9%)	71/108 (65.7%)	1.03 (0.86–1.25)	0.73	NA	NA	Moderate
Preterm birth <34 weeks	2[168,169]	49/174 (28.2%)	56/174 (32.2%)	0.77 (0.26–2.26)	0.63	89	NA	Low
Preterm birth <32 weeks	1[168]	27/106 (25.5%)	23/108 (21.3%)	1.20 (0.73–1.95)	0.47	NA	NA	Low
Preterm birth <28 weeks	1[168]	14/106 (13.2%)	9/108 (8.3%)	1.58 (0.72–3.50)	0.26	NA	NA	Low
Chorioamnionitis	1[169]	2/68 (2.9%)	2/66 (3.0%)	0.97 (0.14–6.69)	0.98	NA	NA	Low
PPROM	2[168,169]	23/174 (13.2%)	27/174 (15.5%)	0.54 (0.09–3.33)	0.51	67	NA	Low
Vaginal discharge	2[168,169]	102/160 (63.8%)	55/163 (33.7%)	1.86 (1.51–2.28)	<0.0001	0	NA	High
Vaginal infection	1[168]	22/89 (24.7%)	11/87 (12.6%)	1.96 (1.01–3.79)	0.047	NA	NA	Moderate
Vaginal bleeding	1[169]	3/68 (4.4%)	3/66 (4.5%)	0.97 (0.20–4.64)	0.97	NA	NA	Low
Pelvic discomfort	1[168]	6/92 (6.5%)	6/97 (6.2%)	1.05 (0.35–3.15)	0.92	NA	NA	Low
Use of tocolytic agents	1[169]	22/68 (32.4%)	29/66 (43.9%)	0.74 (0.47–1.14)	0.17	NA	NA	Low
Cesarean delivery	2[168,169]	96/174 (55.2%)	92/174 (52.9%)	1.05 (0.87–1.27)	0.59	0	NA	Moderate
Maternal death	2[168,169]	0/174 (0.0%)	0/174 (0.0%)	Not estimable	NA	NA	NA	Low
Perinatal outcomes								
Fetal death	2[168,169]	10/348 (2.9%)	10/348 (2.9%)	0.88 (0.20–3.88)	0.86	28	1.04 (0.35–3.11)	Low
Neonatal death	2[168,169]	10/348 (2.9%)	4/348 (1.1%)	2.55 (0.81–8.00)	0.11	NA	3.05 (0.63–14.82)	Low
Perinatal death	2[168,169]	20/348 (5.8%)	14/348 (4.0%)	0.96 (0.14–6.34)	0.96	48	1.54 (0.65–3.66)	Low
Birthweight <1500 g	2[168,169]	58/348 (16.7%)	53/348 (15.2%)	1.05 (0.63–1.74)	0.86	45	1.11 (0.71–1.73)	Low
Birthweight <2500 g	2[168,169]	196/348 (56.3%)	212/348 (60.9%)	0.89 (0.64–1.22)	0.46	76	0.89 (0.65–1.24)	Low

Outcome	No of trials	Pessary	No pessary	Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Respiratory distress syndrome	2[168,169]	39/328 (11.9%)	35/334 (10.5%)	1.16 (0.76–1.78)	0.49	0	1.20 (0.69–2.07)	Moderate
Necrotizing enterocolitis	2[168,169]	5/328 (1.5%)	4/334 (1.2%)	0.98 (0.08–12.26)	0.99	57	0.89 (0.09–8.84)	Very low
Intraventricular hemorrhage	2[168,169]	8/328 (2.4%)	10/334 (3.0%)	0.55 (0.04–6.96)	0.64	66	0.67 (0.06–7.11)	Very low
Neonatal sepsis	2[168,169]	26/328 (7.9%)	25/334 (7.5%)	1.09 (0.65–1.85)	0.74	0	1.11 (0.60–2.05)	Low
Retinopathy of prematurity	2[168,169]	9/328 (2.7%)	2/334 (0.6%)	4.78 (1.05–21.85)	0.04	NA	5.34 (0.63–45.07)	Low
Any composite adverse neonatal outcome	2[168,169]	42/328 (12.8%)	42/334 (12.6%)	0.98 (0.54–1.76)	0.94	39	1.05 (0.62–1.75)	Low
Admission to NICU	1[168]	86/212 (40.6%)	72/216 (33.3%)	1.22 (0.95–1.56)	0.12	NA	1.23 (0.88–1.72)	Moderate
Mechanical ventilation	1[168]	40/192 (20.8%)	28/204 (13.7%)	1.52 (0.98–2.36)	0.06	NA	1.46 (0.81–2.64)	Moderate

Data are n/N.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

[a]Taking into account the non-independence of perinatal outcomes between twins.