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REVIEW ARTICLE

Cervical pessary for preventing preterm birth in twin pregnancies with short cervical length: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the effectiveness of cervical pessary for preventing spontaneous preterm birth (SPTB) in twin pregnancies with an asymptomatic transvaginal ultrasound cervical length (TVU CL) in the second trimester.

Methods: We performed a meta-analysis including all randomized clinical trials (RCTs) comparing the use of cervical pessary (i.e. intervention group) with expectant management (i.e. control group). The primary outcome was incidence of SPTB <34 weeks.

Results: Three trials, including 481 twin pregnancies with short cervix, were analyzed. Two RCTs defined short cervix as TVU CL ≤25 mm and one as TVU CL ≤38 mm. Pessary was not associated with prevention of SPTB, and the mean gestational age at delivery and the mean latency were similar in the pessary group compared to the control group. Moreover, no benefits were noticed in neonatal outcomes.

Conclusions: Use of the Arabin pessary in twin pregnancies with short TVU CL at 16–24 weeks does not prevent SPTB or improve perinatal outcome.

ARTICLE HISTORY

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KEYWORDS

Meta-analysis; review;
cervix; cerclage;
transvaginal ultrasound



Introduction

Spontaneous preterm birth (SPTB) remains the number one cause of perinatal mortality in many countries, including the United States [1]. Multiple gestations are at increased risk of SPTB [1]. A short cervical length (CL) on transvaginal ultrasound (TVU) has been shown to be a good predictor of SPTB, in both singletons and twins [2].

The cervical pessary is a silicone device that has been used to prevent SPTB. The efficacy of the cervical pessary has been assessed in several populations

including singletons with short CL [3], unselected twins [4,5], twins with short CL [6], and triplet pregnancies [7]. Several randomized clinical trials (RCTs) have been published [3–6], and several are ongoing [7–9]. However, no consensus on use of the cervical pessary in pregnancy or guidelines for management has been assessed.

The aim of this systematic review was to assess the effectiveness of the cervical pessary in preventing SPTB in women with twin gestations with an asymptomatic short CL in the second trimester.

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Methods

Eligibility criteria

The review protocol was established by two investigators (G. S. and V. B.) prior to commencement and was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42016035936).

Two authors (G. S. and A. C.) identified trials by independently searching the electronic databases MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials with the use of a combination of the following text words: "pessary," "cervical," "cervix," "cervical length," "preterm birth," "twins," "randomized trial," "preterm delivery," "prematurity" "clinical," and "insufficiency" from inception of each database until February 2016. Agreement regarding potential relevance was reached by discussion with a third reviewer (S. X.).

Study selection

We included all RCTs comparing the use of cervical pessary (i.e. intervention group) with expectant management (i.e. control group) for prevention of SPTB in twin pregnancies with short CL. Trials on singleton gestations and higher-order multiples other than twin gestations were excluded. Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were also excluded.

Risk of bias

The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias [10].

Two authors (G. S. and A. C.) independently assessed inclusion criteria, risk of bias, and data extraction. Disagreements were resolved by consensus through discussion. Data from each eligible study

were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed, and further resolved by common review of the entire process.

Data extraction

Primary and secondary outcomes were defined before data extraction. The primary outcome was incidence of SPTB <34 weeks. The secondary outcomes were SPTB <37, <32, and <28 weeks, PTB <37, <34, <32, and <28 weeks, mean gestational age (GA) at delivery (in weeks), mean latency (i.e. time from randomization to delivery) (in days), and neonatal outcomes, including incidence of low birth weight (LBW) (i.e. BW <2500 grams), incidence of very LBW (VLBW) (i.e. BW <1500 grams), necrotizing enterocolitis (NEC), sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) (grade 3 or 4), admission to neonatal intensive care unit (NICU), fetal mortality (i.e. fetal death after 20 weeks), neonatal mortality (i.e. death of a live-born baby within the first 28 days of life), and perinatal death (i.e. either fetal mortality or neonatal mortality).

We planned to assess the primary outcome (i.e. incidence of SPTB <34 weeks) in subgroup analyses classifying whole trials by interaction test as described by Cochrane Handbook for Systematic Review of Interventions.10 The subgroup analyses entailed: twins with prior SPTB; twins without prior SPTB; TVU CL ≤ 25 mm; and TVU CL ≤ 20 mm.

Data analysis

The data analysis was completed independently by two authors (G. S. and S. X.) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) [10]. The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. On the contrary, if there was evidence of significant heterogeneity between studies included, a random effect model was used [10].

Potential publication biases were assessed statistically by using Begg's and Egger's tests [10]. p values <0.05 was considered statistically significant. Tests for

funnel plot asymmetry were carried out only with an exploratory aim when the total number of publications included for each outcome was less than 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

The summary measures were reported as relative risk (RR) or as mean differences (MD) with 95% confidence interval (CI).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [11].

Results

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information through the different phases of the review. Five RCTs were assessed for eligibility [3–6,12]. Two trials were excluded since they enrolled singleton gestations with a short CL. Three RCTs, which met the inclusion criteria, were included in the meta-analysis [4–6]. Tests for funnel plot asymmetry were carried out only with an exploratory aim because the total number of publications included for each outcome was less than 10. Despite this, the overall risk of bias of the included trials was low (Figure 2). All of the included studies had a low risk of bias in “random sequence generation,” and “incomplete outcome data.” Adequate methods for allocation of women were used in the three RCTs. Blinding was considered not feasible methodologically given the intervention, and none of the included studies were double-blind. Publication bias, assessed using Begg’s and Egger’s tests, showed no significant bias ($p = 0.89$ and $p = 0.73$, respectively). One author provided unpublished additional data from his trial [4].

Table 1 shows the characteristics of the included trials. The mean GA at randomization was approximately 21 weeks in both groups (pessary group and control group). In all three studies, the pessary was removed by a simple vaginal examination at approximately 37 weeks gestation, or earlier if the women presented with rupture of membranes, vaginal bleeding, or painful uterine contractions. Only in Goya et al. the pessary was not initially removed if preterm rupture of membranes occurred: these women were followed up at the hospital, and if labor began or chorioamnionitis was detected, the pessary was removed [6]. However, only one patient in the pessary group developed preterm premature rupture of membranes [6]. All RCTs used the Arabin pessary (Conformite Europeene marking 0482).

The three trials included twin pregnancies with or without a prior preterm birth. The Spanish RCT

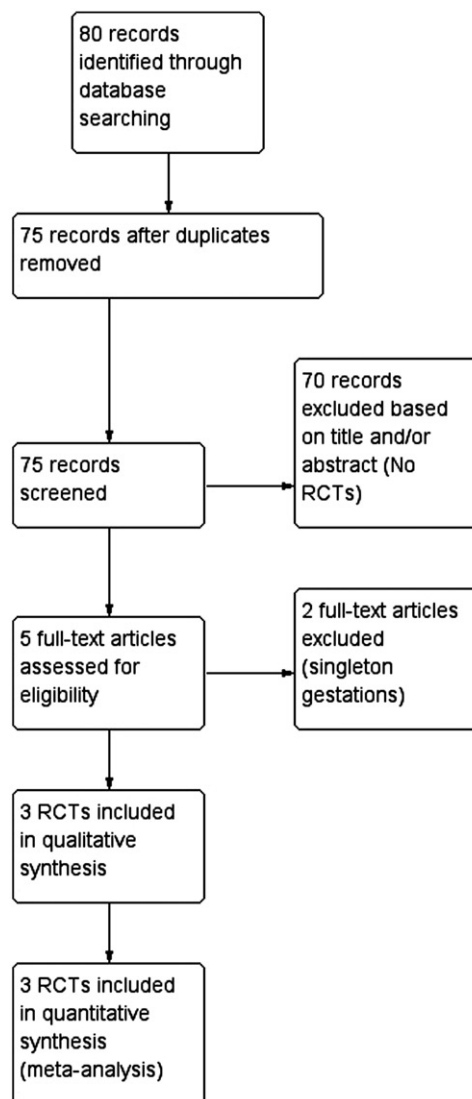


Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [preferred reporting item for systematic reviews and meta-analyses]). RCTs, randomized clinical trials.

enrolled only twin pregnancies with a short CL [6], whereas Nicolaides et al. and Liem et al. enrolled unselected twin pregnancies but performed subgroup analyses in twins with a short CL [4,5]. Only the subsets of women with a short TVU CL were included in the meta-analysis. Two RCTs defined a short CL as TVU CL ≤ 25 mm [4,6], while in the Liem et al.’s trial [5] short cervix was defined as TVU CL ≤ 38 mm. Women with major fetal defects, active vaginal bleeding, placenta previa, twin-to-twin transfusion syndrome or selective fetal growth restriction at the time of the randomization, history of cone biopsy, cervical cerclage *in situ*, painful regular uterine contraction, and ruptured membranes were excluded [4–6].

Regarding the use of progesterone, Goya et al. and Liem et al. did not treat patients with

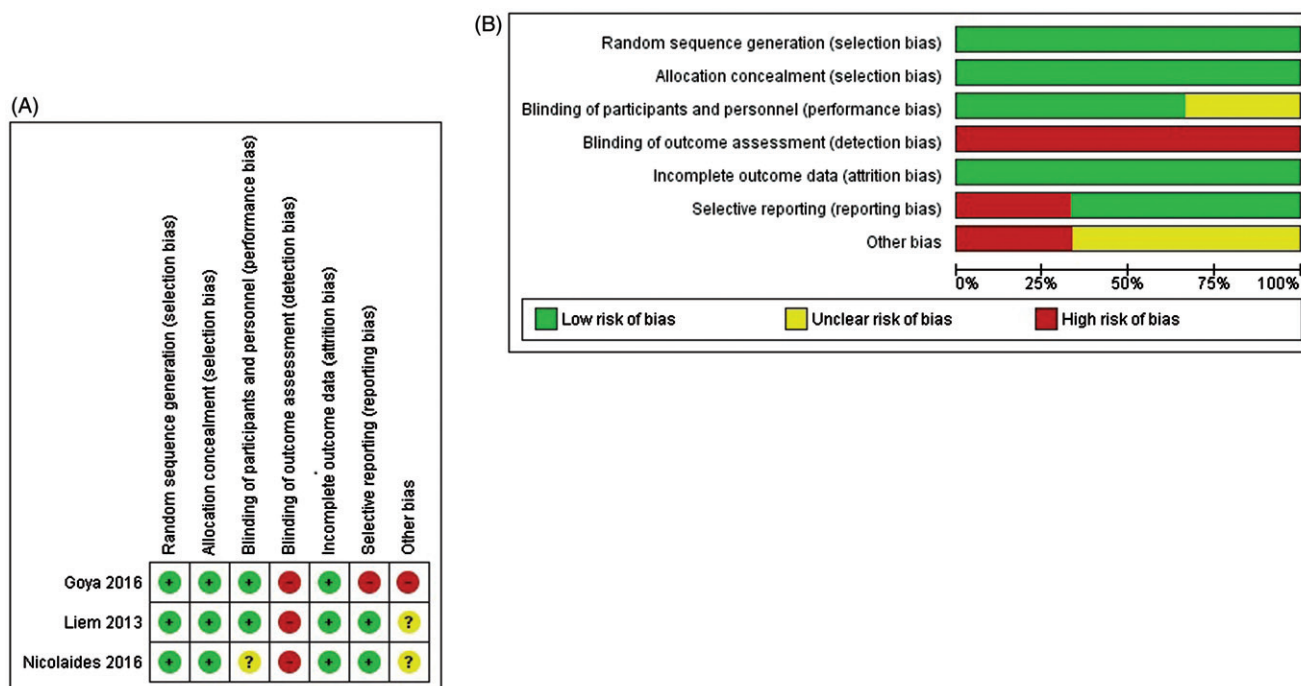


Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Table 1. Descriptive data of the included trials.

	Liem et al. [5]	Nicolaides et al. [4]	Goya et al. [6]
Study location	Netherlands	Multicenter**	Spain
Number of centers	40	23	5
Months of study	30	33	42
Sample size	813 (403 vs. 410)	1,180 (590 vs. 590)	134 (68 vs. 66)
GA at randomization (Range)	16 ⁰ –20 ⁶	20 ⁰ –24 ⁶	18 ⁰ –22 ⁶
GA at randomization (mean ± SD, weeks)	16.9 ± 2.0 vs. 17.0 ± 2.0	22.6 ± 3.2 vs. 22.7 ± 2.8	22.6 ± 3.2 vs. 22.7 ± 2.8
Inclusion criteria	Unselected multiple pregnancies	Unselected twins	Twins with short CL
Monochorionic pregnancy	21.6% vs. 24.4%	18.8% vs. 18.8%	19.1% vs. 17.6%
Definition of short CL	TVU CL ≤ 38mm	TVU CL ≤ 25mm	TVU CL ≤ 25mm
Women with short CL at randomization	133/813 (16.4%)	214/1,180 (18.1%)	134/134 (100%)
Prior SPTB	29/403 (7.2%) vs. 26/410 (6.3%)	20/590 (3.4%) vs. 33/590 (5.6%)	11/68 (16.2%) vs. 12/66 (18.2%)
Type of cervical pessary	Arabin	Arabin	Arabin
Primary outcome	Composite perinatal outcome*	SPTB <34 weeks	SPTB <34 weeks

Data are presented as total number (number in the pessary group vs. number in the control group).

GA, gestational age; CL, cervical length; TVU, transvaginal ultrasound; SPTB, spontaneous preterm birth.

*Composite perinatal outcome, defined as at least one of the following: stillbirth, periventricular leucomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, proven sepsis, and neonatal death.

**United Kingdom, Spain, Germany, Austria, Slovenia, Portugal, Italy, Belgium, Albania, China, Brazil and Chile

progesterone [5,6], while Nicolaides et al. reported the use of vaginal progesterone in two patients in the control group [4]. Liem et al. included also 18 women with triplet pregnancies in the trial [5]. However, only one, who had short TVU CL, was included in our meta-analysis.

Synthesis of results

Out of the 481 women with twin pregnancies with a short TVU CL included in the meta-analysis, 252 (52%) received the Arabin pessary (i.e. intervention group),

while 229 (48%) did not (i.e. control group). Use of Arabin pessary in twin gestations with short CL at 16–24 weeks, was not associated with prevention of SPTB <37, <34 (25.3% vs 31.0%; RR 0.72, 95% CI 0.25 to 2.06; Figure 3), <32 and 28 weeks, compared to no pessary. Data did not change when indicated PTB were added. Indeed, use of Arabin pessary did not reduce the incidence of PTB <37 weeks. A significant decrease in PTB <32 (RR 0.48, 95% CI 0.24 to 0.96) and <28 weeks (RR 0.24, 95% CI 0.07 to 0.83) was noticed, but only one trial [5] was included and therefore data could not be meta-analyzed. Data on PTB

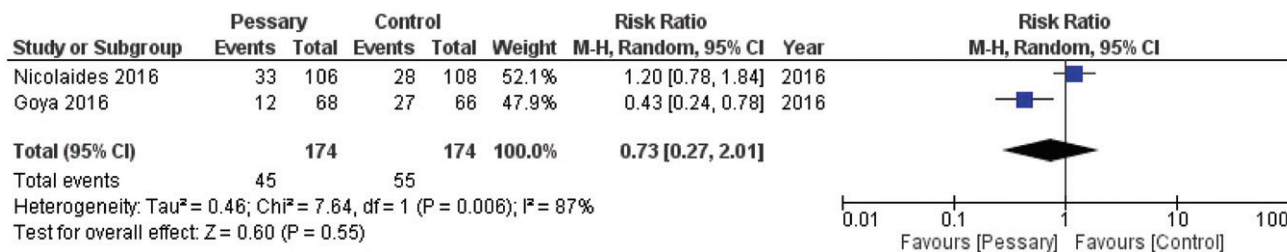


Figure 3. Forest plot for the risk of spontaneous preterm birth <34 weeks. CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

<34 were not available (Table 2). The mean GA at delivery (MD 1.00 week, 95% CI -0.56–2.57) and the mean latency (MD 9.09 days, 95% CI -1.88–16.30) were similar in the pessary group compared to the control group. Regarding neonatal outcomes, no differences were found in the incidence of LBW (78.2% vs. 86.8%; RR 0.87, 95% CI 0.63–1.20), VLBW (21.3% vs. 21.8%; RR 0.97, 95% CI 0.63–1.49), NEC (1.6% vs. 2.2%; RR 0.73, 95% CI 0.17–3.09), RDS (14.7% vs. 13.0%; RR 1.13, 95% CI 0.70–1.84), IVH (4.8% vs. 5.4%; RR 0.53, 95% CI 0.19–1.42), fetal mortality (3.6% vs. 3.5%; RR 1.02, 95% CI 0.37–2.87), neonatal mortality (3.6% vs. 5.2%; RR 0.68, 95% CI 0.27–1.70), and perinatal death (7.1% vs. 8.7%; RR 0.62, 95% CI 0.12–3.31) comparing women in the intervention group with the control group.

Given that none of the included trials stratified data by history of SPTB or by different TVU CL cutoffs, performing subgroup analyses were not feasible, except for TVU CL ≤25 mm. Primary outcome of SPTB <34 weeks was similar for singletons with TVU CL ≤25 mm in the pessary vs. no pessary groups: 45/174 (25.9%) vs. 55/174 (31.6%); RR 0.73, 95% CI 0.27–2.01 (Table 2).

Discussion

Main findings

This meta-analysis from three high-quality RCTs, including 481 twin gestations with short a CL, showed that the use of a cervical pessary did not prevent SPTB or improve perinatal outcome. Our meta-analysis included level 1 data from three appropriately powered, well-designed RCTs. Pooled data available to date point to a lack of efficacy of the Arabin pessary in twin pregnancies with short cervix.

Comparison with existing literature

There is no prior systematic review of the effect of pessary in multiple gestations with short cervix. A

Cochrane review of one trial, including 385 women, showed a beneficial effect of cervical pessary in reducing preterm delivery in singleton gestations with a short cervix [13]. However, this review included only singleton gestations with a short CL. Liem et al. pooled data from six cohort studies, two RCTs, and two quasi randomized studies showing potential effectiveness of a cervical pessary in the prevention of preterm delivery [14].

Strengths and limitations

Our study has several strengths. This meta-analysis included all studies published to date on the topic, studies of high quality and with a low risk of bias according to the Cochrane risk of bias tools. To our knowledge, no prior meta-analysis on this issue is as large, up-to-date, or comprehensive. Key unpublished data were obtained from the original authors [4] (Table 2). The protocol of this review was a priori registered on PROSPERO. Statistical tests showed no significant potential publication biases. Intention-to-treat analysis was used, and both random and mixed effects models were used when appropriate. These are key elements that are needed to evaluate the reliability of a meta-analysis [10].

Limitations of our study are inherent to the limitations of the included RCTs. Only three trials were included in the meta-analysis. Although our meta-analysis represented level-1 data and included well-designed trials, data from two studies came from subgroup analyses which were not appropriately powered for the primary outcome [4,5]. The small number of studies did not permit meaningful stratified meta-analyses to explore the test performance in sensitivity analyses according to the study's risk of bias or in subgroup analyses according to the TVU CL cutoffs. Similarly, since none of the included trials stratified data by obstetric history, performing subgroup analyses in women with prior SPTB and in women

Table 2. Primary and secondary outcomes in twin gestations with short cervical length

	Liem 2013 ⁵	Nicolaides 2016 ⁴	Goya 2016 ⁶	Total	RR or MD (95% CI)
Sample size	133 (78 vs 55) ^d	214 (106 vs 108)	134 (68 vs 66)	481 (252 vs 229)	—
SPTB <34 weeks	Not reported	33/106 (31.1%) vs 28/108 (25.9%)	11/68 (16.2%) vs 26/66 (39.4%)	44/174 (25.3%) vs 54/174 (31.0%)	0.72 (95% CI 0.25 to 2.06)
PTB <34 weeks	Not reported	Not reported	Not reported	—	—
SPTB <37 weeks	Not reported	55/106 (51.9%) vs 50/108 (46.3%) ^a	47/68 (69.1%) vs 48/66 (72.7%)	102/174 (58.6%) vs 98/174 (56.3%)	1.01 (0.85 to 1.20)
PTB <37 weeks	50/78 (64.1%) vs 43/55 (78.2%)	Not reported	Not reported	50/78 (64.1%) vs 43/55 (78.2%)	0.82 (0.66 to 1.02)
SPTB <32 weeks	Not reported	24/106 (22.6%) vs 22/108 (20.4%) ^a	Not reported	24/106 (22.6%) vs 22/108 (20.4%)	1.11 (0.67 to 1.86)
PTB <32 weeks	11/78 (14.1%) vs 16/55 (29.1%)	Not reported	Not reported	11/78 (14.1%) vs 16/55 (29.1%)	0.48 (0.24 to 0.96)
SPTB <28 weeks	Not reported	14/106 (13.2%) vs 8/108 (7.4%) ^a	4/68 (5.9%) vs 9/66 (13.6%)	18/174 (10.3%) vs 17/174 (9.8%)	0.93 (0.23 to 3.71)
PTB <28 weeks	3/78 (3.8%) vs 9/55 (16.4%)	Not reported	Not reported	3/78 (3.8%) vs 9/55 (16.4%)	0.24 (0.07 to 0.83)
GA at delivery (weeks)	36.4 ± 3.1 vs 35.0 ± 2.4	34.0 ± 4.4 vs 34.6 ± 4.1 ^a	35.3 ± 2.9 vs 33.1 ± 3.9	—	1.00 week (-0.56 to 2.57)
Mean ± SD					
Latency (days)	136.5 ± 8.4 vs 126.1 ± 7.8	79.4 ± 31.7 vs 82.1 ± 29.2 ^a	88.9 ± 9.1 vs 72.8 ± 7.7	—	9.09 days (-1.88 to 16.30)
Mean ± SD					
LBW	Not reported	89/106 (77.4%) vs 89/108 (82.4%)	47/68 (34.6%) vs 62/66 (47.7%)	136/174 (78.2%) vs 151/174 (86.8%)	0.87 (0.63 to 1.20)
VLBW	Not reported	24/106 (22.6%) vs 21/108 (19.4%)	13/68 (9.5%) vs 17/66 (13.1%)	37/174 (21.3%) vs 38/174 (21.8%)	0.97 (0.63 to 1.49)
NEC	0/78 vs 1/55 (18%)	4/99 (4.0%) vs 2/102 (1.9%) ^b	0/68 vs 2/66 (1.5%)	4/245 (1.6%) vs 5/223 (2.2%)	0.73 (0.17 to 3.09)
RDS	7/78 (9%) vs 2/55 (4%)	21/99 (21.2%) vs 19/102 (18.6%) ^a	8/68 (5.9%) vs 8/66 (4.6%)	36/245 (14.7%) vs 29/223 (13.0%)	1.13 (0.70 to 1.84)
IVH	0/78 vs 3/55 (5%)	7/99 (7.1%) vs 5/102 (4.9%) ^b	0/68 vs 4/66 (3.0%)	7/245 (4.8%) vs 12/223 (5.4%)	0.53 (0.19 to 1.42)
Fetal mortality ^b	3/78 (3.8%) vs 2/55 (3.6%)	6/106 (5.7%) vs 4/108 (3.7%) ^a	0/68 vs 2/66 (3.0%)	9/252 (3.6%) vs 8/229 (3.5%)	1.02 (0.37 to 2.87)
Neonatal mortality ^b	2/78 (2.6%) vs 10/55 (18.2%)	7/106 (6.6%) vs 2/108 (1.9%) ^a	0/68 vs 0/66	9/252 (3.6%) vs 12/229 (5.2%)	0.68 (0.27 to 1.70)
Perinatal death ^b	5/78 (6.4%) vs 12/55 (21.8%)	13/106 (12.3%) vs 6/108 (5.6%)	0/68 vs 2/66 (3.0%)	18/252 (7.1%) vs 20/229 (8.7%)	0.62 (0.12 to 3.31)
Perinatal death ^c	6/157 (3.8%) vs 19/111 (17.1%)	20/212 (9.4%) vs 12/216 (5.6%)	0/136 vs 2/132 (1.5%)	26/505 (5.1%) vs 33/459 (7.2%)	0.51 (0.09 to 2.79)

Data are presented as total number (number in the pessarary group vs number in the control group) with percentage. Boldface data, statistically significant

RR, relative risk; MD, mean difference; CI, confidence interval; SPTB, spontaneous preterm birth; GA, gestational age; LBW, low birth weight; VLBW, very low birth weight; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage

^aAdditional unpublished data kindly provided by the original authors⁴

^bPregnancy level

^cFetal/Neonatal level

^dOne triplet pregnancy included

without prior SPTB was not feasible. The presence of co-treatments, slightly different gestational ages at inclusion, and CL cutoffs represent other limitations of this systematic review. For example, in the Nicolaides et al.'s trial, vaginal progesterone was used in two women in the control group. Nonetheless, even if these two patients delivered preterm, it would not have influenced the conclusion of this study or the meta-analysis. The CL cutoff of 38 mm used in the Liem et al.'s study [5] has not been established as a risk factor for SPTB in prior studies [15], and is different than the 25-mm cutoff used by the other two included trials [4,6]. Finally, one woman with triplet pregnancy and short TVU CL from the study of Liem et al. [5] was included in our analysis.

Interpretation

The exact mechanism to explain the efficacy of the cervical pessary to prevent SPTB in women with a short CL is not completely clear. Vitsky in 1961 first suggested that the incompetent cervix is aligned centrally, with no support except the nonresistant vagina [16]. A lever pessary, therefore, would change the inclination of the cervical canal, directing it more posteriorly. In doing so, the weight of the pregnancy would be more on the anterior lower segment [17]. However, the suggestion that some physical intervention, such as a pessary, reduces SPTB by changing the uterocervical angle has little biological plausibility and further studies are needed to clarify the mechanism of action of this device. Another proposed mechanism is that the pessary could strengthen the immunological barrier between the chorioamnion-extraovular space and the vaginal microbiological flora as cerclage has been postulated to do [3,7–9,18–22].

There are at least five potential reasons why the pessary was effective in the Goya et al. [6] and Liem et al.'s [5] trials and not in the Nicolaides et al.'s [4] trial. First, while the training is not specifically described, the Nicolaides et al.'s [4] study states that the many research doctors who placed the pessaries did not receive supervised training and that it was “not possible to be certain that there was appropriate insertion.” Goya's study states that “the central team instructed the other centers in the use of the pessary.” [6]. This study reported another mechanism to confirm that the pessary was placed correctly – all of the patients had a TVU to confirm correct placement of the pessary [6]. Second, the Nicolaides et al.'s trial [4] included multiple sites, some of which did not enroll many subjects, raising the possibility of lesser experience with pessary placement and management. Of note, there was no

specific training provided regarding pessary insertion in the Liem et al.'s trial [5] and 40 sites enrolled patients in the trial. Third, Goya et al. [6] did not remove the pessaries in patients with ruptured membranes. Pessaries were removed in patients with ruptured membranes in the Nicolaides et al. [4] and Liem et al.'s [5] trials. Fourth, there were more twin pregnancies with prior SPTB in the Goya et al. [6] (17.2%) and Liem et al. [5] (6.8%) trials compared to the Nicolaides et al.'s trial [4] (4.5%). Pessary may be more effective in women with both prior SPTB and short CL, but this issue could not be further analyzed given the fact that no prior SPTB and prior SPTB subgroup analyses were not reported in any of the trials. Last, the Goya et al. [6] and Liem et al. [5] trials stratified pessary randomization by center, while the Nicolaides et al.'s trial [4] did not stratify randomization by center. It is possible that a greater number of subjects in the Nicolaides et al.'s trial were randomized to the pessary arm at a site with providers who did not have significant experience with pessary insertion. Notably, a recent meta-analysis of six trials including 1420 singleton pregnancies with TVU CL ≤ 25 mm showed that the use of cervical pessary starting at 20⁰–24⁶ weeks does not reduce the rate of spontaneous preterm delivery or improve perinatal outcome [23].

Conclusions

Use of the Arabin pessary in twin pregnancies with short TVU CL at 16–24 weeks may not prevent SPTB or improve perinatal outcome.

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Disclosure statement

The authors declare that they have nothing to disclose.

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References

1. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2011. *Natl Vital Stat Rep* 2012;61:1–20.

2. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. *Obstet Gynecol* 2007;110:405–15.
3. Goya M, Pratcorona L, Merced C, Pesario Cervical para evitar prematuridad (PECEP) Trial Group, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012;379:1800–6.
4. Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. *Am J Obstet Gynecol* 2016;214:3.e1–9.
5. Liem S, Schuit E, Hegeman M, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet* 2013;382:1341–9.
6. Goya M, de la Calle M, Pratcorona L, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). *Am J Obstet Gynecol* 2016;214:145–52.
7. Prevention of preterm birth with a pessary in triplet. *ClinicalTrials.gov* Identifier: NCT02601443. Available from: <http://clinicaltrials.gov/show/NCT01990612> [last accessed 16 Feb 2016].
8. Prevention of preterm birth with a pessary in singleton gestations (POPPS). *ClinicalTrials.gov* Identifier: NCT02056652. Available from: <http://clinicaltrials.gov/show/NCT02056652> [last accessed 16 Feb 2016].
9. Prevention of preterm birth with a pessary in twin gestations (POPPT). *ClinicalTrials.gov* Identifier: NCT02056639. Available from <http://clinicaltrials.gov/show/NCT02056639> [last accessed 16 Feb 2016].
10. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions, version 5.1.0 (update March 2011)*. Copenhagen, Denmark: The Nordic Cochrane Centre, Cochrane Collaboration; 2014. Available from: www.cochrane-handbook.org [last accessed 16 Feb 2016].
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
12. Hui SY, Chor CM, Lau TK, et al. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. *Am J Perinatol* 2013;30:283–8.
13. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. *Cochrane Database Syst Rev* 2013;5:CD007873.
14. Liem SM, van Pampus MG, Mol BW, Bekedam DJ. Cervical pessaries for the prevention of preterm birth: a systematic review. *Obstet Gynecol Int* 2013;2013: 576–723.
15. Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2010; 203:128.e1–12.
16. Vitsky M. Simple treatment of the incompetent cervical os. *Am J Obstet Gynecol* 1961;81:1194–7.
17. Arabin B, Halbesma JR, Vork F, et al. Is treatment with vaginal pessaries an option in patients with sonographically detected short cervix?. *J Perinat Med* 2003;31:122–3.
18. Jones G, Clark T, Bewley S. The weak cervix: failing to keep the baby in or infection out?. *Br J Obstet Gynaecol* 1998;105:1214–15.
19. Does cervical pessary prevent spontaneous preterm birth in twin pregnancies with short cervical length? *ClinicalTrials.gov* Identifier: NCT02708264. Available from: <http://clinicaltrials.gov/show/NCT02708264> [last accessed 16 Aug 2016].
20. Pessary in singleton gestations with short cervix without prior preterm birth *ClinicalTrials.gov* Identifier: NCT02716909. Available from: <http://clinicaltrials.gov/show/NCT02716909> [last accessed 16 Aug 2016].
21. Cervical pessary in women with arrested preterm labor and short cervix (PWK) *ClinicalTrials.gov* Identifier: NCT02849301. Available from: <http://clinicaltrials.gov/show/NCT02849301> [last accessed 16 Aug 2016].
22. Pessary as adjunctive therapy to cerclage for the prevention of preterm birth *ClinicalTrials.gov* Identifier: NCT02678026. Available from: <http://clinicaltrials.gov/show/NCT02678026> [last accessed 16 Aug 2016].
23. Saccone G, Ciardulli A, Xodo S, et al. Cervical pessary for preventing preterm birth in twin pregnancies with short cervical length: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2016;5:1–25. [Epub ahead of print].