Cervical Pessary for Preventing Preterm Birth in Singleton Pregnancies With Short Cervical Length

A Systematic Review and Meta-analysis

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CI, confidence interval; CL, cervical length; GA, gestational age; MD, mean difference; RCT, randomized clinical trial; RR, relative risk; SPTB, spontaneous preterm birth; TVU, transvaginal ultrasound

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Objectives—To evaluate the effectiveness of cervical pessary for preventing spontaneous preterm birth (SPTB) in singleton gestations with a second trimester short cervix.

Methods—Electronic databases were searched from their inception until February 2016. We included randomized clinical trials (RCTs) comparing the use of the cervical pessary with expectant management in singletons pregnancies with transvaginal ultrasound cervical length (TVU CL) ≤25 mm. The primary outcome was incidence of SPTB <34 weeks. The summary measures were reported as relative risk (RR) with 95% confidence interval (CI).

Results—Three RCTs (n = 1,420) were included. The mean gestational age (GA) at randomization was approximately 22 weeks. The Arabin pessary was used as intervention in all three trials, and was removed by vaginal examination at approximately 37 weeks. Cervical pessary was not associated with prevention of SPTB <37 (20.2% vs 50.2%; RR 0.50, 95% CI 0.23 to 1.09), <34, <32, and <28 weeks, compared to no pessary. No differences were found in the mean of GA at, interval from randomization to delivery, incidence of preterm premature rupture of membranes and of cesarean delivery, and in neonatal outcomes. The Arabin pessary was associated with a significantly higher risk of vaginal discharge.

Conclusions—In singleton pregnancies with a TVU CL ≤25mm at 20^0–24^6 weeks, the Arabin pessary does not reduce the rate of spontaneous preterm delivery or improve perinatal outcome. Individual patient data meta-analysis may clarify whether cervical pessary may be beneficial in subgroups, such as only singleton gestations without prior SPTB or by different CL cutoffs.

Key Words—cerclage; cervix; meta-analysis; obstetrics; preterm birth; review; transvaginal ultrasound cervix

Spontaneous preterm birth (SPTB) remains the number one cause of perinatal mortality in many countries, including the United States.[1] In singleton gestations, a short cervical length (CL) on transvaginal ultrasound (TVU) has been shown to be a better predictor of SPTB than digital examination and fetal fibronectin.[2]

The cervical pessary is a silicone device that has been used to prevent SPTB. The leading hypotheses for its mechanisms are two: that the pessary helps to keep the cervix closed, and that the pessary changes the inclination of the cervical canal so that the pregnancy weight is not directly above the internal os. The efficacy of cervical pessary has been assessed in several populations, including singleton gestations with short CL,[3] unselected twins,[4,5] twins with a 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 the use of cervical pessary in pregnancy or guidelines for management have been assessed.

The aim of this systematic review with meta-analysis was to evaluate the effectiveness of cervical pessary for preventing SPTB in singleton gestations with a short cervix in the second trimester.

Materials and Methods

Search Strategy

The review protocol was established by two investigators (G.S., V.B.) prior to commencement and was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD 42016035938).

Two authors (G.S., A.C.) identified trials by searching independently 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," "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 (V.B.).

Study Selection

All RCTs comparing the use of cervical pessary (ie, intervention group) with expectant management (ie, control group) for prevention of SPTB in singleton pregnancies with short CL, defined as TVU CL $\leq$25 mm, were included in the meta-analysis. Trials on multiple pregnancies were excluded. Quasi-randomized trials (ie, trials in which allocation was done on the basis of a pseudo-random sequence; eg, odd/even hospital number or date of birth, alternation) were also excluded.

Data Extraction and Risk of Bias Assessment

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[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., 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.

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 (either spontaneous or indicated) $<$ 34 weeks; mean gestational age (GA) at delivery (in weeks); mean latency (ie, interval from randomization to delivery) (in days); incidence of preterm premature rupture of membranes; incidence of cesarean delivery (CD); maternal side effects (ie, vaginal discharge, bacterial vaginosis); and neonatal outcomes including mean birth weight (in grams), incidence of low birth weight (ie, birth weight $<$ 2500 grams), necrotizing enterocolitis, respiratory distress syndrome, intraventricular hemorrhage (grade 3 or 4), admission to neonatal intensive care unit, fetal mortality (ie, fetal death after 20 weeks), neonatal mortality (ie, death of a live-born baby within the first 28 days of life), and perinatal death (ie, either fetal mortality or neonatal mortality).

Data Analysis

The data analysis was completed independently by two authors (G.S., S.X.) using Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen).[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-effects model was used.[10] We planned subgroup analyses of singleton gestations without prior SPTB and singleton gestations with prior SPTB, and by TVU CL cutoffs of ≤ 20 mm, and ≤ 15 mm, respectively. We planned to assess potential publication biases by using Begg's and Egger's tests. Tests for publication bias were carried out only when the total number of publications included for each outcome was more than 10.

The summary measures were reported as relative risk (RR) or as mean differences (MD) with 95% confidence interval (CI); P value < 0.05 was considered statistically significant.

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

Results

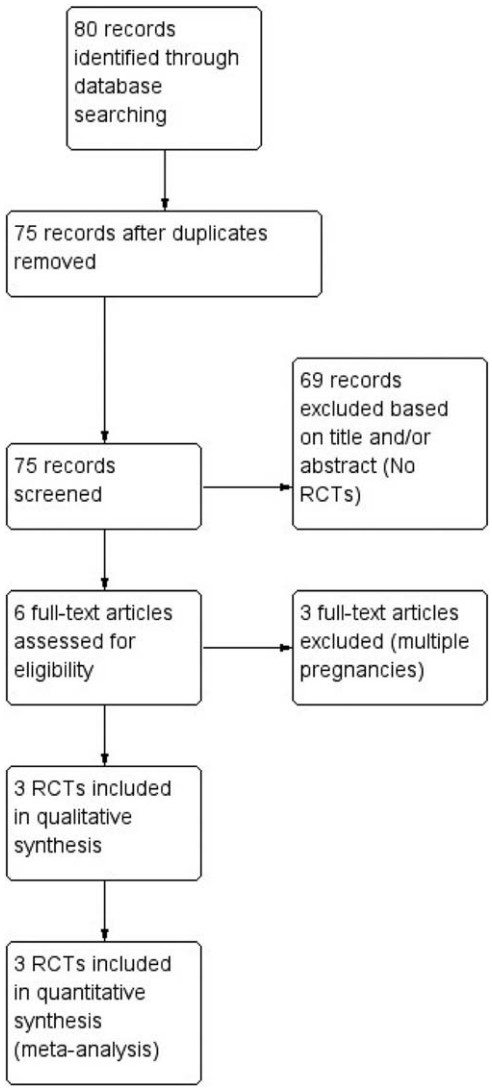
Study Selection and Study Characteristics

Figure 1 shows the flow diagram (PRISMA template) of information through the different phases of the review. Supplemental file S1 shows the full electronic search from the major database (ie, MEDLINE).

Six studies were assessed for eligibility.[3–6,12,13] Three trials including multiple pregnancies were excluded.[4–6] Three RCTs were therefore included in the meta-analysis.[3,12,13] The overall risk of bias of the included trials was low (Figure 2). All studies had a low risk of bias in "random sequence generation," "incomplete outcome data," and "selective reporting." Adequate methods for allocation of women were used. Blinding was considered not feasible methodologically given the intervention, and none of the included studies was double-blind. Publication bias could not be assessed given the small (<10) number of studied included.

All trials enrolled only singleton gestations with TVU CL ≤ 25 mm.[3,12] Women with major fetal abnormalities, painful regular uterine contractions, active vaginal bleeding, ruptured membranes, placenta previa, history of a cone biopsy, and a cerclage in situ were excluded. The mean GA at randomization was about 22 weeks in the 3 studies. The pessary was removed by a simple vaginal examination at about 37 weeks, or earlier if the women presented with rupture of membranes, vaginal bleeding, or painful uterine contractions. Only Goya et al[6] did not remove the pessary in case of rupture of membranes. However, in this trial only 3 women in the cervical pessary group developed premature rupture of

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.



membranes. All 3 studies used the Arabin pessary (Conformité Européenne marking 0482) (Table 1). Regarding the use of progesterone, 2 trials did not use it.[3,12] In Nicolaides et al, 359 women (38.5%), from both the pessary and control groups, with CL ≤15 mm at randomization or subsequent visit, received 200 mg vaginal

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.

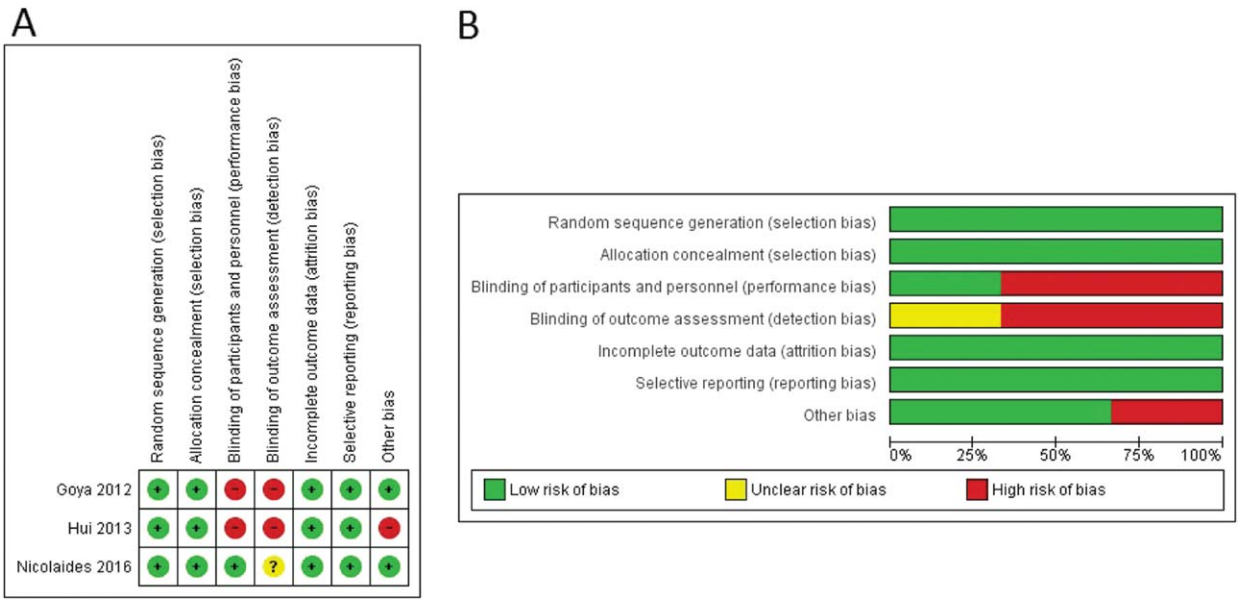


Table 1. Descriptive Data of the Included Trials

	Goya 2012[3]	Hui 2013[12]	Nicolaides 2016[13]
Study location	Spain	China	Multicenter[a]
Number of centers	5	1	16
Months of study	36	29	53
Sample size	380 (190 vs 190)	108 (53 vs 55)	932 (465 vs 467)
GA at randomization (range)	20^0–23^6	20^0–24^6	20^0–24^6
GA at randomization (weeks)	22.2 ± 0.9 vs 22.4 ± 0.9	21.9 ± 3.5 vs 21.7 ± 3.3	23.4 (22.6–24.3) vs 23.6 (22.7–24.4)
Inclusion criteria	Singletons with short CL	Singletons with short CL	Singletons with short CL
Definition of short CL	TVU CL ≤ 25 mm	TVU CL ≤ 25 mm	TVU CL ≤ 25 mm
Use of vaginal progesterone	0/190 vs 0/190	0/53 vs 0/55	177/465 (38.1%) vs 182/467 (39.0%)[b]
Women with prior SPTB	21/190 (11.1%) vs 20/190 (10.5%)	3/53 (5.7%) vs 6/55 (10.9%)	70/465 (15.1%) vs 84/467 (18.0%)
Use of 17P in women with prior SPTB	0/190 vs 0/190	0/53 vs 0/55	0/465 vs 0/467
Cerclage for cervical shortening	0/190 vs 0/190	0/53 vs 0/55	2/465 (0.4%) vs 5/467 (1.1%)
Type of cervical pessary	Arabin	Arabin	Arabin
Primary outcome	SPTB < 34 weeks	SPTB < 34 weeks	SPTB < 34 weeks

Data are presented as total number (number in the pessary group vs number in the control group)
CL, cervical length; GA, gestational age; SPTB, spontaneous preterm birth; TVU, transvaginal ultrasound; 17P, 17-hydroxyprogesterone caproate.*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.
[a]England, Germany, Slovenia, Portugal, Italy, Belgium, Albania, Chile and Australia.
[b]Vaginal progesterone 200 mg daily for TVU CL ≤15 mm.

suppository daily containing natural progesterone up to 33^6 weeks' gestation.[13] None of the three trials used 17-hydroxyprogesterone caproate as prophylactic treatment for women with prior SPTB.

Synthesis of Results

Table 2 shows the pooled results for the primary and the secondary outcomes. Out of the 1420 singleton gestations included, 708 (49.8%) were randomized to the pessary group, and 712 (50.2%) to the expectant management group (ie, control group). Use of a cervical pessary in singleton gestations with a TVU CL $\leq$25 mm starting at 20^0–24^6 weeks was not associated with prevention of SPTB <37 (20.2% versus 50.2%; RR 0.50, 95% CI 0.23 to 1.09), < 34 (10.2% versus 14.6%; RR 0.71, 95% CI 0.21 to 2.42; Figure 3), < 32 (9.9% versus 7.5%; RR 1.32, 95% CI 0.87 to 2.01) and <28 weeks (4.4% versus 4.8%; RR 0.70, 95% CI 0.18 to 2.67) compared to no pessary. No differences were found in the incidence of PTB <34 weeks (11.2% versus 15.3%; RR 0.74, 95% CI 0.23 to 2.38); in the mean of GA at delivery (MD 1.63 weeks, 95% CI −0.82 to 4.07); interval from randomization to delivery (MD 11.91 days, 95% CI −6.97 to 30.79); in the incidence of preterm premature rupture of membranes (3.7% versus 10.2%; RR 0.39, 95% CI 0.09 to 1.71) and of CD (21.6% versus 21.1%; RR 1.02, 95% CI 0.70 to 1.51); and in the neonatal outcomes including birth weight (MD -113.00 grams, 95% CI −364.95 to 138.95), low birth weight (20.6% versus 18.4%; RR 1.15, 95% CI 0.88 to 1.49), necrotizing enterocolitis (0.9% versus 0.8%; RR 0.95, 95% CI 0.11 to 8.07), respiratory distress syndrome (5.4% versus 6.9%; RR 0.80, 95% CI 0.22 to 3.00), intraventricular hemorrhage (1.3% versus 0.8%; RR 0.94, 95% CI 0.15 to 6.04), admission to neonatal intensive care unit (14.1% versus 14.4%; RR 1.02, 95% CI 0.73 to 1.42), fetal mortality (1.1% versus 0.7%; RR 1.61, 95% CI 0.53 to 4.88), neonatal mortality (1.1% versus 0.8%; RR 1.32, 95% CI 0.48 to 3.65), and perinatal death (2.3% versus 1.5%; RR 1.44, 95% CI 0.69 to 3.04) comparing the intervention group with the control group. The Arabin pessary was associated with a significantly higher risk of vaginal discharge (37.3% versus 18.0%; RR 2.12, 95% CI 1.84 to 2.44) but not of bacterial vaginosis (25.8% versus 22.8%; RR 1.14, 95% CI 0.95 to 1.36). Planned subgroup analyses were not feasible, as data were not reported by prior SPTB or not, or by other TVU CL cutoffs.

Comment

Main Findings

This meta-analysis from 3 high-quality RCTs, including a total of 1420 singleton gestations with a short TVU CL $\leq$25 mm, showed that cervical pessary use did not prevent SPTB or improve perinatal outcome. We also found an increased risk of vaginal discharge in women who received the pessary. Our meta-analysis included level 1 data from 3 appropriately powered, well-designed RCTs. Pooled data available to date point to a lack of efficacy of the Arabin pessary in singleton pregnancies with short cervix.

Comparison With Existing Literature

Our data do not support earlier findings of a Cochrane review of only 1 trial,[3] including 380 women, which showed a beneficial effect of cervical pessary in reducing spontaneous preterm deliveryin singleton gestations with a TVU CL $\leq$25 mm.[14]

Strengths and Limitations

One of the strengths of our study is inclusion of only RCT data on prevention of SPTB in a specific population, that is, singleton gestations with short TVU CL.

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

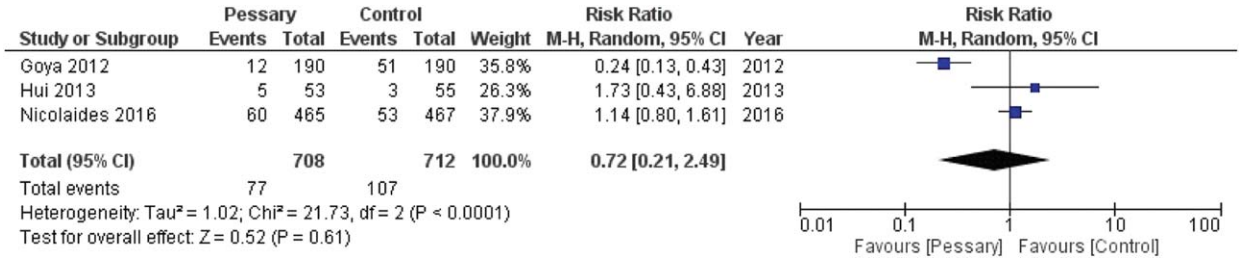


Table 2. Primary and Secondary Outcomes

	Goya 2012[3]	Hui 2013[12]	Nicolaides 2016[13]	Total	I^2	RR or MD (95% CI)
Sample size	380 (190 vs 190)	108 (53 vs 55)	932 (465 vs 467)	1420 (708 vs 712)	—	—
SPTB < 34 weeks	12/190 (6.3%) vs 51/190 (26.8%)	5/53 (9.4%) vs 3/55 (5.5%)	55/465 (11.8%) vs 50/467 (10.7%)	72/708 (10.2%) vs 104/712 (14.6%)	90%	0.71 (0.21 to 2.42)
SPTB < 37 weeks	41/190 (21.6%) vs 113/190 (59.5%)	8/53 (15.1%) vs 10/55 (18.2%)	Not reported	49/243 (20.2%) vs 123/245 (50.2%)	0%	0.50 (0.23 to 1.09)
SPTB < 32 weeks	Not reported	Not reported	46/465 (9.9%) vs 35/467 (7.5%)	46/465 (9.9%) vs 35/467 (7.5%)	—	1.32 (0.87 to 2.01)
SPTB < 28 weeks	4/190 (2.1%) vs 16/190 (8.4%)	2/53 (3.8%) vs 3/55 (5.5%)	25/465 (5.4%) vs 15/467 (3.2%)	31/708 (4.4%) vs 34/712 (4.8%)	78%	0.70 (0.18 to 2.67)
PTB < 34 weeks	14/190 (7.4%) vs 53/190 (27.9%)	5/53 (9.4%) vs 3/55 (5.5%)	60/465 (12.9%) vs 53/467 (11.3%)	79/708 (11.2%) vs 109/712 (15.3%)	90%	0.74 (0.23 to 2.38)
GA at delivery (weeks)	37.7 ± 2.0 vs 34.9 ± 4.0	38.1 ± 3.4 vs 37.8 ± 3.9	38.9 (37.0–40.0)	—	0%	1.63 week (−0.82 to 4.07)
Latency (days)	108.5 ± 14.2 vs 87.5 ± 21.7	113.6 ± 24.0 vs 111.9 ± 28.1	Not reported	—	0%	11.91 days (−6.97 to 30.79)
PPROM	3/190 (1.6%) vs 17/190 (8.9%)	6/53 (11.3%) vs 8/55 (14.5%)	Not reported	9/243 (3.7%) vs 25/245 (10.2%)	72%	0.39 (0.09 to 1.71)
CD	41/190 (21.6%) vs 40/190 (21.1%)	Not reported	Not reported	41/190 (21.6%) vs 40/190 (21.1%)	—	1.02 (0.70 to 1.51)
Vaginal discharge	190/190 (100%) vs 87/190 (45.8%)	25/53 (47.2%) vs 12/55 (21.8%)	49/465 (10.5%) vs 29/467 (6.2%)	264/708 (37.3%) vs 128/712 (18.0%)	0%	2.12 (1.84 to 2.44)
Bacterial vaginosis	45/190 (23.7%) vs 47/190 (24.7%)	1/53 (1.9%) vs 2/55 (3.6%)	137/465 (29.5%) vs 113/467 (24.2%)	183/708 (25.8%) vs 162/712 (22.8%)	0%	1.14 (0.95 to 1.36)
BW (grams)	Not reported	2840 ± 590 vs 2953 ± 740	3120 (2626–3462) vs 3130 (2760–3150)	—	—	-113.00 grams (−364.95 to 138.95)
LBW	Not reported	Not reported	96/465 (20.6%) vs 84/497 (18.4%)	96/465 (20.6%) vs 84/497 (18.4%)	—	1.15 (0.88 to 1.49)
NEC	0/190 vs 2/190 (1.1%)	Not reported	6/465 (1.3%) vs 3/467 (0.7%)	6/655 (0.9%) vs 5/657 (0.8%)	50%	0.95 (0.11 to 8.07)
RDS	5/190 (2.6%) vs 23/190 (12.1%)	5/53 (9.4%) vs 2/55 (3.8%)	28/465 (6.2%) vs 24/467 (5.3%)	38/708 (5.4%) vs 49/712 (6.9%)	83%	0.80 (0.22 to 3.00)
IVH	0/190 vs 2/190 (1.1%)	0/53 vs 1/55 (1.8%)	9/465 (2.0%) 3/467 (0.7%)	9/708 (1.3%) vs 6/712 (0.8%)	45%	0.94 (0.15 to 6.04)
NICU	Not reported	21/53 (39.6%) vs 17/55 (30.9%)	52/465 (11.6 %) vs 58/467 (12.7%)	73/518 (14.1%) vs 75/522 (14.4%)	20%	1.02 (0.73 to 1.42)
Fetal mortality	0/190 vs 0/190	0/53 vs 0/55	8/465 (1.7%) vs 5/467 (1.1%)	8/708 (1.1%) vs 5/712 (0.7%)	—	1.61 (0.53 to 4.88)
Neonatal mortality	0/190 vs 1/190 (0.5%)	1/53 (1.9%) vs 0/55	7/465 (1.5%) vs 5/467 (1.1%)	8/708 (1.1%) vs 6/712 (0.8%)	0%	1.32 (0.48 to 3.65)
Perinatal death	0/190 vs 1/190 (0.5%)	1/53 (1.9%) vs 0/55	15/465 (3.2%) vs 10/467 (2.1%)	16/708 (2.3%) vs 11/712 (1.5%)	0%	1.44 (0.69 to 3.04)

Data are presented as total number (number in the pessary group vs number in the control group) with percentage. Boldface data is statistically significant.
BW, birth weight; CD, cesarean delivery; CI, confidence interval; GA, gestational age; IVH, intraventricular hemorrhage; LBW, low birth weight; MD, mean difference; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; RR, relative risk; SPTB, spontaneous preterm birth.

This population represents one of the most at risk of developing SPTB.[15] Our 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, and included ≥1000 pregnant women. Publication bias could not be assessed given the small (<10) number of studies included. Intent-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 3 trials were included in the meta-analysis. None of the included studies was double-blind. More than half of the women included in the analysis (932 out of the 1420) came from 1 large trial, which therefore drives the summary statistics.[13] All 3 trials included both low-risk (without prior SPTB) and high-risk (with prior SPTB) women. The higher rate of preterm birth in the control group in 1 of the trials (26.8%)[3] is not concordant with those of the control groups of the other 2 trials.[12,13] 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. Similarly, since none of the included trials stratified data by obstetrical history, performing subgroup analyses in women with prior SPTB and in women without prior SPTB, as well as by other TVU CL cutoffs, was not feasible. The small number of available studies and the inequality of their size could have impaired the robustness of the meta-analysis with an increased chance of a type I error.

Implications

Different strategies have been adopted for prevention of SPTB,[16–30] including progesterone[16,22] and cerclage,[17,18] as well as lifestyle modification such as smoking cessation,[23] diet and aerobic exercise,[24] and nutritional supplements,[25–30] including omega-3,[25–28] folic acid,[29] and vitamins.[30]

The evidence supports the use of vaginal progesterone in singleton pregnancies with short cervix,[16] while cervical cerclage seems to be beneficial only in the subgroup of women with both prior SPTB and TVU CL ≤25 mm.[17] Interestingly, only 235 singleton gestations without prior SPTB[18] and 504 singleton gestations with prior SPTB[17] have been included in randomized studies on cerclage for TVU CL ≤25 mm, versus 1216 and 204, respectively, for pessary. Cervical cerclage is an invasive technique currently requiring anesthesia and the operating room. Therefore, growing interest has focused on pessary for prevention of SPTB. Cervical pessary is relatively noninvasive, is easy to use, does not require anesthesia, can be used in an outpatient clinic setting, and is easily removed when necessary.[19] The exact mechanism for possible efficacy of the cervical pessary to prevent SPTB in women with a short CL is not completely clear. Vitsky et al in 1961 first suggested that the incompetent cervix is aligned centrally, with no support except the nonresistant vagina.[20] 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.[19] 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.[3,21]

Most recently, a new large randomized study—the OPPTIMUM study—did not find significant effect of vaginal progesterone in prevention of PTB in 1228 women at risk of SPTB due to 3 major risk factors: prior SPTB; positive fetal fibronectin test; or short TVU CL <25.[31] It is noteworthy that the OPPTIMUM study was underpowered to detect a meaningful difference between vaginal progesterone and placebo in the subgroup of women with a short cervix, with a post hoc statistical power of only 26% to detect a 23% reduction in the risk of SPTB <34 weeks. Individual-level meta-analyses are being performed currently, and the sample sizes for women with prior SPTB and other subgroups may have been underpowered, too. In a meta-analysis of 5 RCTs, including the OPPTIMUM trial, Romero et al showed that in women with a mid-trimester short CL, progesterone is associated with a significant reduction in the risk of preterm delivery and neonatal morbidity and mortality, without any deleterious effects on neurodevelopmental outcome.[32]

There are at least 4 potential reasons why the pessary was effective in the Goya[3] trial and not in the Hui[12] and Nicolaides[13] trials. First, training for pessary insertion might have differed, even slightly. In the Nicolaides study,[13] it is stated that "the research-team members who inserted the pessaries had received practical training in the placement of the device," while the Goya study

states that "the central team instructed the other centers in the use of the pessary."[3] 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,[3] while in Nicolaides study a transvaginal ultrasound was done every 4 weeks to assess cervical length. Of note, there was no specific training provided regarding pessary insertion in the Hui trial.[12] Second, the Nicolaides trial[13] included multiple sites, some of which did not enroll many subjects, raising the possibility of lesser experience with pessary placement and management. Third, there were more women with prior SPTB in the Nicolaides trial[13] (154/932 [16.5%]) compared to the Goya[3] (41/380 [10.8%]) and Hui[12] (9/108 [8.3%]) trials. Pessary may be more effective in singleton gestations with short CL and without prior SPTB, but this issue could not be further analyzed given the fact that no prior SPTB and prior SPTB subgroup analyses were reported in any of the trials.[3,12,13] Last, in the Nicolaides trial, the administration of vaginal progesterone to most women with CL $\leq$15 mm could have masked any benefit from the cervical pessary in this group.[13] It might be noted that Goya et al[3] and Hui et al[12] did not reported any data regarding the use of the progesterone.

In conclusion, prophylactic use of Arabin pessary in singleton gestations with a short TVU CL $\leq$25 mm at 20^0 to 24^6 weeks does not prevent SPTB or improve perinatal outcome. Given the small sample size, further trials are needed.

Individual patient data meta-analysis may clarify whether cervical pessary may be beneficial in subgroups, such as only singleton gestations without prior SPTB or singleton gestations with prior SPTB, or by different TVU CL cutoffs other than $\leq$25 mm.

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