

# Effect of Cervical Pessary on Spontaneous Preterm Birth in Women With Singleton Pregnancies and Short Cervical Length

## A Randomized Clinical Trial

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**IMPORTANCE** Spontaneous preterm birth is a major cause of perinatal morbidity and mortality. It is unclear if a cervical pessary can reduce the risk of spontaneous preterm delivery.

**OBJECTIVE** To test whether in asymptomatic women with singleton pregnancies and no prior spontaneous preterm birth but with short cervical length on transvaginal ultrasound, use of a cervical pessary would reduce the rate of spontaneous preterm birth at less than 34 weeks of gestation.

**DESIGN, SETTING, AND PARTICIPANTS** Parallel-group, nonblinded, randomized clinical trial conducted from March 1, 2016, to May 25, 2017, at a single center in Italy. Asymptomatic women with singleton gestations, no previous spontaneous preterm births, and cervical lengths of 25 mm or less at 18 weeks 0 days to 23 weeks 6 days of gestation were eligible.

**INTERVENTIONS** Patients were randomized 1:1 to receive either cervical pessary (n = 150) or no pessary (n = 150). The pessary was removed between 37 weeks 0 days and 37 weeks 6 days of gestation or earlier if clinically indicated. The control group received standard care. For cervical length of 20 mm or shorter, women in both groups were prescribed vaginal progesterone, 200 mg/d, until 36 weeks 6 days of gestation. No bed rest or activity restriction was recommended.

**MAIN OUTCOMES AND MEASURES** The primary end point was spontaneous preterm birth at less than 34 weeks of gestation. Secondary outcomes were adverse events.

**RESULTS** Among 300 women who were randomized (mean age, 29 [SD, 6.3] years; mean gestational age, 22 [SD, 1.3] weeks), 100% completed the trial. The primary end point occurred in significantly fewer women in the pessary group. During follow-up, the pessary group had a higher rate of increased or new vaginal discharge.

	No. (%) Pessary Group (n = 150)	Control Group (n = 150)	Between-Group Difference, % (95% CI)	Relative Risk (95% CI)
Primary outcome				
Spontaneous preterm birth <34 wk	11 (7.3)	23 (15.3)	-8.0 (-15.7 to -0.4)	0.48 (0.24-0.95)
Adverse events				
Vaginal discharge	130 (86.7)	69 (46.0)	40.7 (30.1 to 50.3)	1.88 (1.57-2.27)

**CONCLUSIONS AND RELEVANCE** Among women without prior spontaneous preterm birth who had asymptomatic singleton pregnancies and short transvaginal cervical length, use of a cervical pessary, compared with no pessary use, resulted in a lower rate of spontaneous preterm birth at less than 34 weeks of gestation. The results of this single-center, nonblinded study among selected pregnant women require confirmation in multicenter clinical trials.

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**P**reterm birth, defined as delivery before 37 weeks of gestation, is a major cause of perinatal morbidity and mortality.<sup>1</sup> About 15 million infants were born prematurely in 2015, causing 1.1 million deaths as well as short- and long-term disability in the survivors.<sup>2,3</sup>

Different strategies have been adopted for prevention of spontaneous preterm birth. The evidence supports use of vaginal progesterone in women with singleton pregnancy with a short cervix,<sup>4,5</sup> while cervical cerclage seems to be beneficial only in the subgroup of singleton pregnancies with both prior spontaneous preterm birth and cervical length of 25 mm or less<sup>6</sup> and not in women without prior spontaneous preterm birth,<sup>7</sup> nor in women with multiple gestations.<sup>8</sup> International guidelines recommend cervical cerclage for such high-risk women.<sup>4</sup>

The cervical pessary is a silicone device that has been used to prevent spontaneous preterm birth.<sup>9-14</sup> The leading hypotheses for its mechanism of action are that the pessary helps keep the cervix closed and changes the inclination of the cervical canal so that the pregnancy weight is not directly above the internal os. The 4 randomized clinical trials (RCTs) in women with singleton pregnancy with a short cervix published so far provided contradictory results,<sup>9-12</sup> and a meta-analysis by Saccone et al<sup>13</sup> concluded that in this subset of women, the cervical pessary does not reduce the rate of spontaneous preterm delivery or improve perinatal outcome. However, clinical heterogeneity within the trials was high, and the studies included women both with and without prior preterm birth.<sup>13</sup>

The hypothesis of this trial was that in asymptomatic women with singleton pregnancy without prior spontaneous preterm birth but with short cervical length on transvaginal ultrasound, the insertion of a cervical pessary would reduce the rate of spontaneous preterm birth at less than 34 weeks of gestation.

## Methods

### Study Design and Participants

This was a single-center, parallel-group RCT of women with asymptomatic singleton pregnancies without prior spontaneous preterm birth but with short cervical length on transvaginal ultrasound who were randomized to receive a cervical pessary (ie, intervention group) or no pessary (ie, control group) at the University of Naples Federico II (Naples, Italy) from March 1, 2016, to May 25, 2017.

The trial was approved by the local ethics committee. All participants in the trial provided written informed consent. The trial protocol is available in [Supplement 1](#).

Eligible women were those referred to the institution for a diagnosis of short cervix during the routine anatomy scan. In Italy, the anatomy scan is a routine ultrasound examination primarily used to assess fetal anatomy and detect the presence of any fetal anomalies conducted between 18 weeks 0 days and 23 weeks 6 days of gestation. At the university, measurement of the cervix using transvaginal ultrasound was repeated and women found to have a cervical length of 25 mm or less were approached by the research staff and consented.

### Key Points

**Question** Does use of a cervical pessary reduce the rate of spontaneous delivery before 34 weeks of gestation among women with singleton pregnancies, short cervical length, and no prior spontaneous preterm birth?

**Findings** In this randomized trial of 300 women, the rates of spontaneous preterm birth at less than 34 weeks were 7.3% with a cervical pessary compared with 15.3% without cervical pessary use, a significant difference.

**Meaning** The use of a cervical pessary among women with singleton pregnancies, short cervical length, and no prior spontaneous preterm birth reduced the risk of spontaneous preterm birth at less than 34 weeks of gestation.

Inclusion criteria were age 18 to 50 years, singleton pregnancy, cervical length of 25 mm or less, and gestational age at randomization between 18 weeks 0 days and 23 weeks 6 days of gestation.

Exclusion criteria were multiple pregnancies, rupture of membranes at the time of randomization, lethal fetal structural abnormality, cerclage in situ, vaginal bleeding at the time of randomization, suspicion of chorioamnionitis, placenta previa or accreta, ballooning of membranes outside the cervix into the vagina, cervical length of 0 mm, painful and regular uterine contractions, or history of spontaneous preterm birth between 16 weeks 0 days and 36 weeks 6 days of gestation.

At the time of randomization, ethnicity of the women was assessed by clinician determination given the different baseline risk of preterm birth according to ethnicity.

### Randomization and Masking

Eligible participants were randomly allocated in a 1:1 ratio to either the cervical pessary or the control group. Women were randomized by a web-based system using random blocks of 2, 4, and 6 to receive the Arabin pessary (Dr. Arabin GmbH & Co) or no pessary. Randomization was stratified by cervical length (<20 mm or ≥20 mm-≤25 mm). The randomization sequence was prepared by an independent statistician and implemented by use of a central telephone number. The recruiters and the trial coordinator did not have access to the randomization sequence. The allocation code was disclosed only after patient initials were confirmed. Clinicians did not have advance access to the randomization sequence.

Outcome assessors, data collectors, and data analysts were blinded to allocated treatment group. Assessment of the outcomes and outcome collection were made by clinicians not involved in the clinical trial and reported in a form with only the trial identification as the identifier. The data analyst was blinded until the entire analysis was completed.

### Interventions

Cervical length was measured by operators with certification of competence in the technique (Fetal Medicine Foundation Certificate of Competence in Cervical Assessment), as described previously.<sup>15,16</sup> The length of the cervix was measured with a transvaginal real-time ultrasound probe placed

in the anterior fornix of the vagina. Endocervical canal length was measured as the distance between the internal and external os by using a straight line with calipers placed at the notches made by the internal os and external os. Three anatomic landmarks defined the appropriate sagittal view: the internal os, the external os, and the endocervical canal. The image was enlarged while visualizing the 3 landmarks simultaneously. This procedure was repeated 3 times. Only the shortest cervical length measurement was recorded. Each examination was performed during a minimum of 5 minutes.

At the time of randomization, all women in both groups underwent a speculum examination, and vaginal swabs were taken for bacteriological analysis. If the results showed infection, appropriate treatment was given without delaying the insertion of the pessary in the intervention group. The pessary was not removed if there was evidence of bacterial infection after device insertion.

All the cervical pessaries used in the trial were certified by European Conformity and were inserted by the attending physicians, who had received practical training in the placement of the device. Pessary insertion training consisted of a didactic session and a hands-on session. All staff were required to demonstrate competence in pessary placement on a live model. All cervical pessaries were purchased from the manufacturer.

In the intervention group, the cervical pessary was placed at the time of randomization and was removed during the 37th week (37 weeks 0 days–37 weeks 6 days) or earlier if clinically indicated. Reason for earlier removal included active vaginal bleeding, preterm labor with persistent contractions and advanced dilatation despite tocolysis, severe discomfort, or participant request.

Women in the control group received the same obstetrical care as those in the intervention group.

For cervical length of 20 mm or less, women in both groups were prescribed vaginal progesterone 200-mg suppositories daily until 36 weeks 6 days of gestation. No recommendation was made about bed rest, activity, or vaginal intercourse.

All participants were followed up in outpatient settings every month until delivery. In the pessary group, a digital examination was done at each monthly visit to ensure proper pessary placement. At each follow-up visit, women were asked whether they experienced any adverse events and about adherence to progesterone therapy. Specifically, women were asked about vaginal discharge, pelvic discomfort, and pelvic pain. Bleeding or lacerations during the insertion and the removal of the pessary were also recorded.

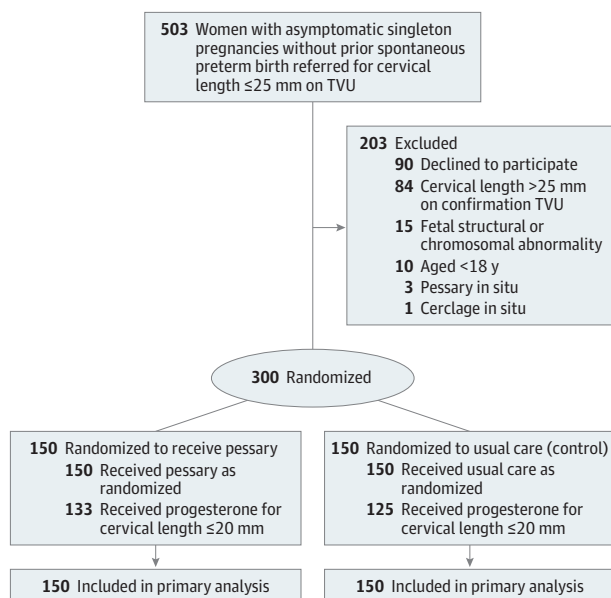
For women in both groups who presented after 26 weeks of gestation with symptoms of preterm labor, tocolytics and glucocorticoids were administered for fetal lung maturation and hospitalization was offered.

### Outcomes

The primary outcome was spontaneous preterm birth at less than 34 weeks of gestation.

Spontaneous preterm birth included either spontaneous onset of preterm labor or preterm premature rupture of membranes. Iatrogenic (medically indicated) preterm deliveries

**Figure 1. Flow of Participants in a Trial of the Effect of Cervical Pessary Use on Spontaneous Preterm Birth in Women With Singleton Pregnancies and Short Cervical Length**



TVU indicates transvaginal ultrasound.

were not included in the primary end point as they are due to fetal or maternal conditions such as fetal distress or maternal preeclampsia and cannot be modified by use of a pessary.

The prespecified secondary outcomes were spontaneous preterm birth at less than 37, 32, and 28 weeks of gestation, gestational age at delivery, latency (time from randomization to delivery), preterm premature rupture of membranes at less than 34 weeks of gestation, mode of delivery, maternal adverse events (vaginal discharge and pelvic discomfort), chorioamnionitis (inflammation of the chorion and amnion by histopathological assessment after delivery), and neonatal outcomes including birth weight, admission to a neonatal intensive care unit, neonatal death (death of a live-born infant within the first 28 days of life) and perinatal death (either fetal death, defined as intrauterine fetal death after 20 weeks of gestation, or neonatal death), and a composite of adverse perinatal outcomes, defined as at least 1 of the following: necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity requiring therapy, blood culture-proven sepsis, and neonatal death.

Post hoc exploratory outcomes included preterm birth (spontaneous and iatrogenic) at less than 37 weeks, 34 weeks, 32 weeks, and 28 weeks of gestation; iatrogenic preterm birth at less than 34 weeks; birth weight less than 2500 g or less than 1500 g; and the components of the composite of adverse perinatal outcomes.

Data on pregnancy outcomes were obtained from hospital maternity records. In case of preterm birth, records were examined to determine whether the delivery was medically indicated (iatrogenic preterm birth) or spontaneous.

Table 1. Participant Characteristics

Characteristics	Pessary Group (n = 150)	Control Group (n = 150)
Age, mean (SD), y	28.5 (6.2)	28.9 (6.5)
Race, No. (%)		
White	133 (88.7)	135 (90.0)
Asian	10 (6.7)	10 (6.7)
Black	7 (4.7)	5 (3.3)
Body mass index, mean (SD) <sup>a</sup>	26.7 (6.2)	26.4 (6.3)
Smoking, No. (%)	19 (12.7)	20 (13.3)
Nulliparous, No. (%)	104 (69.3)	105 (70.0)
Parous, No. (%)	46 (30.7)	45 (30.0)
Prior cervical surgery, No. (%)		
Loop excision of transformation zone	5 (3.3)	4 (2.7)
Cone biopsy	2 (1.3)	1 (0.7)
Gestation time at randomization, mean (SD), wk	22.3 (1.4)	22.4 (1.1)
Cervical length, mean (SD), mm	11.5 (5.7)	12.5 (5.9)
≤20, No. (%)	133 (88.7)	125 (83.3)
≤15, No. (%)	122 (81.3)	115 (76.7)
≤10, No. (%)	56 (37.3)	42 (28.0)
≤5, No. (%)	16 (10.7)	12 (8.0)
Vaginal progesterone, No. (%)	133 (88.7)	125 (83.3)
Positive vaginal swab culture at randomization, No. (%)	36 (24.0)	41 (27.3)
Antibiotics for positive vaginal culture, No. (%)	33 (22.0)	38 (25.3)

<sup>a</sup> Calculated as weight in kilograms divided by height in meters squared.

### Sample Size Calculation

Calculation of the sample size was based on the following considerations: a prevalence of cervical length 25 mm or less of about 1% to 2% in women with singleton gestation,<sup>15</sup> an incidence of preterm birth at less than 34 weeks of gestation of about 25% in women with singleton pregnancy using vaginal progesterone for cervical length 20 mm or less, and a decrease in spontaneous preterm birth by 50% using a cervical pessary.<sup>11</sup> We determined that a sample size of 300 patients (150 per group) would provide a power of 80% to detect a 50% relative reduction in the primary outcome from a baseline risk of 25%, with a 2-sided type I error of .05.

### Statistical Analysis

Data are shown as means or as numbers and percentages. Univariate comparisons of dichotomous data were performed using the  $\chi^2$  test with continuity correction. Comparisons between groups were performed with the use of the *t* test to test group means by assuming equal within-group variances.

The primary analysis was an intention-to-treat comparison of the treatment assigned at randomization. The effect of pessary use on the cumulative incidence of each outcome was quantified in 2 ways: first as the difference between treatment groups in cumulative incidence of the outcome with 95% confidence intervals and second as the unadjusted relative risk and its 95% confidence interval. Ninety-five percent confidence intervals were assessed using the bootstrap method. Original prespecified analysis included the use

of the odds ratio instead of the unadjusted relative risk (Supplement 1). However, given that relative risks are easier to interpret, we decided to quantify the incidence of the primary outcome by using the unadjusted relative risk.

The frequency of spontaneous preterm birth at less than 34 weeks of gestation in relation to gestational age was assessed by Kaplan-Meier analysis. Two different panels were assessed for this analysis: one with any type of delivery (spontaneous and iatrogenic) as the event and one with only spontaneous delivery as the event. Hazard ratios were estimated using the Cox proportional hazards model.

No interim analyses were planned. No adjustment for multiple comparisons was made, so the findings of the secondary outcomes should be considered exploratory. No patients were lost to follow-up and no data were missing. A 2-sided *P* < .05 was considered statistically significant. Statistical analysis was performed using SPSS version 19.0 (IBM Inc).

Post hoc subgroup analyses were performed to examine the effect of a cervical pessary according to progesterone therapy (yes vs no), and cervical length (≤10 mm vs >10 mm). *P* values for the interaction between subgroup and treatment were calculated using the Wald test.

## Results

### Trial Population

From March 2016 to May 2017, of the 503 women referred for short cervical length, 300 asymptomatic women with singleton pregnancies without prior spontaneous preterm birth but with a transvaginal ultrasound cervical length of 25 mm or less between 18 weeks 0 days and 23 weeks 6 days of gestation agreed to take part in the study, underwent randomization, and were enrolled and followed up.

Of the randomized women, 150 (50%) were randomized to the cervical pessary group and 150 (50%) to the control group. No women were excluded after randomization or lost to follow-up (Figure 1). No women in the intervention group had the pessary removed by request or for severe discomfort.

Table 1 shows the baseline demographic and clinical characteristics for each group. There were 133 women (88.7%) in the pessary group and 125 (83.3%) in the control group who had a cervical length of 20 mm or less and received vaginal progesterone; 33 (22.0%) in the pessary group and 38 (25.3%) in the control group received antibiotics because of positive cultures from a vaginal swab at the time of randomization. Use of antibiotic therapy among women with positive vaginal cultures is shown in eTable 1 in Supplement 2.

The mean gestational age at randomization was 22.3 (SD, 1.4) weeks vs 22.4 (SD, 1.1) weeks and the mean cervical length was 11.5 mm (SD, 5.7 mm) vs 12.5 mm (SD, 5.9 mm) in the pessary and control groups, respectively.

### Primary Outcome

Spontaneous preterm birth at less than 34 weeks of gestation occurred in 11 women (7.3%) in the pessary group and 23 women (15.3%) in the control group (between-group difference, -8.0%; 95% CI, -15.7% to -0.4%) (Table 2). In the survival

Table 2. Primary and Secondary Outcomes in the Pessary and Control Groups

Outcomes	Pessary Group (n = 150)	Control Group (n = 150)	Between-Group Difference in % or Mean (95% CI)	Relative Risk (95% CI)	P Value
<b>Primary Outcome</b>					
Spontaneous preterm birth <34 wk, No. (%)	11 (7.3)	23 (15.3)	-8.0 (-15.7 to -0.4) <sup>a</sup>	0.48 (0.24-0.95) <sup>a</sup>	.04
<b>Secondary Outcomes<sup>b</sup></b>					
Spontaneous preterm birth, No. (%)					
<37 wk	30 (20.0)	49 (32.7)	-12.7 (-22.9 to -2.3) <sup>a</sup>	0.61 (0.41-0.91) <sup>a</sup>	.02
<32 wk	10 (6.7)	14 (9.3)	-2.6 (-4.1 to 9.4)	0.71 (0.33-1.56)	.52
<28 wk	6 (4.0)	9 (6.0)	-2.0 (-3.5 to 7.7)	0.67 (0.24-1.83)	.60
Gestational age at delivery, mean (95% CI), wk	37.6 (37.1-38.2)	36.2 (35.5-36.9)	1.4 (0.6 to 2.3) <sup>a</sup>		.001
Time from randomization to delivery, mean (95% CI), d	107.0 (102.1-113.2)	97.0 (91.7-103.3)	10.0 (3.8 to 16.2) <sup>a</sup>		.002
Preterm premature rupture of membranes <34 wk, No. (%)	2 (1.3)	2 (1.3)	0 (-3.6 to 3.6)	1.00 (0.14-7.01)	>.99
Cesarean delivery, No. (%)	45 (30.0)	57 (38.0)	-8.0 (-3.2 to 19.0)	0.79 (0.57-1.09)	.18
Operative vaginal delivery, No. (%)	5 (3.3)	10 (6.7)	-3.4 (-2.1 to 9.1)	0.50 (0.18-1.43)	.29
Spontaneous vaginal delivery, No. (%)	100 (66.7)	83 (55.3)	11.4 (-0.1 to 22.6)	1.20 (1.00-1.45)	.06
<b>Maternal Adverse Effects<sup>b</sup></b>					
Vaginal discharge, No. (%)	130 (86.7)	69 (46.0)	40.7 (30.1 to 50.3) <sup>a</sup>	1.88 (1.57-2.27) <sup>a</sup>	<.001
Pelvic discomfort, No. (%)	5 (3.3)	1 (0.6)	2.7 (-1.0 to 7.0)	5.00 (0.59-42.29)	.22
Chorioamnionitis, No. (%)	5 (3.3)	7 (4.7)	-1.4 (-3.7 to 6.6)	0.71 (0.23-2.20)	.77
<b>Neonatal Outcomes<sup>b</sup></b>					
Birth weight, mean (95% CI), g	2889.9 (2770.3-3009.6)	2644.6 (2513.5-2775.7)	245.3 (69.2 to 421.4) <sup>a</sup>		.006
Neonatal intensive care unit, No. (%)	15 (10.0)	28 (18.7)	-8.7 (-17.1 to -0.3) <sup>a</sup>	0.54 (0.30-0.96) <sup>a</sup>	.04
Neonatal death, No. (%) <sup>c</sup>	1 (0.7)	3 (2.0)	-1.3 (-2.1 to 5.1)	0.33 (0.04-3.17)	.61
Perinatal death, No. (%) <sup>d</sup>	2 (1.3)	4 (2.7)	-1.4 (-2.5 to 5.6)	0.50 (0.09-2.69)	.68
Composite perinatal outcome, No. (%) <sup>e</sup>	22 (14.7)	48 (32.0)	-17.3 (-27.0 to -7.3) <sup>a</sup>	0.46 (0.29-0.72) <sup>a</sup>	.01

<sup>a</sup> Statistically significant.<sup>b</sup> No adjustment for multiple comparisons was made, so the findings of the secondary outcomes should be considered exploratory.<sup>c</sup> Neonatal death is death of a live-born infant within the first 28 days of life.<sup>d</sup> Perinatal death is intrauterine fetal death after 20 weeks of gestation or neonatal death.<sup>e</sup> Participants with the composite perinatal outcome had at least 1 of the following: necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity requiring therapy, blood culture-proven sepsis, or neonatal death.

analysis to 34 weeks of gestation, the incidence of spontaneous preterm birth was significantly lower in the pessary group compared with the control group (hazard ratio, 0.36; 95% CI, 0.54-0.87) (Figure 2).

### Prespecified Secondary Outcomes

The cervical pessary was associated with a significantly lower rate of spontaneous preterm birth at less than 37 weeks of gestation, longer gestational age at delivery and latency from randomization to delivery, higher birth weight, lower rate of admission to a neonatal intensive care unit, and lower incidence of adverse composite perinatal outcome compared with the control group. There was no significant between-group difference in the incidence of spontaneous preterm birth at less than 32 weeks or 28 weeks, but the trial was not powered for these outcomes (Table 2).

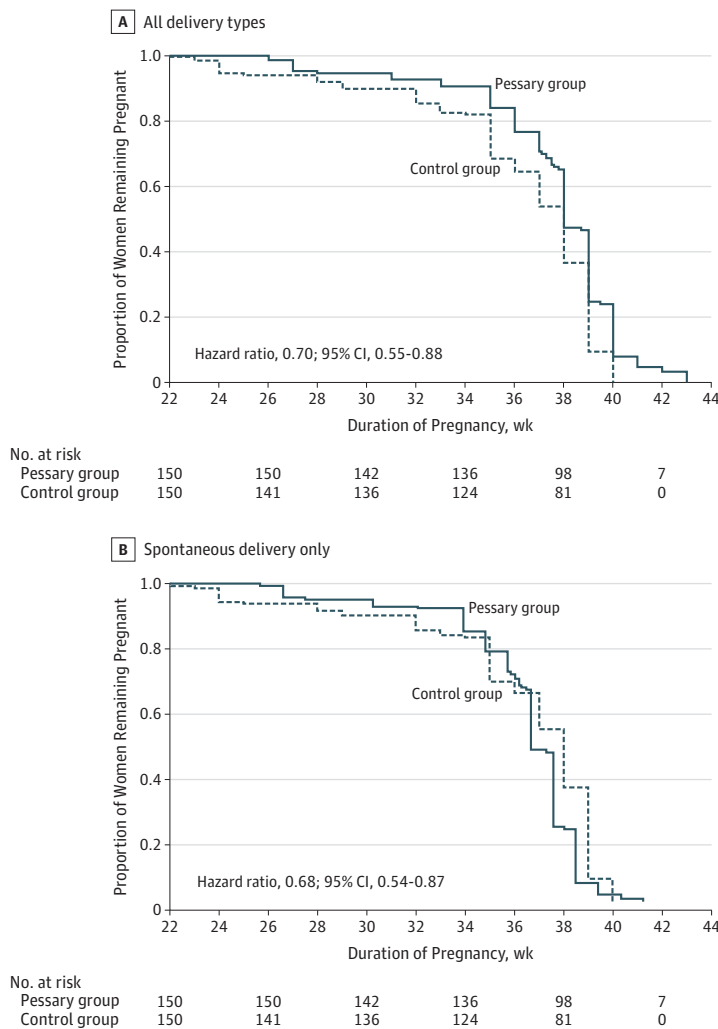
### Post Hoc Outcomes

The cervical pessary was associated with a significantly lower rate of preterm birth at less than 37 weeks and 34 weeks of gestation. The cervical pessary was also associated with significantly lower rates of respiratory distress syndrome and retinopathy of prematurity vs controls and with nonsignificantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, bronchopulmonary dysplasia, and blood culture-proven sepsis (eTable 2 in Supplement 2).

### Adverse Events

During follow-up, the pessary group had a higher rate than the control group of increased or new vaginal discharge (86.7% vs 46.0%; between-group difference, 40.7%; 95% CI, 30.1% to 50.3%), but no significant differences in pelvic discomfort were reported (Table 2).

Figure 2. Kaplan-Meier Plot of the Probability of Continued Pregnancy Without Delivery in the Cervical Pessary and Control Groups



No cases of maternal death or serious injuries during insertion or removal of the pessary were reported.

**Post Hoc Subgroup Analyses**

The tests of interaction for the post hoc subgroup analyses for receipt of concomitant therapy with vaginal progesterone and by cervical length of 10 mm or less vs greater than 10 mm were not significant ( $P=.56$  and  $P=.46$  for interaction, respectively) (eTable 3 in Supplement 2).

**Discussion**

This RCT showed that in asymptomatic women with singleton pregnancies without prior spontaneous preterm birth but with a transvaginal ultrasound cervical length of 25 mm or less, use of a cervical pessary resulted in a statistically significantly lower rate of spontaneous preterm birth than no pessary. Cervical pessary was also associated with a signifi-

cant difference in the secondary outcomes of longer gestational age at delivery, longer latency, and a lower incidence of a composite of adverse neonatal outcomes but with a higher rate of vaginal discharge.

This study did not support earlier findings of a meta-analysis of 3 RCTs that showed no beneficial effect of a cervical pessary in reducing spontaneous preterm birth in women with a singleton gestation and a cervical length of 25 mm or less.<sup>13</sup> None of the included studies<sup>9-11</sup> were blinded for outcome assessors, data collectors, or data analysts. Moreover, the higher rate of preterm birth in the control group in 1 of the trials (26.8%)<sup>11</sup> is not concordant with those of the control groups of the other 2 trials (5.5% and 11.3%).<sup>9,10</sup> More than half of the women included in the meta-analysis (932/1420) came from 1 large trial by Nicolaides et al,<sup>9</sup> which drives the summary statistics. This trial was methodologically very different from our study. Nicolaides et al included both women without prior preterm birth and those with prior preterm birth, and the study included multiple sites, some of which did not enroll many

participants, raising the possibility of lesser experience with pessary placement and management.<sup>9</sup> The current study's trial protocol included hands-on training and a requirement for all staff to demonstrate pessary insertion competence on a live model, while Nicolaides et al<sup>9</sup> did not include this type of training. The median cervical length at randomization was lower in this study compared with the trial by Nicolaides et al (approximately 12 mm vs 20 mm) and the rate of very short cervix was higher (79% vs 29% for cervical length  $\leq 15$  mm). The different results between the trials raises the question of whether a cervical pessary can be effective only at very low cervical length cutoffs, although there was no effect modification by cervical length in the current study.

The results of the current study are consistent with those of the trial by Goya et al,<sup>11</sup> which concluded that a cervical pessary could prevent preterm birth in a population of appropriately selected at-risk women previously screened for cervical length assessment on transvaginal ultrasound at the midtrimester visit. There were more women with prior preterm birth in the trial by Nicolaides et al<sup>9</sup> (154/932 [16.5%]) compared with the trial by Goya et al<sup>11</sup> (41/380 [10.8%]). This raises the question of whether a cervical pessary can be effective only in women with a short cervix but without prior preterm birth.

Different strategies have been adopted for prevention of preterm birth, including progesterone use,<sup>5,17-19</sup> cerclage,<sup>6-8,20,21</sup> cervical pessary use,<sup>9-14</sup> and lifestyle modifications such as smoking cessation,<sup>22</sup> diet,<sup>23</sup> aerobic exercise,<sup>24,25</sup> and nutritional supplements.<sup>26-30</sup> Cervical cerclage is an invasive technique requiring anesthesia and an operating room.<sup>31</sup> Therefore, increasing interest has focused on use of a pessary for prevention of preterm birth. A cervical pessary is relatively non-invasive, is easy to use, does not require anesthesia, can be used in an outpatient clinic setting, and is easily removed when necessary.<sup>32</sup> The exact mechanism of the possible efficacy of a cervical pessary to prevent spontaneous preterm birth in women with short cervical length is not completely clear. Vitsky<sup>33</sup> first suggested in 1961 that the incompetent cervix is

aligned centrally, with no support except the nonresistant vagina. A cervical pessary 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.<sup>32</sup> Another proposed mechanism is that the pessary could strengthen the immunological barrier between the chorioamnio-extraovular space and the vaginal microbiological flora, as cerclage has been postulated to do.<sup>34</sup>

The strengths of the current study included blinding of the outcome assessors, data collectors, and data analysts as well as the 100% follow-up obtained because all women included in the trial delivered at the study institution.

This study has several limitations. First, the open-label nature of the trial could have affected medical decision making, such as the timing of the removal of the pessary when a participant presented with contractions. However, outcome assessors and data analysts were blinded. Second, the exploratory nature of the secondary outcomes and the numerous secondary end points with no adjustment for multiple comparisons could have led to type I error. Third, the single-center nature of the trial raises the question of the external generalizability of the findings. Fourth, all women in both groups underwent vaginal swabs for bacteriological analysis. The practice of screening and treating for vaginal infections during pregnancy is a subject of debate and is not currently recommended.

## Conclusions

Among women without prior spontaneous preterm birth who had asymptomatic singleton pregnancies and short transvaginal cervical length, use of a cervical pessary, compared with no pessary use, resulted in a lower rate of spontaneous preterm birth at less than 34 weeks of gestation. The results of this single-center, nonblinded study among selected pregnant women require confirmation in multicenter clinical trials.

### ARTICLE INFORMATION

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**Correction:** This article was corrected on May 1, 2018, for an error in the definition of cervical length categories, and on May 9, 2019, for a misspelled collaborator name.

**Author Contributions:** Dr Martinelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:** Saccone, Martinelli.

**Drafting of the manuscript:** Saccone, Maruotti, Giudicepietro.

**Critical revision of the manuscript for important intellectual content:** Saccone, Martinelli.

**Statistical analysis:** Saccone.

**Administrative, technical, or material support:** Maruotti, Giudicepietro.

**Supervision:** Saccone, Martinelli.

**Other:** Giudicepietro.

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