

## OBSTETRICS

# Cervical pessary for preventing preterm birth in twin pregnancies with maternal short cervix after an episode of threatened preterm labor: randomised controlled trial



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**BACKGROUND:** No intervention has proved effective to date in reducing the spontaneous preterm birth rate in twin pregnancies following an episode of threatened preterm labor and with a short cervix remaining. This study was designed to ascertain whether cervical pessaries are useful in preventing spontaneous preterm birth in women with twin pregnancies and a short cervix remaining after a threatened preterm labor episode.

**STUDY DESIGN:** This open, randomized, controlled trial was conducted in 132 pregnant women who had not delivered 48 hours after a threatened preterm labor episode and had a short cervix remaining ( $\leq 20$  mm between 24<sup>0</sup> and 29<sup>6</sup> weeks and  $\leq 10$  mm between 30<sup>0</sup> and 33<sup>6</sup> weeks). Patients were randomly assigned to cervical pessary ( $n = 67$ ) or routine management ( $n = 65$ ). The primary outcome was the spontaneous preterm birth rate before 34 weeks. Spontaneous preterm birth before 28 and 37 weeks and neonatal morbidity and mortality were also evaluated in an intention-to-treat analysis.

**RESULTS:** Significant differences were observed in the spontaneous preterm birth rate before 34 weeks between the pessary and routine management groups (11 of 67 [16.4%] in the pessary group vs 21 of 65 [32.3%] in the control group; relative risk, 0.51 [confidence interval, 0.27-

0.97];  $P = .03$ ). No significant differences were observed in the preterm birth rate  $< 28$  weeks or  $< 37$  weeks between groups. The pessary group less frequently required readmission for new threatened preterm labor episodes (4 of 67 [5.6%] vs 14 of 65 [21.5%]; relative risk, 0.28 [confidence interval, 0.10–0.80];  $P = .009$ ). Significant reduction was observed in the number of neonates weighing less than 2500 g (17.9% [24 of 134] vs 70.8% [92 of 130]; relative risk, 0.25 [confidence interval, 0.15–0.43];  $P < .0001$ ).

**CONCLUSION:** Pessary use did significantly lower the spontaneous preterm birth rate before 34 weeks in twin pregnancies with maternal short cervix remaining after a threatened preterm labor episode. Pessary use also reduced the threatened preterm labor recurrence and neonates' weight less than 2500 g.

**Key words:** Arabin pessary, arrested preterm labor, cervical pessary, fetal maturation, high-risk pregnancy, neonatal morbidity, neonatal mortality, preterm birth, preterm birth prevention, respiratory distress syndrome, short cervical length, short cervix, threatened preterm labor, tocolysis, tocolytic treatment, twin pregnancy

Spontaneous preterm birth is the most common cause of perinatal morbidity and mortality worldwide and is responsible for 70% of neonatal deaths and approximately 50% of long-term neurodevelopmental disabilities. Only 2–3% of newborns are products of multiple pregnancies that carry a substantial risk of preterm delivery, accounting for 15–20% of all preterm births.<sup>1</sup> Approximately 60% of twins are born preterm, and 40% of twin pregnancies will suffer spontaneous labor or premature preterm rupture of membranes before 37 weeks of gestation.<sup>2</sup>

Transvaginal sonographic cervical length at 20–24 weeks' gestation is a good predictor of spontaneous preterm birth in asymptomatic women with twin pregnancies.<sup>3–5</sup> Although a meta-analysis published in 2010 concluded that cervical length has limited accuracy in predicting spontaneous preterm birth in women with twin pregnancies and threatened preterm labor,<sup>4</sup> a study including 218 women with twin pregnancies compared with 1077 singleton pregnancies published in 2015 reported that the accuracy of cervical length measurement for predicting preterm birth in a threatened preterm labor episode was similar in both types of pregnancy.<sup>6</sup>

On the other hand, it is also well established that shorter cervical length on transvaginal sonography raises the risk of subsequent spontaneous preterm birth in patients.<sup>7</sup>

Only 22–29% of women with twin pregnancies with threatened preterm

labor will deliver within 7 days.<sup>8</sup> However, the risk of preterm birth is higher in women who remain pregnant after the first threatened preterm labor episode.<sup>9</sup>

Few studies evaluating interventions for preterm prevention after a threatened preterm labor episode and with a remaining maternal short cervix in twin pregnancies have been published. Maintenance tocolysis with nifedipine was ineffective for prolonging gestation in 1 study that included singleton and twin pregnancies.<sup>10</sup>

Two studies using progesterone as maintenance therapy after threatened preterm labor concluded that, given the frequent lack of blinding and the generally poor quality of the trials, a change in clinical care of women with arrested preterm labor could not be currently suggested.<sup>11,12</sup> No studies using cerclage or other maintenance tocolysis in this population at risk of spontaneous preterm birth (ie, twins after a threatened preterm labor episode and with

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## AJOG at a Glance

**Why was this study conducted?**

To identify an intervention among women at high risk of preterm birth.

**Key findings**

Pessary use did significantly lower the spontaneous preterm birth rate before 34 weeks in twin pregnancies with maternal short cervix remaining after a threatened preterm labor episode; pessary use also reduced the threatened preterm labor recurrence rate and some neonatal outcomes such as neonatal weight less 2500 g, necrotizing enterocolitis, and neonatal sepsis.

**What does this add to what is known?**

Only 1 study on pessary intervention to prevent spontaneous preterm birth after arrested preterm labor episodes in twins has been reported to date. However, as those authors stated, an important limitation of that randomized controlled trial was that it was halted for futility after interim analysis (18 twins per arm).

remaining short cervix) have been published.

A previous randomized control trial by our team published in July 2018 showed that cervical pessary reduced the spontaneous preterm birth rate before 37 weeks in singleton pregnancies after a threatened preterm labor episode and with a short cervix remaining.<sup>13</sup> Thus, we aimed to assess the effect of cervical pessary after a threatened preterm labor episode in twin pregnancies.

**Materials and Methods****Trial design**

A prospective open randomised clinical trial was conducted at the Hospital Universitari Vall d'Hebron (Barcelona, Spain) from December 2010 to December 2014. The hospital ethics committee approved the protocol.

**Participants**

Women with twin pregnancies and short cervical length remaining after arrested preterm labor were considered for inclusion in the trial. Threatened preterm labor was defined as regular uterine contractions (3–5 every 10 minutes) on fetal heart rate monitoring between 24<sup>0</sup> weeks and 33<sup>6</sup> weeks of gestation with cervical dilation or transvaginal sonographic cervical length shortening according to gestational age ( $\leq 20$  mm between 24<sup>0</sup> and 29<sup>6</sup> weeks and  $\leq 10$  mm between 30<sup>0</sup> and 33<sup>6</sup> weeks).

Cervical length was measured according to Fetal Medicine Foundation

criteria<sup>14</sup> and the normal Spanish cervical length distribution.<sup>15</sup> If no contractions were reported by the patient or detected on fetal heart rate monitoring between 6 and 12 hours after tocolysis withdrawal (48 hours after admission), the threatened preterm labor episode was considered arrested.

A new transvaginal cervical length measurement was then taken prior to randomization and posterior discharge. Women with remaining a cervical length at or below the reported cutoff points after an arrested preterm labor episode were invited to take part in the trial.

According to our threatened preterm labor protocol, hospitalization was required, tocolytic treatment was initiated, and corticosteroids were administered for fetal maturation (betamethasone 12 mg, intramuscularly daily for 2 days). All patients received tocolysis. Atosiban was the only tocolytic used owing to its low adverse event rate in twin pregnancies.

On admission, vaginal speculum examination was performed to rule out cervical dilation or visible membranes, cervical and vaginal swabs were obtained for microbiological study (culture for trichomonas, candidas, group B streptococcus, and bacterial vaginosis), appropriate treatment given if a vaginal infection was suspected and amniocentesis indicated to rule out subclinical chorioamnionitis (positive Gram, glucose level  $< 15$  mg/dL or positive cultures).

Suspected clinical chorioamnionitis or positive amniotic fluid culture at admission for threatened preterm labor was both exclusion criteria.

Inclusion criteria were twin pregnancies, minimum maternal age 18 years, and gestational age between 24<sup>0</sup> and 33<sup>6</sup> weeks with arrested preterm labor and short cervical length remaining. Exclusion criteria are listed in Figure 1. Gestational age was determined from menstrual history and confirmed by fetal crown-rump length measurement at a first-trimester scan.

Quality control screening, data handling, and verification of protocol adherence at the Hospital Universitari Vall d'Hebron were carried out on a regular basis by trial coordinators. Obstetricians who performed the scans had received extensive training and passed a practical examination supervised by an expert to demonstrate their competence in cervical assessment. All images of the cases included in the trial and all cases of preterm birth were reviewed and discussed.

**Randomization and masking**

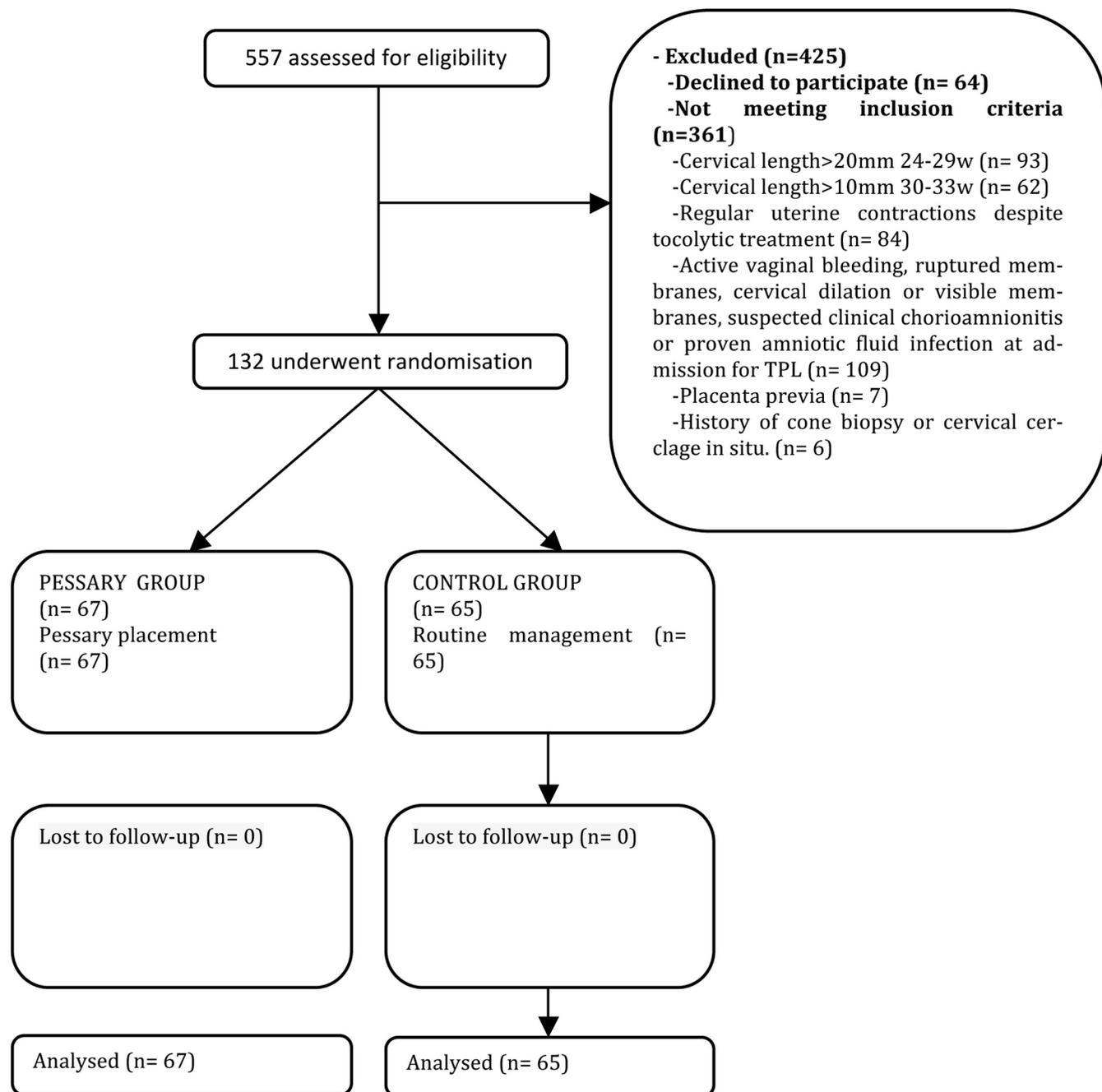
After providing their written informed consent, women were randomly assigned to cervical pessary insertion or routine management at a 1:1 ratio. The randomization was stratified by gestational age (24<sup>0</sup> and 29<sup>6</sup> weeks and between 30<sup>0</sup> and 33<sup>6</sup> weeks). The randomization sequence was computer generated with variable blocks of 2 and 4. The random-number lists were created by the Statistics Unit of the Vall d'Hebron Hospital Research Institute. The allocation code was disclosed after the patient's initials had been confirmed. The randomization sequence was not accessible to the recruiters or the trial coordinator.

This study was open label because masking to intervention was not possible, and therefore, while the attending clinicians were aware of the allocated interventions, the neonatologists and statisticians were not.

**Interventions**

Patients allocated to the pessary group had one inserted and were given detailed

**FIGURE 1**  
Exclusion criteria



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instruction on possible side effects such as vaginal discharge or pessary descent. In both groups, special emphasis was placed on the need to immediately report any adverse symptom(s) such as uterine contractions or hydrorrhea. Sexual intercourse was permitted in both groups.

Correct placement of the pessary was determined by transvaginal ultrasound, and cervical length was measured according to the pessary carrier CL-measuring technique described by our team.<sup>16,17</sup> CE (Communauté Européenne—European Community)—certified one-size cervical pessaries for

preventing spontaneous preterm birth were used: 65 mm × 25 mm × 35 mm purchased from Dr Arabin GmbH & Co (Witten, Germany). All these interventions were performed on the same day.

Both groups were seen every month until delivery. The following were

**TABLE 1**  
**Secondary outcomes**

- Spontaneous delivery before 28 completed weeks.
- Spontaneous delivery before 37 completed weeks.
- Preterm prelabor rupture of membranes.
- Recurrence of threatened preterm labor: number of hospital subsequent admissions due to TPL.
- Interval to delivery in days from randomization.
- Use of tocolytic treatment (type of tocolytic, days of treatment, dosage and number of cycles).
- Significant maternal adverse effects:
  - Heavy bleeding
  - Cervical tear
  - Uterine rupture
  - Physical or psychological intolerance to pessary
- Maternal effects associated with pessary use (discharge, removal rate, and repositioning rate).
- Birthweight: in grams.
- Intrauterine fetal demise: antepartum or intrapartum death.
- Neonatal death: after delivery or within 28 days of birth.
- Neonatal morbidity: major adverse event(s) before hospital discharge [IVH, RDS, RP, NE, S, need for neonatal intensive care, need for ventilation, phototherapy, antibiotics, or blood transfusion].
- Composite adverse outcomes (including IVH, RDS, RP, NE, and S)

IVH, intraventricular hemorrhage; NE, necrotizing enterocolitis; PTL, threatened preterm labor; RDS, respiratory distress syndrome; RP, retinopathy of prematurity; S, proven or suspected sepsis.

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carried out at each visit: (1) transabdominal ultrasound for fetal well-being; (2) vaginal swab for study of microbiological infection; and (3) transvaginal ultrasound for cervical length measurement in the routine management group following the Fetal Medicine Foundation criteria and in pessary carriers according to the previously mentioned measuring technique.

The pessary was removed during the 37th week of gestation. Indications for removal before then were active vaginal bleeding, severe patient discomfort, or persistent uterine contractions despite tocolytic treatment if a new threatened preterm labor episode occurred after study inclusion and pessary placement (more than 5 contractions every 30 minutes, with no reduction or cessation with tocolytic drugs).

The pessary was not removed if vaginal infection was suspected or detected after pessary insertion and

appropriate therapy was prescribed. Preterm premature rupture of membranes was also not a removal indication, and our current hospital preterm premature rupture of membranes protocol (ie, hospitalization if required and appropriate antibiotic treatment given) was followed in these patients; only if delivery began or chorioamnionitis was detected was the pessary removed. Patients whose pessary was removed (even on the day of insertion) remained in the trial.

### Outcome measures

The primary outcome was spontaneous preterm birth before 34 weeks (238 days) of gestation. Secondary outcomes are shown in [Table 1](#).

### Data analysis

Sample-size calculation was based on a reduction in the incidence of spontaneous delivery before 34 weeks from

50% in the routine management group to 25% in the pessary group, with power of 80%. To detect this difference at a significance level of 5% with 5% losses, we needed to recruit 122 patients (61 per arm). Post hoc analyses were made in 2 groups of patients: one in patients randomized before 30 weeks and in the other after 30 or more weeks.

Statistical analysis was performed according to the intention-to-treat principle. Data were expressed as means and SD for quantitative variables and frequency and percentage for qualitative variables. Given that twin pregnancies ended in 2 babies, neonatal outcomes were analyzed as nonindependent data if they occurred in the same birth (cluster by mother analysis).<sup>18</sup>

Relative risk and 95% confidence interval were calculated to estimate pessary effect on spontaneous preterm birth before 28, 34, and 37 weeks and other pregnancy outcomes, safety, and perinatal outcomes. A multivariable logistic regression model was fitted to assess the risk of spontaneous preterm birth before 34 weeks (adjusting for previous preterm birth, cervical length at randomization, gestational age at randomization, ethnicity, smoking, and body mass index).<sup>19</sup>

The risk of spontaneous preterm birth from randomization to 34 weeks and 37 weeks was assessed using Kaplan-Meier analysis,<sup>20</sup> in which gestational age was the time scale, spontaneous delivery was the event, and elective deliveries were treated as censored. For purposes of this analysis, all pregnancies were considered to be no longer at risk at the start of the 34th week or 37th week, respectively.

Hazards ratios were calculated using Cox regression models. The number of patients needed to treat to prevent preterm birth before 34 weeks with the use of cervical pessary was calculated based on relative risk. All *P* values were bilateral and a type I error of 5% was considered. All statistical analyses were performed with the SPSS software package, version 16 (SPSS Inc, Chicago, IL) and Stata 13.1 (Stata Corp, College Station, TX). No interim analysis was planned for this trial.

## Results

The trial was conducted from December 2010 to December 2014. During the study period, 557 women were assessed for eligibility. Of these, 425 were excluded: 64 declined to participate and 361 did not meet the inclusion criteria.

One hundred thirty-two women with twin pregnancies with threatened preterm labor (23.7%) agreed to participate and were randomly assigned to pessary ( $n = 67$ ) or routine management ( $n = 65$ ) (Figure 1). None were lost to follow-up (Figure 1). The groups were well balanced at baseline (Table 2). None of the patients with a history of preterm birth received progesterone before or during study follow-up.

Spontaneous preterm birth before 34 weeks of gestation was 16.4% (11 of 67) in the pessary group and 32.3% (21 of 65) in the routine management group, showing a 50% reduction in our primary outcome. These differences were statistically significant (relative risk [RR], 0.51 [confidence interval (CI), 0.27–0.97];  $P = .03$ ). Thus, the cumulative percentage of patients who did not give birth spontaneously before 34 weeks was significantly higher in the pessary group than in the routine management group (Figure 2A). Three had medically indicated preterm deliveries (1 in the pessary group and 2 in the routine management group).

The risk of spontaneous preterm birth before 34 weeks of gestation did not vary significantly between groups with regard to maternal age, body mass index, race, obstetric history, or cervical length at the time of randomization (multivariate regression model). The number needed to treat to avoid 1 preterm delivery before 34 weeks with the use of a cervical pessary was estimated at 7 (6.3) patients.

However, the spontaneous preterm birth rate before 37 weeks of gestation was 71.6% (48 of 67) in the pessary group and 72.3% (47 of 65) in the routine management group (RR, 0.99 [CI, 0.8–1.23];  $P = .93$ ). The risk of spontaneous preterm birth before 37 weeks of gestation in both groups was assessed using Kaplan-Meier analysis (Figure 2B).

Mean interval to delivery was 47 days in the pessary group and 35 in the

**TABLE 2**  
Characteristics of study participants<sup>a</sup>

Variables	Pessary (n = 67)	No pessary (n = 65)
Maternal age, y	37 (4.5)	36 (5.6)
Body mass index <sup>b</sup>	24.3 (1.5)	24.1 (1.8)
Obstetric history		
Nulliparous	30 (46.15%)	28 (43.75%)
Parous with no previous preterm birth(s)	26 (40%)	26 (40.63%)
Parous with no previous preterm birth(s) Parous with $\geq 1$ previous preterm births	9 (13.85%)	10 (15.63%)
Cigarette smoking during pregnancy	10 (14.9%)	7 (10.8%)
Race/ethnicity <sup>c</sup>		
White	40 (59.7%)	37 (56.9%)
Hispanic	15 (22.4%)	16 (24.6%)
Others	12 (17.9%)	12 (18.5%)
Monochorionic gestations	12 (17.9%)	13 (20%)
Assisted reproduction techniques	22 (32.8%)	20 (30.7%)
At randomization		
Gestational age, wks	28 (3.1)	29 (3)
Cervical length, mm	10 (5.4)	11 (4.5)
Funneling	7 (10.45%)	10 (15.4%)
Sludge	2 (3%)	1 (1.54%)
Positive vaginal cultures	9 (13.43%)	6 (9.23%)
Positive endocervical cultures	8 (11.94%)	6 (9.23%)
Positive amniotic fluid culture	0 (0%)	0 (0%)
Tocolytic therapy		
Oxytocin receptor antagonist	67 (100%)	65 (100%)
B-mimetic	0 (0%)	0 (0%)
Corticosteroid treatment for fetal maturation	67 (100%)	65 (100%)

Data are number (percentage) or mean (SD).

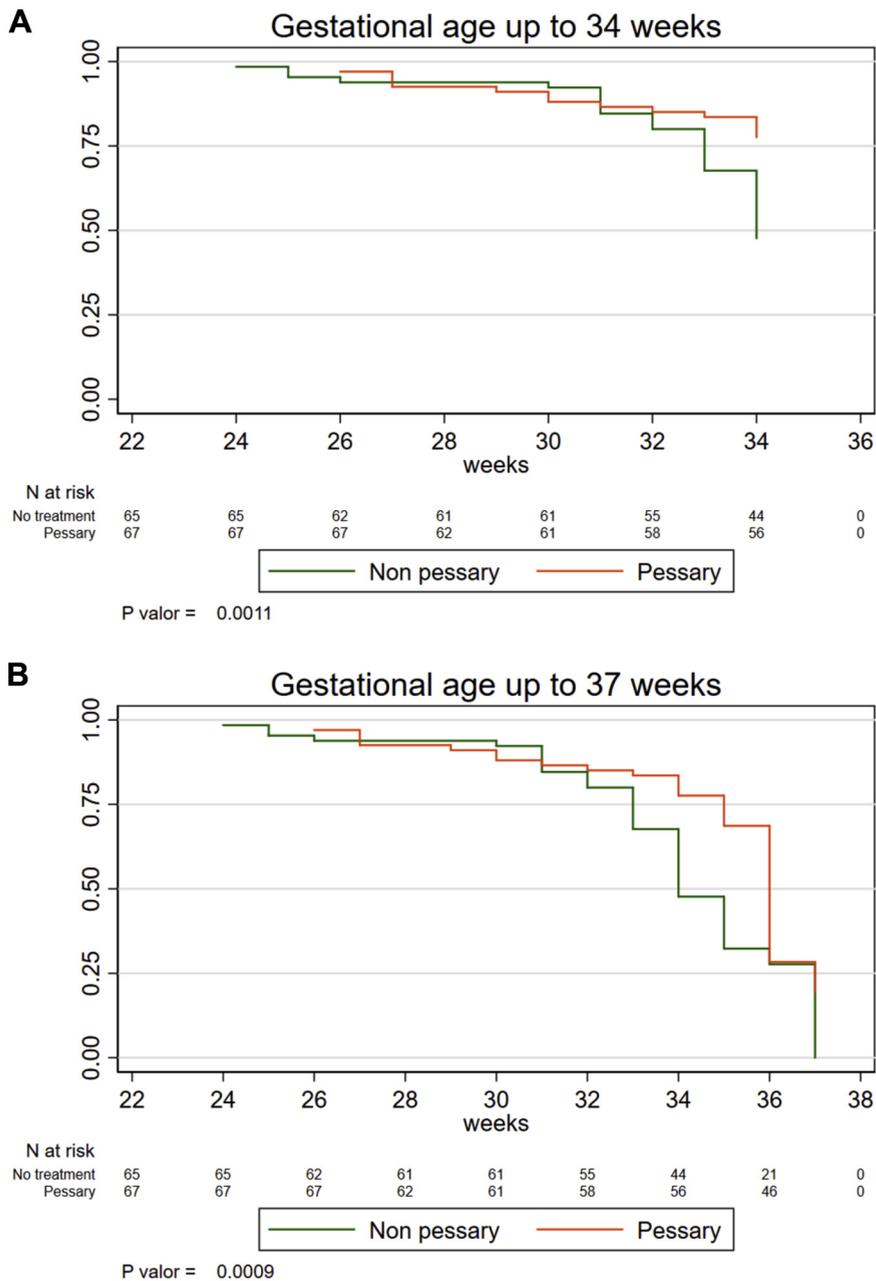
<sup>a</sup> No significant differences between groups, prior to losses to follow-up; <sup>b</sup> Body mass index was weight in kilograms divided by the square of height in meters; <sup>c</sup> Race was self-reported.

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routine management group ( $P = .03$ ). Mean interval to delivery in patients randomized between 24 and 31<sup>6</sup> weeks was 52 days in the pessary and 40 days in the routine management groups ( $P = .04$ ). Patients in the routine management group required readmission for 1 or more threatened preterm labor episodes more frequently than those in the pessary group (21.5% [14 of 65] vs 6% [4 of 67]). These differences were statistically significant (RR, 0.28 [CI, 0.10–0.80];  $P = .009$ ).

No statistical differences in the preterm premature rupture of membranes rate were observed in either group (9.2% [6 of 65] vs 1.5% [1 of 67], RR, 0.16 [CI 0.02–1.31];  $P = .06$ ). However, gestational bleeding occurred, with statistical significance, more frequently in the routine management group than in the pessary group (14.1% [9 of 65] vs 0% [0 of 67]) (Table 3).

No differences were observed in results of vaginal/cervical microbiological study or treatment during follow-up.

**FIGURE 2**  
Gestational ages**A**, Gestational age up to 34 weeks. **B**, Gestational age up to 37 weeks.Merced et al. Cervical pessary in twins after threatened preterm labor. *Am J Obstet Gynecol* 2019.

Oral clindamycin 300 mg every 12 hours for 7 days was the most frequent antibiotic used in both groups.

The cesarean delivery rate was similar between groups (43.08% [28 of 65] vs 42.42% [28/ of 67]) (Table 3).

No major maternal pessary use-related adverse events occurred

(Table 4). However, the following side effects did occur in the pessary group: all pregnant women with a pessary had vaginal discharge after pessary placement (67 of 67), and 14.9% (10 of 67) of patients required pessary repositioning without removal. Pessary removal for preterm delivery was required in 16.4%

patients (11 of 67). Pessary removal on patient request did not occur. No changes in pessary size were required (Table 4).

Regarding neonatal morbidity outcomes, a significant reduction was observed in the number of neonates weighing less than 2500 g: 17.9% (24 of 134) in the pessary group vs 70.8% (92 of 130) in the routine management group (RR, 0.25 [CI, 0.17–0.37];  $P < .0001$ ); necrotizing enterocolitis: 0% (0 of 134) in the pessary group vs 4.6% (6 of 130) in the routine management group; and neonatal sepsis: 0% (0 of 134) in the pessary group vs 6.2% (8 of 130) in the routine management group. No differences were found between groups in terms of composite neonatal outcomes and mortality (Table 5).

The post hoc analyses were made after randomization before and after 30 weeks because the cutoff points differed between groups. The results (Supplemental Tables 1–6) concurred fully with those reported in previous text.

## Comment

### Principal findings

The main aim of this study (to demonstrate a reduction in the preterm birth rate before 34 weeks of gestation) was achieved. Pessary use reduced the prematurity effect in this population (16.4% [11 of 67]) vs 32.3% [21 of 65]). However, no differences were observed in the preterm birth rate before 37 weeks, probably because the majority of twin pregnancies end before 37 weeks, as shown in our study.

The time elapsed between the threatened preterm labor episode and delivery, measured in days, was significantly longer in the pessary users (mean, 12 days,  $P = .03$ ).

The preterm premature rupture of membranes rate was higher in the routine management group than in the pessary group (9.2% [6 of 67]) vs 1.5% [1 of 65]); however, these differences were not significant. Our hypothesis regarding this difference is that the pessary-induced angulation and elongation of the cervical canal protect amniotic membranes from contact with the vaginal medium, thereby preserving their integrity.

**TABLE 3**  
**Results of pregnancy outcomes according to treatment group**

Variables	Pessary (n = 67)	No pessary (n = 65)	RR (CI 95%)	Pvalue
Spontaneous delivery at <34 wks	11 (16.4%)	21 (32.3%)	0.51(0.27–0.97)	.0332
Overall PB (included those induced) at <34 wks	12 (17.9%)	23 (35.4%)	0.56 (0.29–0.96)	.0317
Spontaneous delivery at <28 wks	5 (7.5%)	4 (6.2%)	1.21 (0.34–4.32)	1.000
Overall PB (included those induced) at <28 wks	5 (7.5%)	4 (6.2%)	1.21 (0.34–4.32)	1.000
Spontaneous delivery at <37 wks	48 (71.6%)	47 (72.3%)	0.99 (0.80–1.23)	.93
Overall PB (included those induced) at <37 wks	49 (73.1%)	49 (73.1%)	1.01 (0.87–1.43)	1.03
Gestational age at delivery, wks	35.1 (3.1)	34 (3.0)		.0441
Interval to delivery, d	47 (27.4)	35 (25.3)		.0265
Interval to delivery when randomization occurred <32 wks (days)	52 (26.7)	40 (25.8)		.0366
Positive vaginal cultures throughout pregnancy	7 (10.5%)	4 (6.2%)	1.70 (0.52–5.53)	.37
Ureaplasma urealyticum	5 (71.4%)	2 (50%)		
Escherichia coli	0 (0%)	2 (50%)		
Mycoplasma	2 (28.6%)	0 (0%)		
Positive endocervical cultures throughout pregnancy	6 (9%)	4 (6.2%)	1.46 (0.43–4.92)	.74
Ureaplasma urealyticum	5 (83.3%)	2 (50%)		
E coli	0 (0%)	2 (50%)		
Mycoplasma	1 (16.7%)	0 (0%)		
Chorioamnionitis	0 (0%)	0 (0%)	—	—
Bleeding in pregnancy	9 (14.1%)	0 (0%)	—	—
PPROM	6 (9.2%)	1 (1.5%)	0.16 (0.02–1.31)	.06
Subsequent TPL episodes	4 (6%)	14 (21.5%)	0.28 (0.10–0.80)	.0092
Cesarean delivery	28 (43.1%)	28 (42.4%)	0.98 (0.66–1.46)	.93

PB, preterm birth; PPRM, premature preterm rupture of membranes; RR, relative risk; TPL, threatened preterm labor.  
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The bleeding in pregnancy rate was significantly higher in the routine management group than in the pessary group (14.1% [9 of 65] vs 0% [0 of 67]). More studies are required in this population to fully understand these findings.

Although the sample size of our trial was not estimated to evaluate neonatal outcomes, statistical differences were observed between groups. Statistically significant reductions in neonates weighing less than 2500 g, necrotizing enterocolitis and neonatal sepsis were observed in the pessary group. More studies with an appropriate sample size are needed to ascertain these hopeful outcomes.

Although no differences were observed between groups in terms of obstetric or neonatal outcomes when

groups were stratified at randomization before 30 weeks or at 30 weeks or more, there appeared to be a trend toward a reduction in the preterm birth rate and morbidity in the pessary group. Furthermore, rates of obstetric bleeding and neonates weighing less than 2500 g were statistically and significantly lower in the pessary group when randomization was made before and after 30 weeks, probably because of the small sample size obtained when patients were stratified in 2 groups (sample size was calculated based on total numbers).

### Meaning of the results in context

Only 1 study on pessary intervention to prevent spontaneous preterm birth after arrested preterm labor episodes in twins has been reported to date.<sup>21</sup> However, as

those authors stated, an important limitation of that randomized controlled trial was that it was halted for futility after interim analysis (18 twins per arm). Therefore, they did not reach their required sample size, and thus, their results should be interpreted more cautiously than if they had. Some studies in singletons failed to yield satisfactory results.<sup>22–24</sup>

In relation to comparable trials in preterm birth, although we were not able to collect all core outcomes, we have the majority (maternal mortality, maternal infection or inflammation, prelabor rupture of membranes harm to the mother from intervention, gestational age at birth, offspring mortality, birth-weight, early neurodevelopmental morbidity, gastrointestinal morbidity,

**TABLE 4**  
**Results of pessary**

Variables	Pessary (n = 67)	No pessary (n = 65)	RR (CI 95%)	Pvalue
Side effects				
Vaginal discharge	65 (100%)	0 (0%)		< .0001
Pessary repositioning without removal	10 (14.9%)	—		
Pessary replacement	2 (2.99%)	—		
Pessary removal				
Medical indication	1			
Patient request	0			
Onset of labor despite tocolysis	10			

CI, confidence interval; RR, relative risk.

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infection, respiratory morbidity, and harm to offspring from intervention). The only one lacking is late neurodevelopmental morbidity because this is beyond the scope of our protocol. However, we consider all these outcomes should be included in all preterm birth studies to improve the comparability of trial results in the future.

### Clinical implications

Because a significant reduction in spontaneous preterm birth before 34

weeks was observed in pessary carriers, we could assume that pessary placement is a useful tool for preventing prematurity in this group of patients. Moreover, the significant reduction in neonatal morbidity achieved in our study could signal an improvement in the prognosis of these infants and address one in the most disabling problems in our specialty.

It should be pointed out that, when pessaries are used, patients may have a moderate white, inodorous, vaginal discharge. Furthermore, a proportion of

these patients (14.9% in our group) may report feeling the pessary inside the vagina after weeks without symptoms and require repositioning of the pessary. For this reason, patients should be advised to see their doctor if any abnormal symptom appears. Two cases of pessary replacement were reported in the entire group and tolerability was not an issue.

### Research implications

Although a considerable fall was observed in the spontaneous preterm birth rate, no significant reduction was found in composite neonatal morbidity. However, statistically significant reductions in neonates weighing less than 2500 g, necrotizing enterocolitis, and neonatal sepsis were found. The reason for this is unclear, and a larger sample may be necessary to demonstrate such a finding; the trial was not designed with sufficient power to address these endpoints.

The mechanism of action of cervical pessaries remains to be clarified. Theoretically, the potential effect relies on their mechanical ability to bend the cervix backward, slightly elongating it, and changing the uterocervical angle, in some way preserving its integrity.<sup>17,25</sup> Another mechanism of action to be

**TABLE 5**  
**Results of perinatal outcomes according to treatment group**

Variables	Pessary (n = 134)	No pessary (n = 130)	RR (CI 95%)	Pvalue
Fetal death	0	0	—	—
Neonatal death	0	0	—	—
Birthweight <1500 g	16 (11.9%)	18 (13.9%)	0.84 (0.30–2.36)	
Birthweight <2500 g	24 (17.9%)	92 (70.8%)	0.09 (0.04–0.21)	< .0001
Adverse outcomes				
Necrotizing enterocolitis	0 (0%)	6 (4.6%)	—	.01
Intraventricular hemorrhage	0 (0%)	0 (0%)	—	—
Respiratory distress syndrome	10 (7.5%)	12 (9.23%)	0.79 (0.23–2.75)	.71
Retinopathy	0 (0%)	2 (1.5%)	—	—
Treatment for sepsis	0 (0%)	8 (6.2%)	—	.003
Composite adverse outcomes	10 (7.5%)	14 (10.8%)	0.67 (0.20–2.23)	.51

CI, confidence interval; RR, relative risk.

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considered is the change in vaginal microbioma that may occur with the use of the cervical pessary in these high-risk patients and its role as a cause or effect.<sup>26,27</sup>

### Strengths and limitations

This randomized trial, the first to be conducted to date on the use of a cervical pessary for preterm birth prevention after a threatened preterm labor episode and a remaining maternal short cervix in twin pregnancies, yielded a reduction in the spontaneous preterm birth rate for which no useful tool to reduce the risk is available to date.

Although masking was impossible owing to the nature of the intervention, use of the pessary might have affected medical decision making. We believe that the nonmasked nature of this trial did not cause substantial bias because the endpoint of the trial was gestational age at delivery (objective outcome).

A further strength of our trial was that the research team comprised the clinicians who usually attend to women in the specialized preterm delivery unit; consequently, their pregnancies were followed by up fully experienced physicians, even those included in a trial, and not a separate research team. Patients also had rapid access to the clinic if any abnormal symptom or clinical change was perceived.

### Conclusion

A statistically significant reduction in the spontaneous preterm birth rate before 34 weeks was demonstrated, with no severe maternal or fetal side effects, indicating that the cervical pessary may be considered an economical (35 euros/unit) and reliable tool for reducing the risk of spontaneous preterm birth in twin pregnancies of women with a short cervix remaining after a threatened preterm labor episode, a high-risk population in whom no intervention has proven efficacious to date.

The threatened preterm labor recurrence rate was also reduced with pessary placement from 20% to 6%. Neonatal morbidity was also improved in the pessary group (neonate weight less than

2500 g, necrotizing enterocolitis, and neonatal sepsis), which could potentially lead to considerable social and financial savings. Further studies with larger sample sizes would be required to confirm these findings.

### Other information

#### Contributors include the following

Dr. Merced was the principal investigator at the Hospital Vall d'Hebron, contributed to study design, follow-up of patients and data collection, and wrote the first draft of both the protocol and manuscript. She is the guarantor for the paper. Dr Goya was the trial coordinator; contributed to study design, follow-up of patients, and data collection; and wrote the protocol and manuscript with Dr Goya. Drs Pratcorona and Rodó contributed to the study design and data collection. Dr Llurba was a member of the research group. Dr Higuera was the cervical assessment coordinator. Drs Carreras and Cabero reviewed both the protocol and the manuscript. Dr Cabero was the chairman. All authors had complete access to the data at the end of the trial and the decision to submit the manuscript for publication was taken at a joint meeting of the team, and all reviewed and approved the final version of the manuscript. The corresponding author then submitted it.

### Trial management

In addition to the authors, the following institutions and investigators participated in the PECEP-RETARD Trial Group: Silvia Arévalo, Mayte Avilés, Inés Calero, Manel Casellas, Marina Folch, Andrea Gascón, Manel Mendoza, Angeles Sanchez, and Anna Suy. ■

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SUPPLEMENTAL TABLE 1

Characteristics of study participants when randomization was <30 weeks<sup>a</sup>

Variables	Pessary (n = 43)	No pessary (n = 38)
Maternal age, y	37 (4.6)	36.5 (5.9)
Body mass index <sup>b</sup>	24.5 (1.5)	23.85 (1.6)
Obstetric history		
Nulliparous	22 (52.38%)	17 (45.95%)
Parous with no previous preterm birth(s)	13 (30.95%)	15 (40.54%)
Parous with $\geq 1$ previous preterm births	7 (16.67%)	5 (13.51%)
Cigarette smoking during pregnancy	6 (14%)	5 (13.2%)
Race/ethnicity <sup>c</sup>		
White	29 (67.44%)	25 (65.79%)
Hispanic	7 (16.28%)	7 (18.42%)
Others	7 (16.28%)	6 (15.79%)
At randomization		
Gestational age, wks	26 (1.8)	26 (1.9)
Cervical length, mm	13 (5.5)	13 (4.1)
Funneling	6 (14%)	2 (5.3%)
Sludge	2 (4.7%)	1 (2.6%)
Positive vaginal cultures	6 (14%)	4 (10.53%)
Positive endocervical cultures	5 (11.6%)	4 (10.5%)
Positive amniotic fluid culture	0	0
Tocolytic therapy		
Oxytocin receptor antagonist	43 (100%)	38 (100%)
B-mimetic	0 (0%)	0 (0%)
Corticosteroid treatment for foetal maturation	43 (100%)	38 (100%)
Assisted reproduction techniques	14 (32.6%)	15 (39.5%)
Monochorionic gestations	7 (16.3%)	11 (29%)

Data are number (percentage) or mean (SD).

<sup>a</sup> No significant differences between groups, prior to losses to follow-up; <sup>b</sup> Body mass index was weight in kilograms divided by the square of height in meters; <sup>c</sup> Race was self-reported.

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## SUPPLEMENTAL TABLE 2

## Results when randomization was before 30 weeks: pregnancy outcomes according to treatment group

Variables	Pessary (n = 43)	No pessary (n = 38)	RR (CI 95%)	Pvalue
Spontaneous delivery at <34 wks	8 (18.6%)	14 (36.84%)	0.5 (0.24–1.07)	.06
Spontaneous delivery at <28 wks	5 (11.6%)	4 (10.52%)	1.10 (0.32–3.82)	
Spontaneous delivery at <37 wks	31 (72.1%)	29 (76.3%)	0.94 (0.73–1.22)	.66
Gestational age at delivery, wks	36 (3.5)	34 (3.6)		.08
Interval to delivery, d	62 (26.3)	53 (26.5)		.07
Positive vaginal cultures throughout pregnancy	6 (13.9%)	2 (5.3%)		.27
Ureaplasma urealyticum	4 (66.7%)	1 (50%)		
Escherichia coli	0 (0%)	1 (50%)		
Mycoplasma	2 (33.3%)	0 (0%)		
Positive endocervical cultures throughout pregnancy	5 (11.6%)	2 (5.3%)		.43
Ureaplasma urealyticum	4 (80%)	1 (50%)		
E coli	0 (0%)	1 (50%)		
Mycoplasma	1 (20%)	0 (0%)		
Chorioamnionitis	0 (0%)	0 (0%)	—	—
Bleeding in pregnancy	0 (0%)	8 (21.6%)	—	.0013
PPROM	1 (2.33%)	4 (10.53%)	0.22 (0.03–1.89)	.18
Subsequent TPL episodes	4 (9.3%)	12 (31.6%)	0.29 (0.10–0.84)	.0120
Cesarean delivery	22 (52.4%)	13 (34.2%)	1.53 (0.90–2.59)	.10

CI, confidence interval; PPRM, premature preterm rupture of membranes; TPL, threatened preterm labor; RR, relative risk.

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## SUPPLEMENTAL 3

## Results: perinatal outcomes according to treatment group

Variables	Pessary (n = 86)	No pessary (n = 76)	RR (CI 95%)	Pvalue
Fetal death	0	0	—	—
Neonatal death	0	0	—	—
Birthweight <1500 g	14 (16.3%)	12 (15.8%)	1.04 (0.31–3.46)	.95
Birthweight <2500 g	16 (18.6%)	60 (79.0%)	0.06 (0.02–0.18)	< .0001
Adverse outcomes				
Necrotising enterocolitis	0 (0%)	6 (7.9%)	—	—
Intraventricular haemorrhage	0 (0%)	0 (0%)	—	—
Respiratory distress syndrome	10 (11.6%)	12 (15.8%)	0.70 (0.19–2.53)	.58
Retinopathy	0 (0%)	2 (2.6%)	—	—
Treatment for sepsis	0 (0%)	6 (7.9%)	—	—
Composite adverse outcomes	10 (11.6%)	12 (15.8%)	0.70 (0.19–2.53)	.58

CI, confidence interval; RR, relative risk.

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SUPPLEMENTAL TABLE 4

Characteristics of study participants when randomization was  $\geq 30$  weeks<sup>a</sup>

Variables	Pessary (n = 24)	No pessary (n = 27)
Maternal age, y	33 (4.3)	35 (5.3)
Body mass index <sup>b</sup>	24.2 (1.6)	24.4 (2.0)
Obstetric history		
Nulliparous	16 (66.7%)	16 (59.3%)
Parous with no previous preterm birth(s)	13 (56.5%)	11 (40.7%)
Parous with $\geq 1$ previous preterm births	2 (8.7%)	5 (18.5%)
Cigarette smoking during pregnancy	4 (16.7%)	2 (7.4%)
Race/ethnicity <sup>c</sup>		
White	11 (45.8%)	12 (44.4%)
Hispanic	8 (33.3%)	9 (33.3%)
Others	5 (20.8%)	6 (22.2%)
At randomization		
Gestational age, wks	31.5 (1.14)	32 (1.12)
Cervical length, mm	9 (2.7)	8 (2.5)
Funneling	1 (4.2%)	8 (29.6%)
Sludge	0	0
Positive vaginal cultures	3 (12.5%)	2 (7.4%)
Positive endocervical cultures	3 (12.5%)	2 (7.4%)
Positive amniotic fluid culture	0	0
Tocolytic therapy		
Oxytocin receptor antagonist	24 (100%)	27 (100%)
B-mimetic	0 (0%)	0 (0%)
Corticosteroid treatment for foetal maturation	24 (100%)	27 (100%)
Assisted reproduction techniques	8 (33.3%)	5 (18.5%)
Monochorionic gestations	5 (20.8%)	2 (7.4%)

Data are number (percentage) or mean (SD).

<sup>a</sup> No significant differences between groups, prior to losses to follow-up; <sup>b</sup> Body mass index was weight in kilograms divided by the square of height in meters; <sup>c</sup> Race was self-reported.

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SUPPLEMENTAL TABLE 5

Results when randomization was  $\geq 30$  weeks: pregnancy outcomes according to treatment group

Variables	Pessary (n = 24)	No pessary (n = 27)	RR (CI 95%)	Pvalue
Spontaneous delivery at <34 wks	3 (12.5%)	7 (25.9%)	0.48 (0.14–1.66)	.30
Spontaneous delivery at <37 wks	17 (70.8%)	18 (66.7%)	1.06 (0.73–1.54)	.74
Gestational age at delivery, wks	36 (2.1)	34 (1.8)		.13
Interval to delivery, d	32.5 (14.9)	20 (11.5)		.12
Positive vaginal cultures throughout pregnancy	1 (4.2%)	2 (7.4%)		1.00
Ureaplasma urealyticum	1 (50%)	1 (50%)		
<i>Escherichia coli</i>	1 (50%)	1 (50%)		
Mycoplasma	0 (0%)	0 (0%)		
Positive endocervical cultures throughout pregnancy	1 (4.2%)	2 (7.4%)		1.00
Ureaplasma urealyticum	1 (100%)	1 (50%)		
<i>E coli</i>	0 (0%)	1 (50%)		
Mycoplasma	0 (0%)	0 (0%)		
Chorioamnionitis	0 (0%)	0 (0%)	—	—
Bleeding in pregnancy	0 (0%)	1 (3.7%)	—	—
PPROM	0 (0%)	2 (7.4%)	—	—
Subsequent TPL episodes	0 (0%)	2 (7.4%)	—	—
Cesarean delivery	6 (25%)	15 (55.56%)	0.45 (0.21–0.97)	.0269

CI, confidence interval; PPRM, premature preterm rupture of membranes; TPL, threatened preterm labor; RR, relative risk.

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SUPPLEMENTAL TABLE 6

## Results: perinatal outcomes according to treatment group

Variables	Pessary (n = 48)	No pessary (n = 54)	RR (CI 95%)	Pvalue
Fetal death	0	0	—	—
Neonatal death	0	0	—	—
Birthweight <1500 g	2 (4.2%)	6 (11.1%)	0.38 (0.0-1.77)	0.27
Birthweight <2500 g	8 (16.7%)	32 (59.3%)	0.14 (0.04-0.52)	<0.0001
Adverse outcomes				
Necrotising enterocolitis	0	0	—	—
Intraventricular haemorrhage	0	0	—	—
Respiratory distress syndrome	0	0	—	—
Retinopathy	0	0	—	—
Treatment for sepsis	0 (0%)	2 (3.7%)	—	—
Composite adverse outcomes	0 (0%)	2 (3.7%)	0.70 (0.28–1.73)	.44

CI, confidence interval; RR, relative risk.

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