*Original Research*

# Pessary Plus Progesterone to Prevent Preterm Birth in Women With Short Cervixes

## *A Randomized Controlled Trial*

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**OBJECTIVE:** To test the effectiveness of cervical pessary in addition to vaginal progesterone for the prevention of preterm birth in women with midpregnancy short cervixes.

**METHODS:** We performed a multicenter, open-label, randomized controlled trial in 17 perinatal centers. Asymptomatic women with singleton or twin pregnancies and cervical lengths of 30 mm or less, measured at 18 0/7–22 6/7 weeks of gestation, were randomized to cervical pessary plus vaginal progesterone (pessary plus progesterone group) or vaginal progesterone only (progesterone-only group) (200 mg/day). Treatments were used from randomization to 36 weeks of gestation or delivery. The primary outcome was a composite of neonatal mortality and morbidity. Secondary outcomes were delivery before 37 weeks and before 34 weeks of gestation. Analysis was performed according to intention to treat.

**RESULTS:** Between July 9, 2015, and March 29, 2019, 8,168 women were screened, of whom 475 were randomized to pessary and 461 to progesterone only. The composite perinatal outcome occurred in 19.2% (89/463) of the women in the pessary group compared with 20.9% (91/436) of the women in the progesterone-only group (adjusted risk ratio [aRR] 0.88, 95% CI 0.69–1.12). Delivery rates before 37 weeks of gestation were 29.1% compared with 31.4% (aRR 0.86, 95% CI 0.72–1.04); delivery rates before 34 weeks were 9.9% compared with 13.9% (aRR 0.66, 95% CI 0.47–0.93). Women in the pessary group had more vaginal discharge (51.6% [245/476] vs 25.4% [117/479] [$P<.001$]), pain (33.1% [157/476] vs 24.1% [111/479] [$P=.002$]), and vaginal bleeding (9.7% [46/476] vs 4.8% [22/479] [$P=.004$]).

**CONCLUSION:** In asymptomatic women with short cervixes, the combination of pessary and progesterone did not decrease rates of neonatal morbidity or mortality when compared with progesterone only.

**CLINICAL TRIAL REGISTRATION:** Brazilian Clinical Trial Registry (ReBec), UTN:U1111-1164-2636.

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Globally, the prematurity rate is 10.6%,[1] resulting in approximately 1 million neonatal deaths each year.[2] Goals proposed by the World Health Organization of reducing preterm birth rates and reducing birth-attributable mortality due to preterm birth by 50% by 2025 have not resulted in improvement so far.[3]

Approximately one third of all preterm births are medically indicated, and the rest occur spontaneously. Midpregnancy short cervix is associated with a five times higher risk for spontaneous preterm birth.[4] In women with short cervixes, progestogens (in a natural form that can be used vaginally or as synthetic 17α-hydroxyprogesterone caproate) and cervical pessary have been proposed to reduce the risk of preterm birth.[5,6] The cervical pessary is a silicone device placed circumferentially around the cervix, thereby changing its inclination angle, relieving the uterine pressure over the internal cervical os.[7]

Although there is evidence that vaginal progestogens lower the rate of spontaneous preterm birth in women with short cervixes and women with previous preterm births,[8,9] it is unknown whether addition of a pessary further reduces the risk of preterm birth. Studies that evaluate cervical pessaries show conflicting results.[10–15] Some studies indicate a reduction in preterm birth,[13,16–19] whereas other studies report no effect at all.[11,15,20,21] In view of this divergence, and hypothesizing that a mechanical (pessary) treatment would add to the reduction of preterm birth in combination with a biochemical (progesterone) treatment, we conducted a multicenter randomized controlled trial (RCT) that compared cervical pessary plus vaginal progesterone compared with vaginal progesterone only in women with short cervixes in midpregnancy.

## METHODS

We performed a multicenter, open-label RCT between July 15, 2015, and March 29, 2019. The study was conducted in 17 hospitals that collaborate in the "Network for Studies in Reproductive and Perinatal Health." The P5 (Pessary Plus Progesterone to Prevent Preterm Birth) trial was submitted for registry within the Brazilian Clinical Trial Registry as UTN: U1111-1164-2636 before enrollment of the first participant. The trial registry platform finished internal procedures and published the online protocol after enrollment started without any changes to the submitted protocol. The National Research Ethics approved the protocol under number u38417114.0.1001.5404 and each center received protocol approval through their local Institutional Review Boards.

As a screening process, women with pregnancies (singleton or twin) between 18 0/7 and 22 6/7 weeks of gestation were offered cervical length measurement. Cervical length was measured by transvaginal ultrasonography using GE Logic C5 equipment. Before trial initiation, all ultrasonographers participating in the P5 trial were trained in cervical measurement according to the Fetal Medicine Foundation training program and received an online training program through explanatory videos and tutorials produced by the coordinator center on the Moodle platform. An informed consent was obtained from all participants before cervical length measurement.

For the cervical length measurement, the participant was placed in the lithotomy position with an empty bladder, and a 5-MHz transducer was introduced into the vagina until reaching the anterior fornix, avoiding pressure on the cervix. Cervical length was measured in a sagittal view, defined as the straight-line distance between the internal and external os. The presence or absence of funneling and amniotic sludge were also recorded.

Women with short cervixes, defined as cervical length of 30 mm or less, were eligible for the RCT. Women with painful contractions, vaginal bleeding, a cerclage in situ, preterm prelabor rupture of membranes, severe liver disease (including cholestasis), previous or current thromboembolism, placenta previa, cervical dilation greater than 1 cm, monoamniotic twin pregnancy, higher order multifetal gestation (triplets or higher), major fetal malformation, and stillbirth of at least one fetus were not eligible.

Women were counseled by a physician, nurse, or nurse technician. After written informed consent, sociodemographic, medical, and obstetric history, in addition to information about the current pregnancy were collected using a structured questionnaire. Women were randomly allocated to vaginal pessary plus vaginal progesterone (pessary plus progesterone group) or vaginal progesterone only (progesterone only).

Randomization was stratified by center, number of fetuses (one or two), and cervical length (26–30 mm or 25 mm or less) using a 1:1 ratio and variable block sizes (2, 4, and 6). Randomization was performed centrally in an online database using a computer-generated algorithm, which was concealed to investigators. The research assistants at the participating centers logged into a web platform (https://www.gsdoctor.com.br/Default.aspx), where they had access to research forms; after including basic information and checking eligibility, they filled out a randomization form. Only then did they receive the allocation

group. To support randomization, a central team was on call 12 hours a day, 6 days a week to perform the randomization using the web system. Due to the nature of the intervention, the study was not masked.

Women allocated to the pessary plus progesterone group had the pessary inserted within 72 hours of the randomization. We used the Ingamed AM silicone pessary (unique size: outer diameter 70 mm, height 25 mm and inner diameter 40 mm with indentations—similar to the largest ARABIN Cerclage Pessary perforated). The pessary was placed in the outpatient clinic by a trained obstetrician, with the smaller diameter placed upwards encompassing the cervix. All local investigators were trained in a face-to-face workshop before recruitment, and they trained their local clinical teams in pessary placement and removal. There was also an online training program periodically sent to the research assistants for ongoing training in pessary placement and removal.

The pessary was not removed until the 36th week of gestation, except in cases of premature rupture of the membranes, active vaginal bleeding or signs of preterm labor, defined as severe discomfort with regular uterine contractions or medically indicated birth before 36 weeks of gestation.

Participants in both groups received vaginal progesterone 200 mg per day until 36 weeks of gestation. Women were instructed to insert the progesterone pills into the vagina at night, as they were going to sleep. Women in both the pessary plus progesterone and progesterone-only groups received otherwise similar obstetric care, with antenatal care according to local protocols.

Consistent with the CROWN (Core Outcomes in Women's and Newborn Health) initiative on studying preterm birth prevention,[22] the primary outcome was a composite of neonatal adverse events that occurred within 10 weeks after birth, including periventricular leukomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, periventricular hemorrhage grade II or higher, necrotizing enterocolitis, proven sepsis before discharge, stillbirth, or neonatal death. Secondary outcomes were overall, spontaneous, and medically indicated preterm birth rates before 28, 32, 34, and 37 weeks of gestation; short-term neonatal outcomes (1- and 5-minute Apgar scores, neonatal intensive care unit [NICU] admission and length of stay in NICU); and each individual component of the composite neonatal outcome.

Safety and adverse events were registered during each antenatal care visit. Additionally, every inpatient admission was communicated to the local research assistants who recorded details of the hospital admission.

We primarily intended to study a high-risk group of women (cervical length of 25 mm or less) but were also interested in estimating the effect of pessary in women with cervical length between 25 and 30 mm, who also have an elevated risk of preterm birth[23] and no available evidence-based treatment. Therefore, enrollment was stratified by cervical length. To demonstrate or refute a reduction in the primary outcome from 17.3% to 8.65% in a subgroup analysis for cervical length of 25 mm or less,[23,24] we needed to include 468 women for this subgroup (234/arm, power 80%, type I error 5%). We assumed half of the women had cervical length of 25 mm or less. Thus, the final sample should be composed of 936 women (468/arm).

Analysis was performed according to the intention-to-treat principle. We considered the primary outcome a binomial random variable, indicating whether at least one of a list of neonatal adverse events happened, and we estimated both crude and adjusted risk ratios (aRRs) with 95% CIs. For comparisons of the primary outcome at the mother level (experiencing neonatal adverse events in at least one child if multiple pregnancy), we used a generalized linear model, with Poisson log link function and robust variance estimate. For the primary outcome at the neonatal level, to account for possible non-independence among neonates from the same pregnancy, we used generalized estimating equations. Both mother level and neonatal level models included the treatment and study center as main effects, and a full factorial of number of fetuses (twin or singleton) and cervical length (two categories). We also calculated the number needed to treat for the primary outcome.

Secondary binary outcomes were analyzed using the same methods as the primary outcome. Covariates in most models for secondary outcomes included study center as the main effect and a full factorial of number of fetuses and cervical length, except for a few secondary outcomes where only main effects of number of fetuses and cervical length were retained due to rare event rates. For continuous maternal outcomes, generalized linear models with negative binomial distribution or linear regression were used. For continuous neonatal outcomes, generalized estimating equations with appropriate family and link were used. The time from randomization to delivery was assessed by Kaplan-Meier curves and tested with a log rank test. The assumption of proportional

hazards was not satisfied; therefore, the Cox proportional hazard model was not performed.

Differences in treatments among subgroups were assessed in two ways. The first one considered effect sizes in separate populations of each subgroup, and the second one assessed an interaction term (subgroup factor×treatment) in the models. We analyzed the following predefined subgroups: singleton or twin pregnancies, cervical length (25 mm or less or greater than 25 mm), nulliparous or multiparous, previous spontaneous preterm birth, minor uterine malformation, cervical funneling, or sludge at randomization.

A post hoc subgroup analysis was performed in nulliparous women with singleton pregnancies and cervical length of 25 mm or less. All statistical analyses were conducted in R for Windows 3.6.3 or Stata 16.0.

The Data Safety Monitoring Board met at predetermined intervals: one after half of the randomized participants were enrolled and another after two thirds of the randomized participants were enrolled. The Data Safety Monitoring Board recommended continuing the trial until the prespecified sample size was met. The Haybittle-Peto boundary was used to decide whether to stop the trial and the final analysis was evaluated using a 0.05 level of significance. The study was overseen by a steering committee from the conceptualization until the report of the results. The steering committee was composed of the principal investigators, researchers with recognized national and international clinical trial experience, a representative of a nongovernmental organization (Abrace Institute, https://institutoabrace.org.br/) that deals with preterm birth patients, and members of the funding agencies to evaluate the progress of the study and suggest corrections in strategies to comply with the protocol when necessary. There was no change in the protocol from the time it was submitted for registration.

The anonymized data generated from the trial can be assessed by other researchers on request for individual patients metanalysis after receipt of Research Ethics Council approval. We followed the CONSORT (Consolidated Standards of Reporting Trials) guideline instructions for randomized clinical trials.

## RESULTS

Between July 9, 2015, and March 29, 2019, we screened 8,168 women, of whom 1,146 had cervical length of less than 30 mm and 1,118 were eligible. Of these, 182 women declined participation, and 936 women gave informed consent and were randomly assigned to pessary plus progesterone (n=475) or progesterone only (n=461) (Fig. 1).

Baseline characteristics are shown in Table 1. Median cervical length at randomization was 25.0 (20.7–27.0) mm in the pessary plus progesterone group and 25.0 (21.1–27.0) mm in the progesterone-only group, with 57% of the measurements performed between 21 0/7 and 22 6/7 weeks of gestation. There were 43 women pregnant with twins in the pessary plus progesterone group and 28 women pregnant with twins in the progesterone-only group.

A flow diagram of participant enrollment is shown in Figure 1. There were no difficulties reported by women or by local researchers regarding the insertion or expulsion of progesterone in those with a pessary.

For the primary outcome, at either the mother level and the neonatal level, the rates of composite perinatal outcome in the pessary plus progesterone group and progesterone-only group were similar (Table 2). The pessary plus progesterone group had significantly lower rates of overall preterm deliveries before 28, 30, 32, and 34 weeks of gestation, compared with those in the progesterone-only group, and had and lower rates of spontaneous preterm deliveries before 28 (aRR 0.19, 95% CI 0.07–0.54), 32 (aRR 0.48, 95% CI 0.26–0.88), and 34 (aRR 0.61, 95% CI 0.39–0.96) weeks of gestation compared with those in the progesterone-only group (Table 2). The median gestational age at birth was 37.4 weeks in the pessary plus progesterone group and 36.9 weeks in the progesterone-only group (adjusted $P$=.006). Time-to-event analysis indicated no overall difference between the groups for time to delivery since randomization (proportional hazard assumption not met, Cox not performed) (Fig. 2).

There were no significant differences in the rates of medically indicated preterm delivery. The cesarean birth rate was 44.4% in the pessary plus progesterone group compared with 34.0% in the progesterone-only group (aRR 1.27, 95% CI 1.09–1.49) (Table 2).

No significant differences between groups were found regarding maternal outcomes, use of medication, preterm prelabor rupture of membranes, mode of delivery, birth weight, or short-term neonatal outcomes (5-minute Apgar score, NICU admission, and length of stay in NICU). Rates of periventricular hemorrhage and stillbirth were lower in the pessary plus progesterone group, compared with those in the progesterone-only group (aRR 0.29, 95% CI 0.08–0.99, and aRR 0.30, 95% CI 0.09–0.98, respectively) (Table 2 and Appendix 2 [Appendix 2 is available online at http://links.lww.com/AOG/C519]).

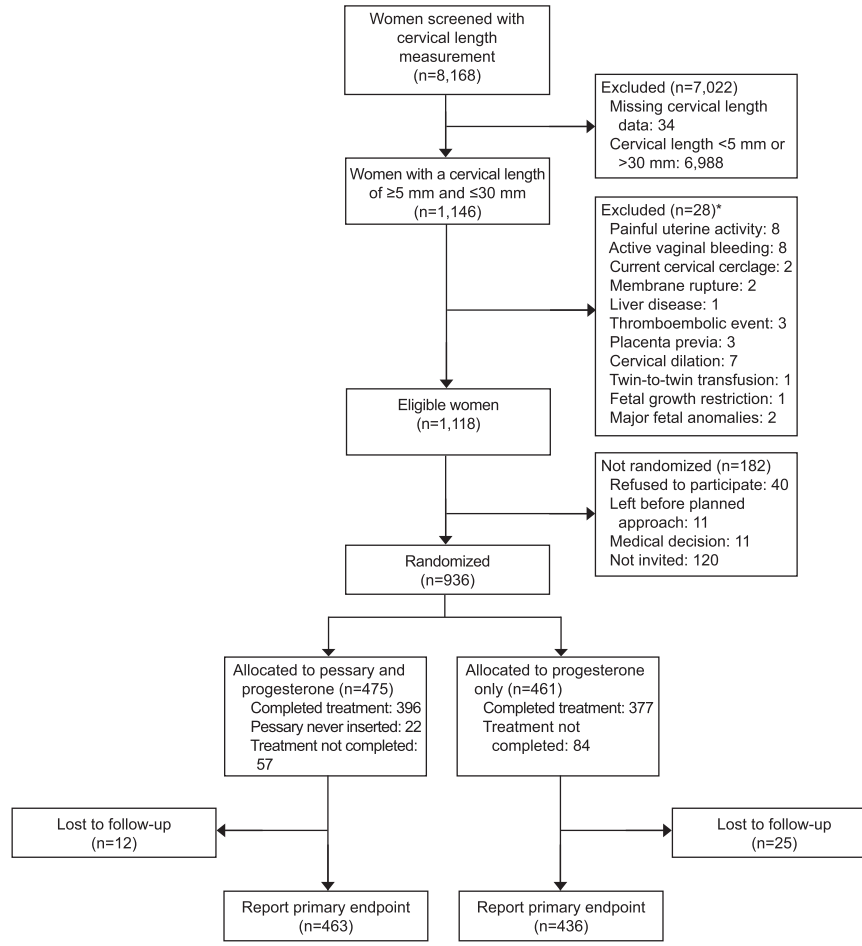


**Fig. 1.** Flowchart of participant enrollment. *Items not mutually exclusive.

*Pacagnella. Pessary and Progesterone for Preterm Birth. Obstet Gynecol 2021.*

In terms of side effects, vaginal discharge (51.6% [245/476] vs 25.4% [117/479], $P<.001$), vaginal discharge requiring treatment (22.3% [106/476] vs 6.6% [26/479], $P<.001$), pain (33.1% [157/476] vs 24.1% [111/479], $P=.002$), pain requiring treatment (10.3% [49/476] vs 6.5% [30/479, $P=.03$), and vaginal bleeding (9.7% [46/476] vs 4.8% [22/479], $P=.004$) occurred more frequently in the pessary plus progesterone than in the P-only group. Urinary tract infection and other conditions (constipation, chorioamnionitis, fetal growth restriction, and preeclampsia) did not significantly differ between groups (Table 3).

The pessary was removed not according to the protocol in 12.6% of participants in the pessary plus progesterone group for the following reasons: pessary not placed, pain, vaginal discharge, technical difficulties or pessary not in place, participant request, vaginal bleeding (Appendix 3, available online at http://links.lww.com/AOG/C519).

No significant differences were found in the subgroup analysis of the composite neonatal outcome for singleton compared with twin pregnancies, cervical length (25 mm or less vs greater than 25 mm, or spontaneous preterm birth history. In nulliparous women, the composite perinatal outcome occurred in 14.9% (37/247) of pregnancies in the pessary plus progesterone group and in 24.2% (58/240) of pregnancies in the progesterone-only group (risk ratio 0.62, 95% CI 0.43–0.83, $P$ for interaction 0.019) (Table 4).

In a post hoc subgroup analysis, there was a trend that the effects of the pessary plus progesterone group on overall preterm deliveries before 28, 30, 32, and 34 weeks of gestation were more prominent in women with singleton pregnancies who had cervical length of 25 mm or less (Appendix 4, available online at http://links.lww.com/AOG/C519). In nulliparous women with singleton pregnancies and cervical length of 25 mm or less, there were also lower frequencies of the composite neonatal outcome in the pessary plus progesterone group (15.8% vs 27.5%; aRR 0.59, 95% CI 0.37–0.94). Overall preterm birth rates before 37, 34, 32, 30, and 28 weeks of gestation were also

**Table 1. Baseline Characteristics of Participants**

| Baseline Characteristics | Pessary Plus Progesterone (n=475) | Progesterone (n=461) |
|---|---|---|
| Maternal age (y) | 26.5±7.0 | 26.3±6.6 |
| BMI | 25.9±5.2 | 26.0±5.6 |
| Years of schooling | | |
| No school, preschool, or elementary | 113 (23.8) | 96 (20.8) |
| Middle school | 307 (64.6) | 304 (65.9) |
| High school or higher education | 55 (11.6) | 61 (13.2) |
| Marital status | | |
| Living with a partner | 376 (79.2) | 370 (80.3) |
| Not living with a partner | 99 (20.8) | 91 (19.7) |
| Total no. of previous pregnancies | | |
| 0 | 192 (40.4) | 197 (42.7) |
| 1 | 122 (25.7) | 123 (26.7) |
| 2 or more | 161 (33.9) | 141 (30.6) |
| Previous vaginal birth | 181 (38.1) | 170 (36.9) |
| Previous cesarean birth | 60 (12.6) | 63 (13.7) |
| Previous preterm birth | 91 (19.2) | 85 (18.4) |
| Previous miscarriage | 143 (30.1) | 128 (27.8) |
| Chronic disease | 80 (16.8) | 71 (15.4) |
| History of cervical conization | 11 (2.3) | 16 (3.5) |
| Uterine anomaly | 11 (2.3) | 9 (2.0) |
| Previous cerclage | 5 (1.1) | 5 (1.1) |
| Type of pregnancy | | |
| Singleton | 432 (90.9) | 433 (93.9) |
| Twin | 43 (9.1) | 28 (6.1) |
| Conception method | | |
| Natural | 470 (98.9) | 457 (99.1) |
| ART | 5 (1.1) | 4 (0.9) |
| Cervical length at randomization (mm) | 25.0 (20.7–27.0) | 25.0 (21.1–27.0) |
| Greater than 25 | 215 (45.3) | 212 (46.0) |
| 25 or less | 260 (54.7) | 249 (54.0) |
| Sludge at randomization | 73 (15.4) | 70 (15.2) |
| Cervical funneling at randomization | 110 (23.2) | 115 (24.9) |
| Gestational age at randomization (wk) | 21.2 (20.0–22.3) | 21.1 (20.0–22.1) |
| 18 | 51 (10.7) | 45 (9.8) |
| 19 | 61 (12.8) | 67 (14.5) |
| 20 | 83 (17.5) | 95 (20.6) |
| 21 | 124 (26.1) | 109 (23.6) |
| 22 | 156 (32.8) | 145 (31.5) |

BMI, body mass index; ART, assisted reproductive technology.
Data are mean±SD, n (%), or median (interquartile range).

significantly lower for pessary plus progesterone among nulliparous women (Appendix 5, available online at http://links.lww.com/AOG/C519).

## DISCUSSION

In this multicenter RCT, treatment with a cervical pessary for women with midpregnancy cervical length of 30 mm or less, in addition to progesterone alone, did not reduce the rate of our primary adverse neonatal outcome. However, the pessary reduced the rate of preterm delivery before 34 weeks of gestation. The strongest effect of the pessary was found in nulliparous women with singleton pregnancies and cervical length of 25 mm or less.

In our study, all participants received vaginal progesterone treatment. Because it is now clear that progestogens reduce the risk of preterm birth in women with short cervixes,[25] we hypothesized that adding a mechanical (pessary) strategy to a biochemical (progesterone) one would reduce the risk even further. Some cohort studies have demonstrated possible benefits from this combination of pessary and progesterone.[12,26–28] Few RCTs, however, included information of the use of progesterone in the pessary group, as was done in the earlier studies.[10,14,24]

Our RCT has several strengths. It has a large sample size and nearly complete follow-up. Cervical length was measured by appropriately trained

**Table 2. Outcomes for Pessary Plus Progesterone Compared With Progesterone Only***

| Delivery Components | Pessary Plus Progesterone | Progesterone Only | Crude RR (95% CI) | Adjusted RR (95% CI) |
|---|---|---|---|---|
| Primary outcome (composite perinatal outcome) | | | | |
| Mother level | 89/463 (19.2) | 91/436 (20.9) | 0.92 (0.71–1.20) | 0.88 (0.69–1.12) |
| Neonatal level | 98/503 (19.4) | 100/461 (21.7) | 0.9(0.69–1.17) | 0.85 (0.66–1.10) |
| Secondary outcomes | | | | |
| Overall PTB rate | | | | |
| Before 37 wk | 138/474 (29.1) | 144/458 (31.4) | 0.93 (0.76–1.13) | 0.86 (0.72–1.04) |
| Before 34 wk | 47/474 (9.9) | 64/458 (13.9) | 0.71 (0.50–1,01) | 0.66 (0.47–0.93) |
| Before 32 wk | 27/474 (5.7) | 45/458 (9.8) | 0.58 (0.37–0.92) | 0.55 (0.35–0.86) |
| Before 30 wk | 19/474 (4.0) | 35/458 (7.6) | 0.54 (0.30–0.90) | 0.49 (0.29–0.85) |
| Before 28 wk | 10/474 (2.1) | 25/458 (5.5) | 0.39 (0.19–0.80) | 0.37 (0.18–0.74) |
| Spontaneous PTB rate | | | | |
| Before 37 wk | 74/461 (16.1) | 84/435 (19.3) | 0.85 (0.64–1.13) | 0.77 (0.59–1.01) |
| Before 34 wk | 29/461 (6.3) | 41/435 (9.4) | 0.68 (0.43–1.08) | 0.61 (0.39–0.96) |
| Before 32 wk | 15/461 (3.3) | 28/435 (6.4) | 0.52 (0.28–0.96) | 0.48 (0.26–0.88) |
| Before 30 wk | 12/461 (2.6) | 21/435 (4.8) | 0.55 (0.27–1.11) | 0.50 (0.25–1.01) |
| Before 28 wk† | 4/461 (0.9) | 18/435 (4.1) | 0.21 (0.07–0.63) | 0.19 (0.07–0.54) |
| Medically indicated PTB rate | | | | |
| Before 37 wk | 62/461 (13.5) | 51/435 (12) | 1.17 (0.83–1.66) | 1.07 (0.76–1.51) |
| Before 34 wk | 17/461 (3.7) | 19/435 (4.4) | 0.86 (0.46–1.64) | 0.80 (0.42–1.50) |
| Before 32 wk | 11/461 (2.4) | 15/435 (3.5) | 0.71 (0.33–1.53) | 0.65 (0.30–1.41) |
| Before 30 wk | 7/461 (1.5) | 13/435 (3.0) | 0.52 (0.21–1.29) | 0.48 (0.19–1.21) |
| Before 28 wk | 6/461 (1.3) | 6/435 (1.4) | 0.97 (0.31–2.97) | 0.91 (0.29–2.80) |
| Preterm PROM | 26/474 (5.5) | 19/458 (4.2) | 1.32 (0.74–2.36) | 1.28 (0.73–2.23) |
| Cesarean birth | 210/473 (44.4) | 154/453 (34.0) | 1.31 (1.11–1.54) | 1.27 (1.09–1.49) |
| Maternal components | | | | |
| Corticosteroid use | 77/463 (16.6) | 79/437 (18.1) | 0.92 (0.69–1.22) | 0.86 (0.65–1.12) |
| Magnesium sulfate use | 28/463 (6.0) | 30/435 (6.9) | 0.88 (0.53–1.44) | 0.87 (0.53–1.39) |
| Composite of maternal morbidity and mortality | 77/466 (16.5) | 77/440 (16.7) | 0.94 (0.71–1.26) | 0.94 (0.71–1.25) |
| Maternal ICU admission† | 3/475 (0.6) | 2/461 (0.4) | 1.46 (0.24–8.67) | 1.39 (0.21–9.20) |
| Neonatal components | | | | |
| NICU admission | 104/506 (20.6) | 88/464 (19.0) | 1.08 (0.82–1.44) | 1.01 (0.79–1.30) |
| SGA | 57/499 (11.4) | 57/458 (12.4) | 0.92 (0.63–1.33) | 0.86 (0.59–1.24) |
| Periventricular leukomalacia† | 5/497 (1.0) | 3/450 (0.7) | 1.51 (0.28–8.23) | 1.37 (0.23–8.08) |
| Severe respiratory distress syndrome | 91/499 (18.2) | 86/450 (19.1) | 0.95 (0.72–1.27) | 0.91 (0.70–1.19) |
| Bronchopulmonary dysplasia† | 8/497 (1.6) | 10/450 (2.2) | 0.72 (0.25–2.08) | 0.64 (0.22–1.84) |
| Periventricular hemorrhage (grade 2 or higher)† | 4/497 (0.8) | 11/450 (2.4) | 0.33 (0.10–1.11) | 0.29 (0.08–0.99) |
| Necrotizing enterocolitis† | 3/497 (0.6) | 4/450 (0.9) | 0.68 (0.15–3.01) | 0.61 (0.12–2.93) |
| Proven sepsis before discharge† | 9/497 (1.8) | 6/450 (1.3) | 1.36 (0.44–4.16) | 1.22 (0.39–3.84) |
| Stillbirth† | 4/509 (0.8) | 12/468 (2.6) | 0.31 (0.10–0.97) | 0.30 (0.09–0.98) |
| Neonatal death† | 11/499 (2.2) | 19/450 (4.2) | 0.52 (0.23–1.17) | 0.47 (0.21–1.06) |

RR, risk ratio; PTB, preterm birth; PROM, prelabor rupture of membranes; NICU, neonatal intensive care unit; SGA, small for gestational age.

Data are n/N (%) unless otherwise specified.

* Model covariates included study center and a full factorial of number of fetuses and cervical length unless specified.

† Model covariates included number of fetuses and cervical length due to limited number of events.

ultrasonographers who were certified before recruitment started. The trial conduct followed a predefined protocol. There are also limitations. The nature of the pessary does not permit blinding of participants or health care practitioners. Also, although the medical team was trained on the use of a pessary before the study, the recruitment period lasted longer than planned, leading to change of personnel on research teams. There was an imbalance in the distribution of women with twin pregnancies between treatment groups, with more twins in the pessary plus progesterone group. This imbalance occurred before stratification in one center that first started recruitment and could not be corrected in the course of the

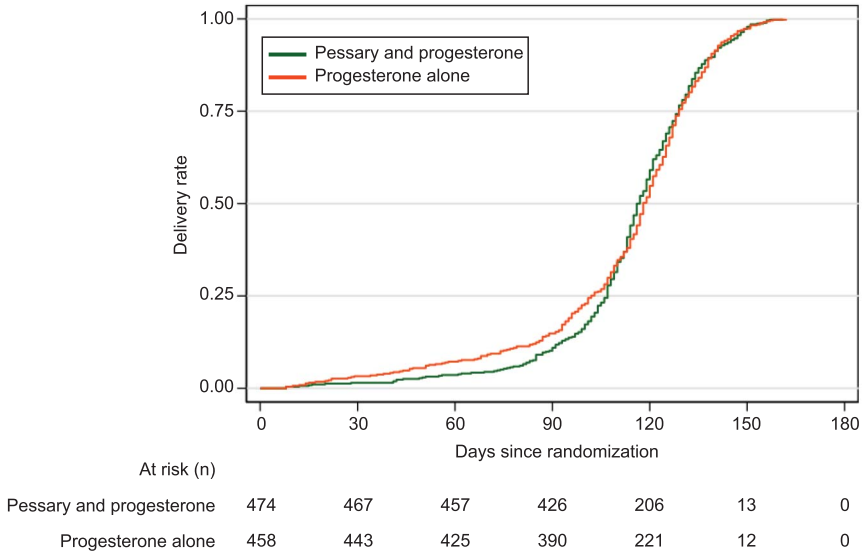


**Fig. 2.** Kaplan-Meier curves for time from randomization to delivery in the two treatment arms (*P* for log-rank test=.70).

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study. However, the number of imbalanced twins was small, and we controlled for multifetal gestation in all models. Also, as there were more twins in the pessary plus progesterone group, the imbalance is likely to reduce our estimate of the effectiveness of pessary.

We also identified a significant difference in cesarean birth rates between the pessary and nonpessary groups. Brazil has one of the higher rates of cesarean birth globally and a high prevalence of medically indicated preterm birth. Early spontaneous preterm births are more likely to be delivered vaginally than late preterm births.[29,30] Therefore, the fact that we had more late preterm births in the pessary plus progesterone group may have contributed to the higher rates of cesarean birth observed in that group.

Although we found a similar rate of our primary adverse neonatal outcome, there was a reduction in the risk of preterm birth before 34 weeks of gestation. Adverse neonatal outcomes are multifactorial and preterm birth is only one of the risk factors. Adverse neonatal outcomes that occur in late preterm or term pregnancy will not be prevented by cervical pessary.

Similarly, we found no statistically significant effect of pessary on preterm delivery before 37 weeks of gestation, but cervical pessary reduced preterm birth at all prespecified gestational ages before 34 weeks, with the strongest reduction in spontaneous preterm birth before 28 weeks of gestation from 4% to 1%, which is in line with the mechanism by which a pessary is supposed to work. Indeed, when we limited

**Table 3. Side Effects for Pessary Plus Progesterone Compared With Progesterone Only**

| Characteristics | Pessary Plus Progesterone | Progesterone Only | *P** |
|---|---|---|---|
| Vaginal discharge | | | |
| No treatment | 245 (51.6) | 117 (25.4) | <.001 |
| Treatment | 106 (22.3) | 26 (6.6) | <.001 |
| Pain | | | |
| No treatment | 157 (33.1) | 111 (24.1) | .002 |
| Treatment | 49 (10.3) | 30 (6.5) | .03 |
| Urinary tract infection | 47 (9.9) | 52 (11.3) | .5 |
| Vaginal bleeding | 46 (9.7) | 22 (4.8) | .004 |
| Other symptoms | 36 (46.5) | 29 (51.8) | .5 |
| Clinical conditions | 25 (72.4) | 21 (69.4) | |
| Constipation | 4 (11.1) | 1 (3.5) | |
| Chorioamnionitis | 1 (2.8) | 1 (3.4) | |
| Fetal growth restriction | 3 (8.3) | 2 (6.9) | |
| Preeclampsia | 3 (8.3) | 4 (13.8) | |

Data are n (%) unless otherwise specified.
* All analyses using $\chi^2$ test.

**Table 4. Subgroup Analysis for Composite Perinatal Outcome at Mother Level**

| Subgroup for Primary Outcome (Mother Level) | Pessary Plus Progesterone | Progesterone Only | Adjusted RR (95% CI) | Adjusted *P* | *P* Interaction |
|---|---|---|---|---|---|
| Multiple pregnancy | | | | | .766 |
| No | 68/421 (16.2) | 76/409 (18.6) | 0.86 (0.65–1.14) | .302 | |
| Yes | 21/42 (50.0) | 15/27 (55.6) | 1.01 (0.64–1.60) | .958 | |
| Cervical length (mm) | | | | | .328 |
| 25 or less | 58/257 (22.6) | 63/233 (27.0) | 0.82 (0.61–1.10) | .193 | |
| Greater than 25 | 31/206 (15.0) | 28/203 (13.8) | 0.99 (0.63–1.55) | .960 | |
| Parity | | | | | .019 |
| Nulliparous | 37/247 (14.9) | 58/240 (24.2) | 0.62 (0.43–0.89) | .010 | |
| Multiparous | 52/216 (24.1) | 33/196 (16.8) | 1.17 (0.80–1.72) | .420 | |
| Previous spontaneous preterm birth | | | | | .169 |
| No | 64/375 (17.1) | 73/356 (20.5) | 0.81 (0.60–1.08) | .145 | |
| Yes | 25/88 (28.4) | 18/80 (22.5) | 1.24 (0.76–2.01) | .388 | |
| Obstetric ultrasonographic abnormalities (uterine malformation, funneling, sludge) | | | | | .857 |
| Yes | 34/152 (23.4) | 46/143 (32.2) | 0.76 (0.52–1.12) | .162 | |
| No | 55/311 (17.7) | 45/293 (15.4) | 1.05 (0.74–1.48) | .786 | |

RR, risk ratio.
Data are n/N (%) unless otherwise specified.

our analysis to nulliparous women with singleton pregnancies and cervical length of 25 mm or less, cervical pessary reduced the risk of our composite adverse perinatal outcomes.

There was a significant difference in the side effect profile between groups. Women using cervical pessary had more vaginal discharge and pain than those not using the device, but there were no severe side effects compromising the safety of the treatment. This is in accordance with other studies[10,12] and should be considered when selecting a treatment option.

Our results are consistent with most other RCTs that show the significant effect of pessary placement on spontaneous early preterm birth. In 2012, Goya et al[13] showed a lower rate of spontaneous and overall deliveries before 37, 34 and 28 weeks of gestation in the pessary group, compared with no treatment. The same effect was observed by Saccone et al[31] in singletons, who found a significant reduction in preterm birth rates before 37 and 34 weeks of gestation in the group using pessaries, compared with a group using progesterone also.

Other studies with small sample sizes could not confirm this effect.[15,32] A larger study by Nicolaides et al[11] also did not find a benefit of pessaries. In women with twin pregnancies, cervical pessaries are not effective in an unselected population[10,20,21]; in women with short cervixes, cervical pessaries seem to reduce preterm birth in most studies,[20,21] but, again, not in the study of Nicolaides et al. Given these mixed data, we consider questions about the role of cervical pessary to prevent preterm birth still open. Our data will be included in a planned individual participant meta-analysis that investigates the effectiveness of cervical pessary (PROSPERO 2018 CRD42018067740) in the prevention of preterm birth.

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**Authors' Data Sharing Statement**

Will individual participant data be available (including data dictionaries)? *Data are available upon request.*

What data in particular will be shared? *Anonymized data from the trial (core variables and outcomes) are available upon request.*

What other documents will be available? *Statistical plan of analysis, protocols and ethical approval along with the dataset are available upon request.*

When will data be available (start and end dates)? *Data will be available for 5 years from the submission of the manuscript.*

By what access criteria will data be shared (including whom, for what types of analyses, and by what mechanism)? *Data will be available to the editors for checking the reliability of the results and for other researchers to perform additional IPD meta-analysis.*

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