Cervical Pessary Compared With Vaginal Progesterone for Preventing Early Preterm Birth

A Randomized Controlled Trial

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OBJECTIVE: To compare the effectiveness of a cervical pessary and vaginal progesterone to prevent spontaneous preterm births in pregnant women with cervical lengths 25 mm or less as measured by transvaginal ultrasonography.

METHODS: This was a multicenter, open-label, randomized, noninferiority trial. Women with singleton pregnancies and a short cervix (25 mm or less) measured transvaginally at the second-trimester ultrasonogram were invited to participate. They were computer-randomized (one to one) into cervical pessary placement or treatment with vaginal progesterone (200 mg/24 hours). The primary outcome was spontaneous preterm delivery before 34 weeks of gestation. The noninferiority margin was set at 4% with a 0.025 one-sided α level and a statistical power of 80%. That is, if the 95% CI upper bound exceeded 4%, the pessary could not be deemed noninferior. A sample size of 254 women was required to show noninferiority of the pessary to progesterone.

RESULTS: The trial was conducted from August 2012 to April 2016 with the participation of 27 Spanish hospitals. A total of 254 patients were enrolled and 246 included in the intention-to-treat analysis. Demographic and baseline characteristics were similar across groups. The rate of spontaneous delivery before 34 weeks of gestation was 14% (n=18/127) in the pessary group and 14% (n=17/119) in the progesterone group with a risk difference of −0.11% (95% CI −8.85% to 8.62%; P=.99), that is, noninferiority was not shown for the pessary. The incidence of increased vaginal discharge (87% vs 71%, P=.002) and discomfort (27% vs 3%, P<.001) was significantly higher in the pessary group.

See related editorial on page 833.

**For a list of members in the PESAPRO study group, see Appendix 1 online at http://links.lww.com/AOG/B147.*

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CONCLUSION: A cervical pessary was not noninferior to vaginal progesterone for preventing spontaneous birth before 34 weeks of gestation in pregnant women with short cervixes.

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Preterm birth is the second most frequent direct cause of death in children younger than 5 years old[1–3] and it is the leading cause of perinatal morbidity and mortality in developed countries.[1] Although all deliveries before 37 weeks of gestation are considered preterm, the highest proportion of complications and neonatal death occurs in those born at less than 34 weeks of gestation.[4]

Since 1996 multiple publications have described that asymptomatic women with a short cervical length (25 mm or less) are at increased risk of spontaneous preterm delivery.[5–14] Meta-analyses of randomized trials involving pregnant women who had a short cervical length have shown that the prophylactic use of progesterone results in a significantly lower rate of preterm delivery and neonatal death than the rate with placebo.[15,16] An alternative approach is the transvaginal placement of a cervical pessary; this device is a silicone ring that tips the cervix toward the posterior vaginal wall and corrects the cervical angle. The randomized controlled trials that have been published about the use of a cervical pessary in singleton pregnancies in women with a short cervix[17–19] provided contradictory results.

We report the results of our multicenter, randomized, noninferiority trial to compare the efficacy of the two treatments in terms of spontaneous births before 34 weeks of gestation in women with a short cervix detected by transvaginal ultrasonography.

MATERIALS AND METHODS

A prospective, open-label, multicenter, randomized, noninferiority clinical trial was conducted in 27 hospitals in Spain. All participating obstetric units routinely perform transvaginal ultrasonography in the second trimester as a screening method to detect women at risk of preterm birth. Pregnant women with singleton pregnancies and a short cervix (25 mm or less) at the second-trimester morphology ultrasonography (19–22 weeks of gestation) were eligible to enroll in the trial. Exclusion criteria were a maternal age younger than 18 years, major fetal or uterine abnormality, cervical cerclage in situ, placenta previa, a history of cone biopsy or a loop electrosurgical excision procedure, three or more previous preterm births, painful regular uterine contractions, active vaginal bleeding, ruptured membranes, or abnormal physical findings before randomization that disproportionately increased the risk of very early delivery (eg, prolapsing membranes).[20]

All participants in the trial provided written informed consent. The study was approved by the University Hospital Puerta de Hierro Research Ethics Committee, local committees of all participating hospitals, and by the Spanish Regulatory Authority for medicines and medical devices. The trial was registered in the EU Clinical Trials Register (2012-000241-13), in ClinicalTrials.gov (NCT01643980), and the study protocol was published in a peer-reviewed journal.[20] A specific insurance policy was contracted to cover compensation to patients in the event of injuries in compliance with the requirements of Spanish law regarding clinical trials. This study was reported according to CONSORT guidelines.[21]

Consecutive eligible patients were randomly allocated in a one-to-one ratio to one of the two treatment groups (cervical pessary or vaginal progesterone). The randomization sequence was computer-generated using EpiDat 3.1[22] and it was protected and managed exclusively by the Clinical Pharmacology Service at University Hospital Puerta de Hierro, which had no role in recruitment. The investigators received the patient's identification number and the assigned treatment by phone after written informed consent was obtained from the women. An auditable registry of the date of inclusion, patient identification number, and assigned treatment was stored in the sponsor's records. This study was open label because of the nature of the intervention, but the allocation sequence was kept concealed at all times.

Gestational age was determined from menstrual history and confirmed by measurement of fetal crown–rump length at a first-trimester scan carried out routinely at all participating hospitals. After randomization, demographic, medical and obstetric history, and physical examination data (including a speculum examination with vaginal and cervical swabs taken) were collected from each participant. Next, patients allocated to the pessary group had the device inserted by an obstetrician who had received training in use of the device, and patients allocated to the progesterone group were instructed in the use of vaginal progesterone and were supplied with the medication, 200 mg micronized progesterone per day by vaginal route (women self-administered the medicine once daily, preferably before going to bed). The cervical pessary used in this study was a perforated

cerclage-type pessary, a hypoallergenic silicon medical device certified by European conformity (CE0482, MED/CERT ISO 9003/EN 46003; Dr Arabin). The progesterone was commercial progesterone (PROGEFFIK) that was bought and relabeled by the Clinical Trials Pharmacy Unit of the University Hospital Puerta de Hierro and then distributed to all participating centers.

The treatment was to be initiated between 20 1/7 and 23 6/7 weeks of gestation and both groups were seen by the clinical team of the trial at each center every month until delivery. If the bacterial culture performed at randomization showed abnormal results, the appropriate antibiotic therapy was given and allocated treatment continued. At the monthly visits, we performed transvaginal measurement of cervical length (according to the technique described by Goya in pessary-carrying patients[23]), transabdominal ultrasonography (for determination of fetal well-being), and administered a clinical questionnaire asking about any symptoms that had developed since the beginning of treatment for assessment of adverse events. Sexual intercourse was not prohibited in either group.

Both treatments were discontinued between 37 0/7 and 37 4/7 weeks of gestation. Indications for discontinuation of treatment before this time were active vaginal bleeding, active labor, severe patient discomfort, or at the participant's request. Patients whose treatment was discontinued (even on the day of insertion) or those who received both treatments remained in the trial because of the intention-to-treat principle.

The study was conducted in accordance with the Good Clinical Practice guidelines, the guiding principles of the Declaration of Helsinki, and all applicable local regulations. An independent trained monitor was responsible for controlling all the data during the trial.

The primary outcome was the proportion of spontaneous births before 34 weeks of gestation. The secondary outcomes were the following: proportion of spontaneous preterm births before the 37th and 28th week, the rate of prelabor rupture of membranes before 34 and 37 weeks of gestation, the need of tocolysis treatment and maternal corticosteroid treatment for fetal maturation, vaginal side effects, the rate of chorioamnionitis, symptomatic vaginal or urinary tract infections, the number of visits to the emergency departments during the treatment period, and the proportion of participants with adverse events.

Neonatal outcomes included birth weight (mean, less than 2,500 g and less than 1,500 g), the rate of perinatal (fetal and neonatal) death, and a composite of major adverse events in the neonate (admission to the neonatal intensive care unit, mechanical ventilation, any grade of intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity [any], or necrotizing enterocolitis). Based on the results of previous studies,[15,17] we assumed a proportion of spontaneous delivery before 34 weeks of gestation of 6% in the pessary group (considered the experimental group) and 12.4% in the progesterone group (reference group). A noninferiority margin of 4% with a 0.025 one-sided α level, a statistical power of 80%, and a dropout rate of 5% was set. Thus, a sample size of 254 women was required to show noninferiority of the pessary to progesterone.

The primary analysis was conducted for both a modified intention-to-treat and a per-protocol population according to the recommendations for a noninferiority hypothesis.[24] Nonspontaneous deliveries (medically induced) before 34 weeks of gestation and participants who did not comply with the progesterone treatment were included in the modified intention-to-treat analysis and excluded from the per protocol. All the demographic and safety variables were analyzed according to the intention-to-treat principle.

The noninferiority hypothesis was tested by estimating treatment rate differences against the noninferiority margin (4%). The survival function of the event "time to delivery" and their corresponding 95% CIs were estimated by means of the Kaplan-Meier method and treatment effects were compared using the log-rank test. The rest of the variables were analyzed using the Fisher exact test to compare categorical data, the *t* test for continuous variables, and the Mann-Whitney test for ordinal and nonnormally distributed variables.

Subgroup analyses were performed to compare the effectiveness of the pessary compared with progesterone to prevent spontaneous birth before 34 weeks of gestation in six predefined categories: 1) cervical length at randomization (15 mm or less or greater than 15 mm); 2) parity (nulliparous, parous); 3) previous premature delivery history; 4) presence of intraamniotic sludge (an ultrasonographic finding defined as a free-floating hyperechogenic material within the amniotic fluid in close proximity to the uterine cervix)[25] at any of the followup visits; 5) the results of the vaginal and cervical cultures taken at the randomization visit (normal vs pathologic); and 6) absence of the ultrasonographic cervical gland area, an hyperechoic or hypoechoic zone surrounding the cervical canal,[26,27] at the inclusion visit. This analysis is shown as a forest plot.

Stata 15.1 and SAS 9.2 were used for all statistical analyses. No interim analyses were contemplated in the protocol.

An independent Data Safety Monitoring Board met to review the data when 70% of the sample size was recruited, and based on the information reviewed, the Data Safety Monitoring Board recommended the continuation of the trial protocol without amendments.

The study was fully funded with public funds obtained in competitive calls: grant EC11/086 of the Ministry of Health Call for Independent Clinical Research in year 2011 and grant PI12/02240 from the Institute of Health Carlos III. The study was performed and monitored with support of the Spanish Clinical Research Network, funded by grant PT13/0002/0005 from the National R+D+I 2013–2016 Plan of the Institute of Health Carlos III (AES 2013).

The investigators had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The trial was conducted from August 2012 to April 2016 with the participation of 27 Spanish hospitals. A total of 254 patients were randomized and included in the trial (Fig. 1). There were eight patients excluded from the final analysis because they did not meet the inclusion and exclusion criteria or did not receive at least one dose of progesterone or the pessary was not inserted. Thus, a total of 246 patients were included in the modified intention-to-treat analysis. Of those, there were two patients who had medically induced deliveries before 34 weeks of gestation and another who had a major deviation from the protocol (did not receive progesterone for more than 7 days), so these patients were excluded from the per-protocol population (N=243).

There were no significant differences between the pessary group and the progesterone group for the baseline characteristics of the trial participants (Table 1).

During the course of the trial, 11 participants (six of the pessary group and five of the progesterone group) received double therapy (pessary+progesterone) and three participants underwent cervical cerclage (one in the pessary group and two in the progesterone group) as a result of medical indication by their obstetrician because they continued to shorten the length of their cervix.

Spontaneous delivery before 34 weeks of gestation occurred in 18 of 127 participants in the pessary group (14%) and in 17 of 119 participants in the progesterone group (14%) with an absolute risk reduction of −0.11% (95% CI −8.85% to 8.62%) (modified intention-to-treat population). For the population by protocol, the incidence of spontaneous delivery before 34 weeks of gestation was 14% (18/125) in the pessary group compared with 14% (17/118) in the progesterone group with an absolute risk reduction of −0.01% (95% CI −8.84 to 8.83%; Table 2).

The estimated cumulative incidence of participants who did not give birth spontaneously before 34 weeks of gestation in the pessary group was 0.856

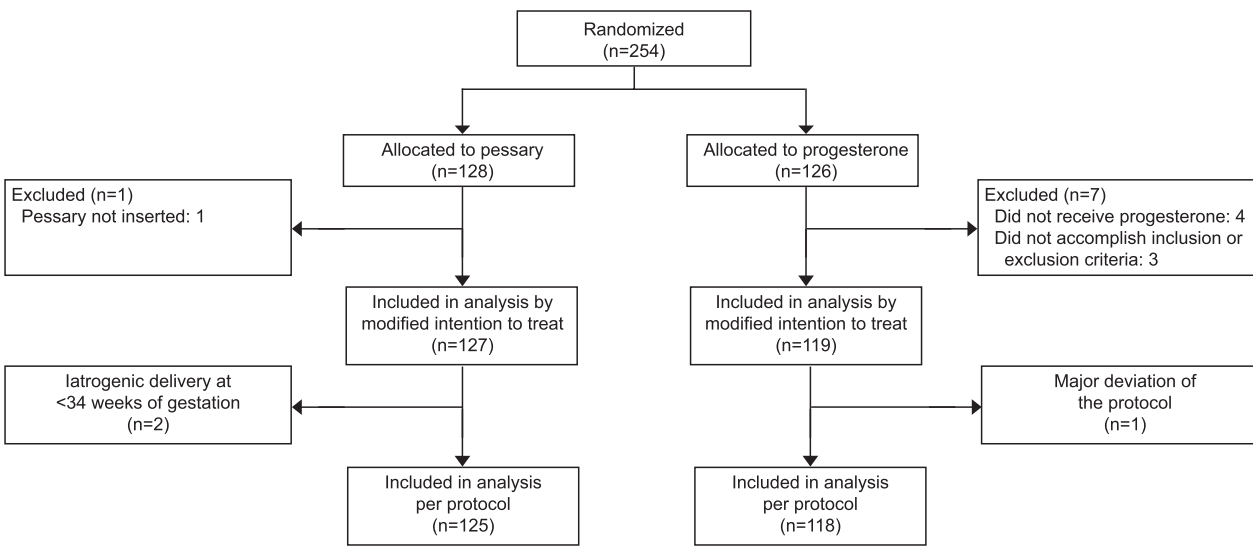

Fig. 1. Trial profile.

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Table 1. Characteristics of the Trial Participants by Intention to Treat

Variable	Treatment Group	
	Pessary (n=127)	Progesterone (n=119)
Maternal age (y)	32.5±5.3	33·1±5.5
Ethnic origin		
White	100 (78.7)	91 (76.4)
Black	8±6.3	5±4.2
Asian	0±0.0	1±1.0
Latin American	11±6.3	15±12.5
Other	8±8.7	7±5.9
BMI (kg/m^2)	24.4±4.8	23.7± 3.9
Cigarette smoker	21 (16.7)	20 (16.8)
No. of cigarettes/d	6 (5–10)	7±4–12
Gestational age at randomization (wk)	21.2±0.97	21.38±0.94
Median cervical length at randomization (mm)	20.81±4.2	20.96±4.1
Cervical length at randomization 15 mm or less	11 (8.7)	13 (10.9)
Obstetric history		
Nulliparous	58 (45.7)	54 (45.4)
Parous	57 (44.9)	49 (41.2)
History of previous preterm birth	12 (9.4)	16 (13.4)
Absent cervical gland area	44 (36.7)	42 (36.2)
Cultures at randomization		
Unrealized	11 (9)	7 (6)
Normal	75 (59)	76 (64)
Abnormal		
Total	41 (32)	36 (30)
Ureaplasma	21 (51)	21 (58)
Mycoplasma	2 (5)	2 (5)
Chlamydia trachomatis	1 (2)	0 (0)
Neisseria gonorrhoeae	0 (0)	0 (0)
Trichomonas vaginalis	0 (0)	0 (0)
Gardnerella vaginalis	1 (2)	3 (8)
Candida	21 (51)	13 (36)
Need of treatment	37 (90)	29 (80)

BMI, body mass index.
Data are mean±SD, n (%), or mean (range).

(95% CI 0.781–0.907) and 0.856 (95% CI 0.779–0.908) in the progesterone group (Fig. 2). In the subgroup analyses, the risk of the primary outcome was not affected by grouped cervical length (cervix 15 mm or less or 15 mm or greater), parity (parous or nulliparous), status with respect to previous preterm delivery, status of the bacteriologic cultures at randomization, or the identification by transvaginal ultrasonography of sludge at any of the follow-up visits (Fig. 3). In the subgroup of patients with absent cervical gland area at the inclusion visit, we observed that those of the progesterone group had fewer spontaneous deliveries before 34 weeks of gestation (26% vs 7%, P=.02; Fig. 3). There were no significant between-group differences in any of the maternal secondary outcomes analyzed (Table 2) or in any of the neonatal outcomes evaluated (Table 3).

The registered adverse event rate was 16% in the pessary group and 11% in the progesterone group (P=.27). No significant differences were observed between treatment groups considering the need of taking sick leave (58% vs 67%, respectively, P=.15) or the number of visits to the emergency department (41% vs 39%, P=.82). When we analyzed this last variable over time, we realized that pessary carriers visited the emergency department more frequently during the first month of the study than the patients receiving progesterone (25% vs 15%, P<.05) but did not identify differences between groups after the first month.

The pessary group participants reported a higher rate of increased vaginal discharge than those of the progesterone group (87% vs 71%, P=.002) and also more vaginal discomfort (27% vs 3%, P<.001) at any of the follow-up visits. No significant differences were observed between treatment groups in relation to other vaginal symptoms (itching or pelvic pain), sexual activity, nor the incidence of infections (chorioamnionitis or symptomatic vulvovaginal or urinary tract infections).

The pessary insertion was described as an unpleasant experience by 22% of the patients (28/127), whereas only 3% (4/127) of them reported it as unbearably painful. The pessary was removed before 34 weeks of gestation as a result of tolerability reasons in 4 of 127 participants (3%): one because of intense vaginal bleeding, two because of significant vaginal discomfort, and another because of repeated expulsion of the pessary in a multiparous woman.

DISCUSSION

The cervical pessary was not noninferior to vaginal progesterone for preventing spontaneous birth before 34 weeks of gestation in pregnant women with short cervixes because the 95% CI of the difference in the rate of this outcome between groups exceeded the prespecified noninferiority margin of 4%, although the observed rates of spontaneous birth at less than 34 weeks of gestation were similar for both treatment groups (14% vs 14%).

The sample size would have been adequate to conclude noninferiority if preterm birth rates had been lower, as we expected from the results of the only randomized study on a pessary published before the start of our trial.[17] The PECEP Trial showed a great reduction of spontaneous delivery at less than

Table 2. Maternal Outcomes According to Trial Group by Per Protocol

Outcome	Treatment Group: Pessary (n=125)	Treatment Group: Progesterone (n=118)	Risk Difference* (%) (95% CI)	*P*
Primary outcome				
Spontaneous delivery before 34 wk of gestation	18 (14)	17 (14)	−0.01 (−8.84 to 8.83)	.99
Secondary outcomes				
Spontaneous delivery before 37 wk of gestation	27 (22)	25 (21)	0.41 (−9.90 to 10.73)	.94
Spontaneous delivery at less than 28 wk of gestation	10 (8)	9 (8)	0.37 (−6.38 to 7.12)	.91
Preterm PROM before 34 wk of gestation	7 (6)	7 (6)	−0.33 (−6.20 to 5.53)	.91
Preterm PROM before 37 wk of gestation	12 (10)	11 (9)	0.28 (−7.08 to 7.64)	.94
Gestational age at delivery (wk)	37.3	37.5	—	.71
Tocolytic treatment	10 (8)	14 (12)	−3.86 (−11.39 to 3.66)	.31
Corticosteroid treatment for fetal maturation	23 (19)	28 (25)	−5.23 (−15.85 to 5.38)	.33

PROM, prelabor rupture of membranes.
Data are n (%) or mean unless otherwise specified.
* Risk difference expressed as the rate in the progesterone group minus the rate in the pessary group (95% CI).

34 weeks of gestation (6% vs 27%); this magnitude of effect has not been confirmed in the two other randomized trials[18,19] later published (9.4% vs 5.5% and 12% vs 10.8%). The PECEP Trial showed a high rate of spontaneous delivery in the nonintervention group (27%), higher than the rate of preterm birth showed in the subsequent published trials. However, we consider that the rate of preterm birth in the control group in the PECEP trial is likely the real rate of occurrence, because it is consistent with other previously published data.[5,9] On the other hand, the trial showing the lower rate of preterm birth in the control arm (10.8% vs 12% with pessary) reported that 46.9% of the participants in the nonintervention group were treated with progesterone.[19] Therefore, a progesterone effect cannot be ruled out as a reason to explain the low preterm birth rate.

The two groups were well balanced at demographic and baseline characteristics and comparable with the participants of other trials.[17,19] No significant differences were found in our study between groups of treatment for any of the secondary outcomes evaluated (maternal or neonatal). However, we did find differences in the analysis of tolerability and adverse events: patients with the pessary had a significantly higher rate of increased vaginal discharge and vaginal discomfort, findings consistent with the other pessary studies.[17–19] Also, during the first month of treatment, pessary participants visited the emergency department more, probably as a result of the fact that some required time

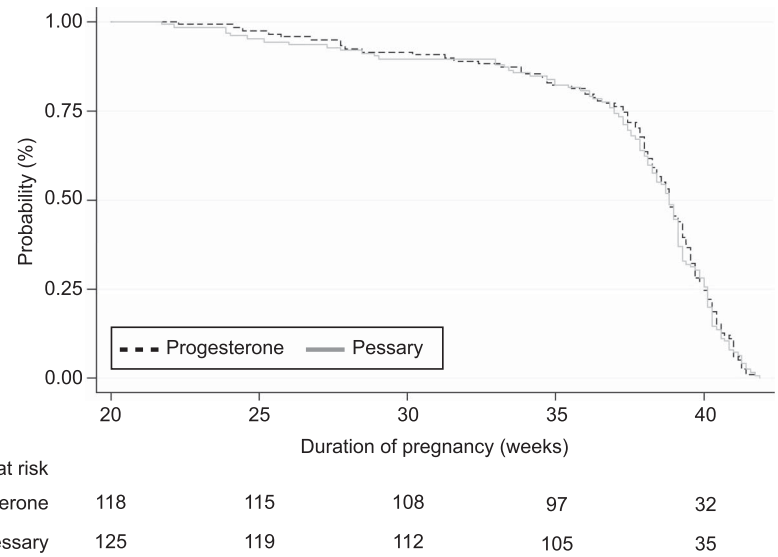

Fig. 2. Kaplan-Meier plot of continued pregnancy without delivery. Log-rank test (Mantel-Cox) *P*=.717, χ^2=0.131.

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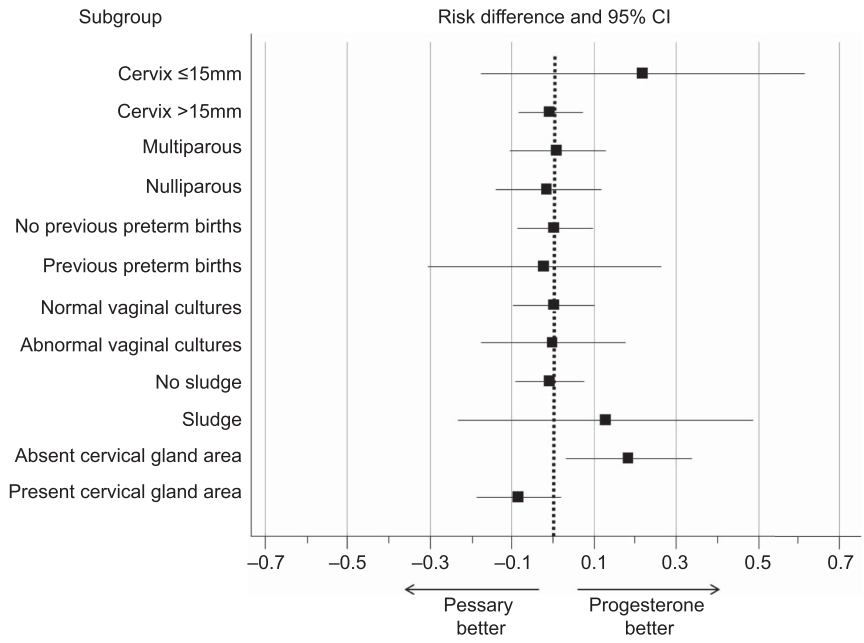

Fig. 3. Forest plot for subgroup analysis.

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to adapt to the device. Nevertheless, the pessary had an acceptable side effect profile and only needed to be removed for tolerability reasons in 3% of the participants.

The inclusion of a third arm with a placebo control was discussed in the original design of our study because it would have been very valuable to additionally demonstrate the superiority of both treatments compared with a nonintervention strategy. However, in 2012, it was discarded as a result of ethical and feasibility issues after taking into consideration the most recent publications that showed the effectiveness of both therapies, vaginal progesterone[15] and a cervical pessary.[17]

As an exploratory analysis, we compared the efficacy of both treatments in six predefined subgroups of patients without finding any differences, except for one of them. We identified that for those who had the ultrasonographic cervical gland area absent at the inclusion visit, the vaginal progesterone seemed to offer better performance than the pessary preventing spontaneous delivery at less than 34 weeks of gestation (7% vs 25%). This is an exploratory finding with a biological background based on the idea that the ultrasonographic absence of a cervical gland area corresponds with the absence of normal mucosal glands of the cervix and it is consistent with a more mature cervix.[26,27]

Table 3. Neonatal Outcomes According to Trial Group by Per Protocol

Variable	Treatment Group		*P*
	Pessary (n=125)	Progesterone (n=118)	
Neonate birth weight (g)	2,855±793	2,921±802	.52
Birth weight less than 1,500 g	10 (8)	10 (8)	.92
Birth weight less than 2,500 g	32 (26)	25 (21)	.38
Fetal and neonatal death	6 (5)	3 (3)	.35
Adverse neonatal outcome			
Composite adverse outcomes	24 (19)	20 (17)	.65
Admission to NICU	14 (12)	14 (12)	.90
Respiratory distress syndrome	7 (6)	6 (5)	.81
Mechanical ventilation	8 (7)	10 (9)	.58
Intraventricular hemorrhage	0 (0)	1 (0.9)	.31
Necrotizing enterocolitis	2 (1.7)	0 (0)	.16
Retinopathy of prematurity	2 (1.7)	1 (0.9)	.58

NICU, neonatal intensive care unit.
Data are mean±SD or n (%) unless otherwise specified.

Therefore, we hypothesize that in patients with a short cervix and absent cervical gland area, the biochemical effect of the progesterone was greater than the physical effect of the pessary and we consider that this finding could open future lines of research.

The fact that it was an open-label study was a potential limitation to this trial, although masking was impossible because of the nature of the interventions. However, the allocation sequence was kept concealed at all times. The biggest contribution of this trial is that it is a randomized trial that compares the use of the cervical pessary and vaginal progesterone, two interventions that are commonly used in clinical practice. Another strength of the trial is its multicenter character and pragmatic design that allows an acceptable external validity and extrapolation of the results to clinical practice. Considering that there is good-quality clinical evidence supporting the effectiveness of progesterone and a higher rate of vaginal discharge and discomfort reported by pessary users, we recommend the use of vaginal progesterone as a first option. However, the pessary could be considered a similar effective alternative and could be a preferred choice for women reluctant to use daily medication.

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