Articles

Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial

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Summary

Background Most previous studies of the use of cervical pessaries were either retrospective or case controlled and their results showed that this intervention might be a preventive strategy for women at risk of preterm birth; no randomised controlled trials have been undertaken. We therefore undertook a randomised, controlled trial to investigate whether the insertion of a cervical pessary in women with a short cervix identified by use of routine transvaginal scanning at 20–23 weeks of gestation reduces the rate of early preterm delivery.

Methods The Pesario Cervical para Evitar Prematuridad (PECEP) trial was undertaken in five hospitals in Spain. Pregnant women (aged 18–43 years) with a cervical length of 25 mm or less were randomly assigned according to a computer-generated allocation sequence by use of central telephone in a 1:1 ratio to the cervical pessary or expectant management (without a cervical pessary) group. Because of the nature of the intervention, this study was not masked. The primary outcome was spontaneous delivery before 34 weeks of gestation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00706264.

Findings 385 pregnant women with a short cervix were assigned to the pessary (n=192) and expectant management groups (n=193), and 190 were analysed in each group. Spontaneous delivery before 34 weeks of gestation was significantly less frequent in the pessary group than in the expectant management group (12 [6%] *vs* 51 [27%], odds ratio 0·18, 95% CI 0·08–0·37; p<0·0001). No serious adverse effects associated with the use of a cervical pessary were reported.

Interpretation Cervical pessary use could prevent preterm birth in a population of appropriately selected at-risk women previously screened for cervical length assessment at the midtrimester scan.

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Introduction

Spontaneous preterm birth, which arises in roughly 5–13% of pregnancies, is the leading cause of perinatal morbidity and mortality.[1–4] However, the rates have not changed much over the past 10 years. Improvements in neonatal care have increased survival rates in very premature infants. Nevertheless, a major reduction in rates of mortality and morbidity in premature babies will only be achieved with increased precision in the identification of women at risk of spontaneous preterm birth and through the development of an effective prevention for this complication.

A strategy for the prevention of spontaneous preterm births in which therapeutic intervention is restricted to women with a previous preterm birth is likely to have a small effect on the overall rate of prematurity since only about 10% of spontaneous preterm births arise in women with such a history.[5] Ultrasonographic measurement of cervical length at 20–23 weeks of gestation can increase the identification of women at risk of either singleton or twin pregnancies.[6–8] Asymptomatic women with a short cervical length (≤25 mm) are at increased risk of spontaneous early preterm delivery.

Cervical pessary is a silicone device that has been used in the past 50 years to prevent preterm birth.[9] Most of the reported studies were either retrospective or case controlled and the results showed that a cervical pessary can be used as a preventive strategy for patients at risk of preterm birth.[10] No randomised controlled trials have been undertaken. We therefore assessed the effect of cervical pessary on the spontaneous early preterm birth rate in asymptomatic women.

Methods
Participants and trial design

A prospective, open-label, randomised clinical trial was undertaken in five hospitals in Spain. Pregnant women (aged 18–43 years) with singleton pregnancies who were undergoing routine second trimester ultrasonography at 18–22 weeks of gestation were given the option of transvaginal ultrasonographic measurement of cervical length as a predictor of spontaneous preterm birth.[11] Cervical length was measured according to the criteria of the Fetal Medicine Foundation.[12] Women with a cervical length of 25 mm or less were invited to take part in the Pesario Cervical para Evitar Prematuridad (PECEP) trial. Exclusion criteria were major fetal abnormalities, painful regular uterine contractions, active vaginal bleeding, ruptured membranes, placenta praevia, and a history of cone biopsy or cervical cerclage in situ.

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Gestational age was judged from the menstrual history and confirmed by measurement of fetal crown-rump length at a first trimester scan, which was done routinely in all participating hospitals.

Trial coordinators regularly undertook quality control of screening, data handling, and verification of adherence to protocols at the different centres. Obstetricians who did the scans had received extensive training and passed a practical examination administered by an expert to demonstrate their competence in cervical assessment. All the images of the cases included in the trial were reviewed centrally. All cases of preterm birth were reviewed and discussed centrally. Dr Arabin, Witten, Germany, very kindly provided, free of charge, advice, recommendations, and suggestions for the use of cervical pessaries in pregnant women. The central team then instructed the other centres about the use of the pessary (figure 1).

The ethics committees for all participating hospitals approved the protocol.

Randomisation and masking

After written informed consent was obtained from women, they were randomly allocated to the cervical pessary group or expectant management group in a 1:1 ratio. The randomisation sequence was computer generated by the Statistics Unit of the Vall d'Hebron Hospital Research Institute, Barcelona, Spain, with variable block sizes of two and four, stratified for centre and parity, and implemented by use of central telephone. The recruiters or the trial coordinator did not have access to the randomisation sequence. The allocation code was disclosed after the patient's initials were confirmed. This study was open label because of the nature of the intervention.

Interventions

Cervical and vaginal swabs were taken from all patients for bacteriological analysis. If visual evidence existed of infection, appropriate treatment was given and insertion of the pessary was delayed by 1 week. Vaginal examination was done to detect cervical dilation or visible membranes. The pessary was not removed if there was evidence of bacterial infection after device insertion; however, appropriate antibiotic treatment was given. Patients allocated to the pessary group had the device inserted and were given detailed instructions about its subsequent management. Special emphasis was placed on the need to report any adverse symptoms immediately.

We used cervical pessaries certified by European Conformity (CE0482, MED/CERT ISO 9003/EN 46003; Dr Arabin, lower larger diameter 65 mm, height 25 mm, and upper smaller diameter 32 mm) during the study.

Both groups were seen by the clinical team of the trial at each centre every month until delivery. Transabdominal ultrasonography was done for fetal biometries and wellbeing, clinical questionnaire was administered for confirmation of correct device placement in the pessary group (figure 2), vaginal swab was taken for study of bacteriological infection, and transvaginal ultrasonography was done to measure cervical length (figure 3).

The pessary was removed during the 37th week of gestation. Indications for pessary removal before this time were active vaginal bleeding, risk of preterm labour with persistent contractions despite tocolysis, or severe patient discomfort.

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Figure 1: **Photograph of the silicone cervical pessary**
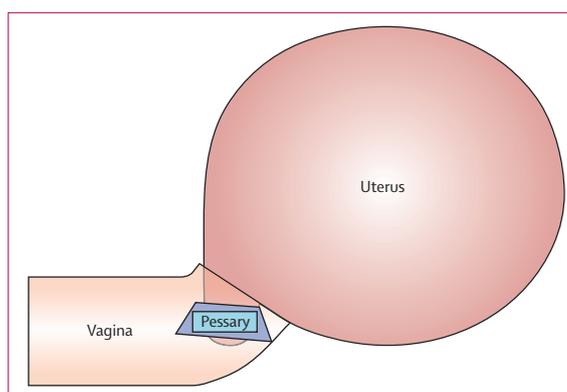(A) Inner diameter. (B) Outer diameter. (C) Lateral view.

Figure 2: **Cervical pessary**
The smaller diameter of the pessary is fitted around the cervix and the larger diameter faces the pelvic floor, thus rotating the cervix to the posterior vaginal wall and correcting the cervical angle.
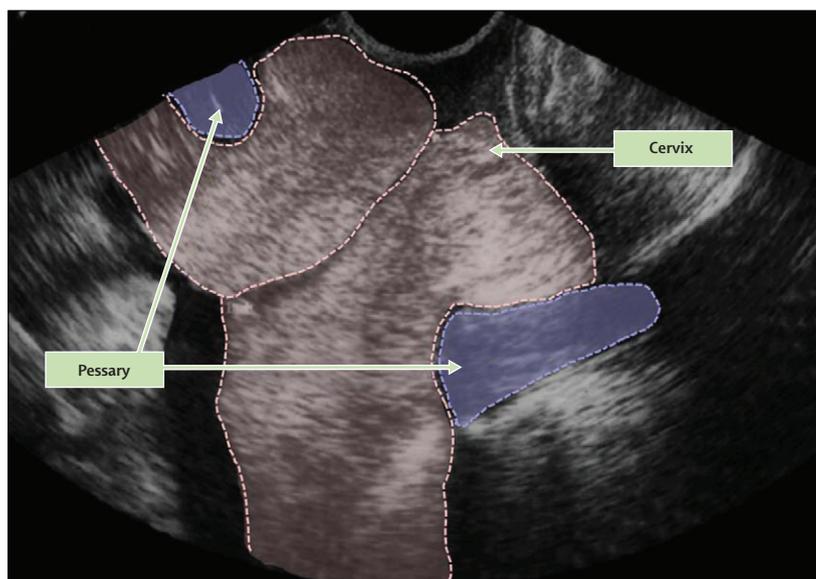

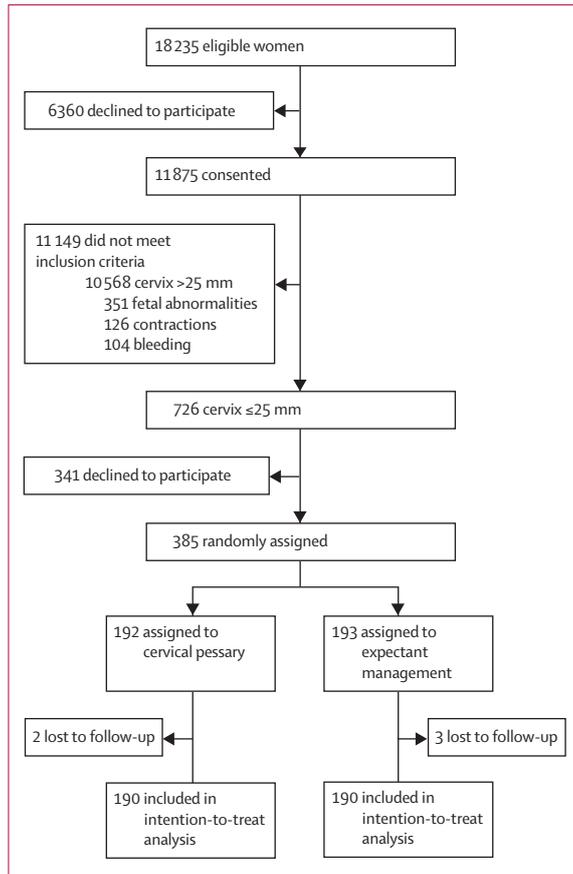*Figure 3:* **Ultrasound visualisation of cervical length in women using a cervical pessary**[13]

Figure 4: Trial profile

	Cervical pessary group (n=190)	Expectant management group (n=190)
Maternal age (years)	30·3 (5·1)	29·6 (5·4)
Body-mass index (kg/m²)	24·9 (4·6)	24·5 (4·3)
Obstetrical history		
Nulliparous	94 (49%)	96 (51%)
Parous with no previous preterm births	75 (39%)	74 (39%)
Parous with at least one previous preterm birth	21 (11%)	20 (11%)
Cigarette smoking during pregnancy	37 (19%)	38 (20%)
Ethnic origin (self reported)		
White	107 (56%)	110 (58%)
Latin American	58 (31%)	56 (29%)
Other	25 (13%)	24 (13%)
Gestational age at randomisation (weeks)	22·2 (0·9)	22·4 (0·9)
Cervical length at randomisation (mm)	19·0 (4·6)	19·0 (4·9)
Funnelling at randomisation (yes)	81 (43%)	85 (45%)
Sludge at randomisation (yes)	5 (3%)	4 (2%)

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

Table 1: Baseline characteristics of participants in the cervical pessary and expectant management groups

Patients whose pessaries were removed (even on the same day of insertion) remained in the trial because of the intention-to-treat principle.

Statistical analysis

The primary outcome was spontaneous preterm birth before 34 weeks (238 days) of gestation. Secondary outcomes are shown in the appendix. Chorioamnionitis was defined as inflammation of the chorion and amnion by histopathological assessment after delivery.

Calculation of sample size was based on a reduction in the incidence of spontaneous delivery before 34 weeks from 28% in the expectant management group to 14% in the pessary group, with a power of 80%. To detect this difference at a significance level of 5%, we needed to recruit 380 patients with cervical length of 25 mm or less. If the prevalence of cervical length of 25 mm or less is 8%, a total of 4750 women would need to be scanned to identify 380 cases of short cervix.

Statistical analysis was based on the intention-to-treat principle. The mean and SD summarised baseline data for the pessary and expectant management groups. Comparisons between groups were made with the Mann-Whitney U test. Univariate comparisons of dichotomous data were done with Fisher's exact test. The p values for all hypotheses were two sided, and p values of less than 0·05 were judged to be significant. The risk of spontaneous preterm birth before 34 weeks was quantified by use of the odds ratio and 95% CI. Multivariate analysis was done by use of logistic regression.[14] The risk of spontaneous preterm birth from randomisation until 34 weeks was assessed with Kaplan-Meier analysis,[15] in which gestational age was the timescale, spontaneous delivery was the event, and elective deliveries were censored. For purposes of this analysis, all pregnancies were judged to be no longer at risk at the start of the 34th week. SPPS software package (version 16.0) was used for all statistical analyses. Interim analyses were done every 6 months.

The trial is registered with ClinicalTrials.gov, number NCT00706264.

Role of the funding source

The sponsor of the study had no role in study design, data gathering, data analysis, data interpretation, or writing of the report. 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 PECEP trial was undertaken from June, 2007, to June, 2010. During the study period, 18 235 women with singleton pregnancies were invited to have transvaginal ultrasonographic measurement of cervical length during the second trimester scan; 11 875 provided written informed consent (figure 4). Median cervical length was 34 mm (range 3–68) and 25 mm or less in

726 (6%) women. 385 (53%) women with a short cervix agreed to participate in the trial. They were randomly assigned to the pessary or expectant management group (figure 4).

Table 1 shows the baseline characteristics. No cervical dilation or visible membranes were noted, although four (2%) of 190 patients had a very short cervix (≤5 mm) in the pessary group (minimum cervical length of 4 mm) versus six (3%) of 190 in the expectant management group (minimum cervical length 3 mm).

The primary outcome rate—spontaneous birth before 34 weeks of gestation—was significantly higher in the expectant management group (table 2). Four women (two in each group) had medically indicated preterm deliveries. The cumulative percentage of patients who did not give birth spontaneously before 34 weeks was significantly higher in the pessary group than in the expectant management group (figure 5). The risk of spontaneous preterm birth before 34 weeks of gestation did not vary significantly with respect to maternal age, body-mass index, ethnic origin, obstetrical history, or cervical length at the time of randomisation (odds ratio adjusted for maternal age, body-mass index, ethnic origin, obstetrical history, and cervical length at the time of randomisation 25·8, 95% CI 7·7–87·1). No difference was noted in terms of bacterial vaginosis between groups at the time of randomisation (pessary group 45 [24%] of 190 vs expectant management group 47 [25%] of 190).

Need for tocolysis was higher in the expectant management group (table 2). The most frequently administered tocolytic drug was atosiban, given for 48 h; more patients in the expectant management group also required more than one cycle of tocolysis. The need for corticosteroid treatment for fetal maturation (two doses of betamethasone 12 mg per day, intramuscularly, for 2 days) was greater in the expectant management group (table 2). No differences were noted in terms of chorioamnionitis (table 2).

Significant differences were noted in secondary outcomes between groups (table 2). The pessary group had significant reductions in the rate of birthweight less than 2500 g, respiratory distress syndrome, treatment for sepsis, and composite adverse outcomes. No differences were noted in neonatal mortality rates.

Additionally, no differences were noted in terms of iatrogenic delivery rate (any delivery rate excluding spontaneous delivery rate was two in each group). Rate of premature preterm rupture of membranes was higher in the expectant management group (table 2). No major adverse events were reported in the pessary group (table 2). However, all women in the pessary group had vaginal discharge after placement of the pessary and some of these women required pessary repositioning without removal and one patient needed removal and replacement of the pessary (table 2). According to the results of the maternal satisfaction questionnaire,[16] pain during pessary insertion was ranked as a mean of 4 (scale 0–10) and pain during removal as 7 (0–10); and

	Cervical pessary group (n=190)	Expectant management group (n=190)	Odds ratio (95% CI)	p value
Pregnancy outcome				
Spontaneous delivery before 28 weeks	4 (2%)	16 (8%)	0·23 (0·06–0·74)	0·0058
Spontaneous delivery before 34 weeks	12 (6%)	51 (27%)	0·18 (0·08–0·37)	<0·0001
Any delivery before 34 weeks	14 (7%)	53 (28%)	0·21 (0·10–0·40)	<0·0001
Spontaneous delivery before 37 weeks	41 (22%)	113 (59%)	0·19 (0·12–0·30)	<0·0001
Gestational age at delivery (weeks)	37·7 (2·0)	34·9 (4·0)	··*	<0·0001
Tocolytic treatment	64 (34%)	101 (53%)	0·23 (0·16–0·35)	<0·0001
Corticosteroid treatment for fetal maturation	80 (42%)	121 (64%)	0·41 (0·26–0·64)	<0·0001
Chorioamnionitis	5 (3%)	6 (3%)	0·82 (0·20–3·32)	0·7596
Pregnancy bleeding	7 (4%)	9 (5%)	0·77 (0·24–2·38)	0·6094
Premature preterm rupture of membranes	3 (2%)	17 (9%)	0·16 (0·03–0·58)	0·0013
Caesarean delivery	41 (22%)	40 (21%)	··	0·418
Side-effects				
Vaginal discharge	190 (100%)	87 (46%)	··	0·002
Pessary repositioning without removal	27 (14%)	··	··	··
Pessary withdrawal	1 (<1%)	··	··	··
Perinatal outcome				
Fetal death	0	0	··	··
Neonatal death	0	1 (<1%)	··	··
Birthweight less than 1500 g	9 (5%)	26 (14%)	0·31 (0·13–0·72)	0·0040
Birthweight less than 2500 g	17 (9%)	56 (29%)	0·23 (0·12–0·43)	<0·0001
Adverse outcomes				
Necrotising enterColitis	0	2 (1%)	··	0·4987
Intraventricular haemorrhage†	0	2 (1%)	··	0·4987
Respiratory distress syndrome	5 (3%)	23 (12%)	0·20 (0·06–0·55)	0·0003
Retinopathy	0	2 (1%)	··	0·4987
Treatment for sepsis	3 (2%)	12 (6%)	0·24 (0·04–0·90)	0·0317
Composite adverse outcomes	5 (3%)	30 (16%)	0·14 (0·04–0·39)	<0·0001

Data are number (%) or mean (SD), unless otherwise indicated. *p value close to zero, odds ratio tends towards infinity. †Grade 2 in all infants.

Table 2: Primary and secondary outcomes in the cervical pessary and expectant management groups

181 (95%) of 190 patients recommended this intervention to other people.

Data for pregnancy outcome were also obtained from 11 518 (97%) of 11 875 women in whom cervical length was originally measured; 227 (2%) of 11 518 women had a spontaneous preterm birth before 34 weeks. 152 (21%; 12 in pessary group, 51 in expectant management group, and 89 declined to participate) of 726 women with a cervical length of 25 mm or less and 75 (<1%) of 10 792 with a length greater than 25 mm delivered preterm.

Discussion

The rate of spontaneous birth before 34 weeks of gestation was lower in the pessary group. So far, this study is the first multicentre, randomised trial of the use of a cervical pessary for prevention of preterm birth. However, the potential benefits of this device have been
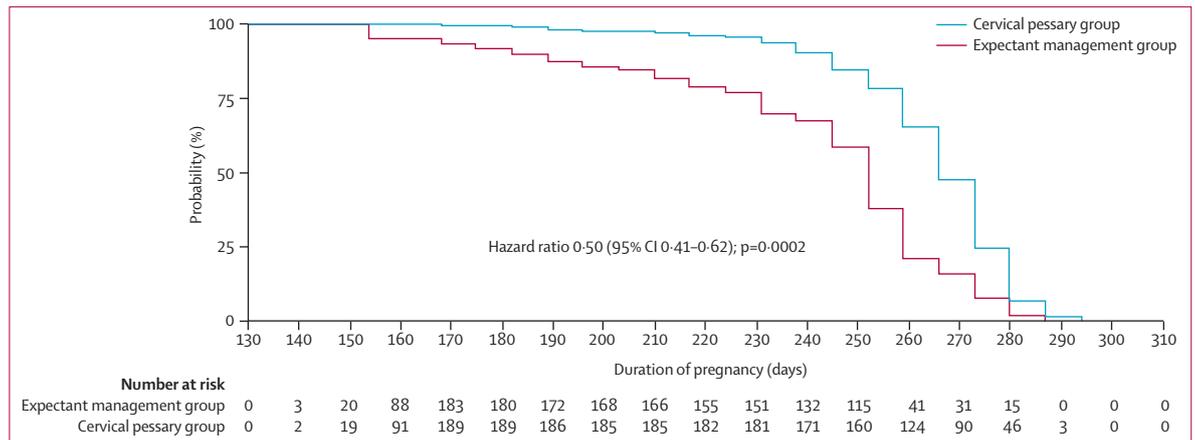
Figure 5: Kaplan-Meier plot of the probability of continued pregnancy without delivery in the cervical pessary and expectant management groups

Number at risk																		
Expectant management group	0	3	20	88	183	180	172	168	166	155	151	132	115	41	31	15	0	0	0
Cervical pessary group	0	2	19	91	189	189	186	185	185	182	181	171	160	124	90	46	3	0	0

Panel: Research in context

Systematic review

We searched PubMed and our professional networks using the search terms "cervical pessary" and "preterm birth" for all publications related to use of cervical pessaries for the prevention of preterm birth and reviewed all research studies in which preventive interventions for preterm birth were assessed. Results of non-randomised trials showed benefits of cervical pessaries in prevention of preterm birth[16,17] and well designed randomised controlled trials to confirm or refute the benefit of cervical pessaries were identified in a Cochrane review.[18]

Interpretation

The Pesario Cervical para Evitar Prematuridad (PECEP) trial is the first randomised study of the use of cervical pessary for prevention of preterm birth. Our results confirm the benefit of pessary use in pregnant women with a short cervix. In the context of the published reports, our results provide evidence that the use of a cervical pessary is an effective intervention for prevention of preterm birth. Clinicians should consider using a cervical pessary in asymptomatic pregnant women with cervical lengths of 25 mm or less who are at high risk of preterm birth at 20–23 weeks of gestation, but should take appropriate steps to ensure adverse effects are kept to a minimum.

tested successfully in the past—Arabin and colleagues[16] reported a preterm birth rate before 34 weeks of zero when they inserted pessaries into women with short cervical lengths at 22 weeks compared with nearly 50% in a matched control group (panel). Despite the limitation of not being a randomised trial, the results were sufficiently promising to warrant further study.

Sieroszewski and colleagues[17] described a case series of 54 pregnant women. Insertion of a pessary in those with cervical lengths between 15 mm and 30 mm resulted in

an incidence of preterm birth before 29 weeks of 1·9% and a birth-at-term rate of 83·3%. The results of our study are strengthened by the recruitment of nearly 15 000 pregnant women after a midtrimester anomaly scan. These patients were asked to have a cervical length assessment, permitting us to detect about 6% of this population of women at increased risk of preterm birth. The women who agreed to participate were randomly assigned centrally at the Vall d'Hebron Hospital, and the follow-up and pessary insertion techniques were thoroughly controlled. Use of this model conferred further support to our findings since, although more patients than in other studies were included in our study, the results matched those of previous studies—a low rate of birth at less than 34 weeks of gestation (6%) in the pessary group compared with the expectant management group (27%).

The two groups were well balanced at baseline, which suggests that the pessary could have potential value as a treatment for women at high risk of preterm birth, could be beneficial in pregnant women with a short cervix irrespective of their obstetrical history, and might reduce the risk of preterm birth in nulliparous women. The increase in gestational age at birth in nulliparous women matched the results of a preliminary report by Arabin and colleagues.[16]

Interim analysis was done every 6 months. However, no conditions for stopping the trial were noted by the external data monitoring group.

We selected the 25 mm cutoff based on the fifth centile in the Spanish population[19] and its relation with a substantially increased risk of preterm birth, which has been extensively documented.[20] Previously, the preterm birth rate for this group was roughly 30%.[21] The results of a recent meta-analysis confirm that 25 mm is the best cutoff for prediction of preterm birth before 35 weeks.[22] Our results were better than we had expected.

Measurement of cervical length, as a screening test, is used because of its fairly low cost, short learning curve,

and tolerability in patients.[23] Additionally, placement of a pessary is an affordable procedure, non-invasive, and easy to insert and remove when required;[16] also, we described a new technique for measuring cervical length in pregnant women inserted with a pessary.[13] Furthermore, assessment of some of our secondary outcomes showed that severe adverse symptoms were very low in the treatment group. However, patients did have a slight increase (daily occurrence) in white, inodorous, vaginal discharge. Furthermore, 15% of these patients could feel the pessary inside the vagina after weeks without any symptoms. For this reason, patients should be advised to see their doctor if they have any abnormal symptoms such as feeling the pessary in the vagina. Only one case of pessary withdrawal was reported in the entire group and tolerability was not an issue, even in this case. Our satisfaction questionnaire showed that patients had more pain during pessary removal than during insertion; however, most recommended this intervention to others. No severe bleeding was reported in the pessary group compared with the expectant management group.

The mechanism of action of cervical pessaries remains to be clarified. Theoretically, the effect relies on their mechanical ability to bend the cervix backwards, not only slightly elongating it but also changing the uterocervical angle, which not only strengthens the cervical canal but also diminishes the contact of intact membranes with the vagina, somehow preserving its integrity. The suggestion that some physical intervention, such as a pessary, reduces preterm birth by the change in the uterocervical angle has little biological plausibility. The precise mechanism by which a pessary confers a benefit is not known, but it might support the immunological barrier between the chorioamnion-extraovular space and the vaginal microbiological flora as cerclage has been postulated to do. Further studies are needed to clarify the mechanism of action of this device.

This trial was an open-label study and this could be a limitation. Although masking was impossible because of the nature of the intervention, the use of a pessary might have affected medical decision making.

The results of our study did show a significant reduction in the rate of neonatal morbidity. However, the trial was not designed to assess the rate of neonatal morbidity or mortality as a primary outcome. For this reason, the effect size should be considered. Further studies are needed to confirm this finding. The findings of our trial are based on only about 50% of patients who could have taken part in the trial and might have been due to this being the first time routine cervical length measurement had been done transvaginally at the hospitals. However, a randomised trial was undertaken with balanced groups. To use pessaries in the general population, two concepts must be taken into account—extensive competence in cervical assessment is required and strict instructions to see a doctor should be given to patients with a pessary. We have planned a long-term follow-up of the infants until the age of 2 years to detect and compare developmental impairments in the two groups.

Historically, efforts to reduce prematurity have been frustrating. Even the use of pessaries has been questioned in the past, but the Cochrane reviewers agree that there is a paucity of well designed trials in this respect.[18] Finding a safe, economical way (38 euros per pessary) of reducing the incidence of preterm birth in the world and reducing the burden of prematurity and its sequelae is a worthwhile goal. Our results open the door to further research into the use of this device and give us hope of finding a way to substantially reduce the incidence of prematurity and its consequences worldwide. Further trials, with much larger samples and the possible commitment of a large number of centres in several countries, are not only needed but also warranted.[24]

In conclusion, the cervical pessary is an affordable, safe, and reliable alternative for prevention of preterm birth in a population of appropriately selected at-risk pregnant women who have been screened for cervical length assessment at the midtrimester scan.

Contributors
MG was the principal investigator at Hospital Vall d'Hebron and wrote the first drafts of the protocol and report, and is the guarantor for the report. LP, CM, and CR contributed to study design and data gathering at Vall d'Hebron Hospital. LV was the principal investigator at the Hospital Materno-Infantil de Canarias. ARom contributed to the study design and data gathering at this hospital. MJ was the principal investigator at the Hospital Son Llatzer. ARod was the principal investigator at the Institut Universitari Dexeus. BM was the principal investigator at the Hospital Sant Joan. BS was the principal investigator at the Hospital de Fuenlabrada. JCBM was the trial statistician. EL was a member of the investigating group at the Hospital Vall d'Hebron. TH was the cervical assessment coordinator. EC was the trial coordinator and had the initial idea for the study. LC was the chairman and was responsible for the overall supervision of the trial management. All authors reviewed and approved the final version of the report.

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