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Cervical cerclage vs cervical pessary in women with cervical insufficiency: A multicentric, open-label, randomised, controlled pilot trial [the CEPEIC trial]

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ABSTRACT

Objective: Cervical insufficiency accounts for 8 % of preterm births. Pessary and cerclage are considered preventive approaches for preterm birth. These interventions were compared in terms of reducing the prematurity rate in women with previous preterm birth, due to cervical insufficiency or due to having a short cervix in their current pregnancy.

Methods: This was a prospective, multicentric, open-label, randomised, pilot, controlled trial. Participants were women with singleton pregnancies who had previous preterm birth caused by cervical insufficiency or previous preterm birth and a short cervix [≤ 25 mm] in their current pregnancy. Women were randomised [1:1] to either cerclage or pessary. The primary outcome was to assess the feasibility of a trial on cervical pessary vs. cerclage to prevent preterm birth before 34 weeks in women with cervical insufficiency. As a secondary outcome, we studied the morbidity rate of the pessary versus the cerclage in women with cervical insufficiency and assessed the financial impact of using both devices in these women. The sample size was calculated based on the estimated population that we could potentially recruit: 60 women, 30 for each group, to ascertain whether the rate of preterm birth < 34 weeks of gestation may be reduced from 34 % to at least 27 % in the pessary group, as in the results obtained with the cerclage.

Results: No significant differences in preterm birth < 34 weeks of gestation were observed in our study, although it was underpowered to detect these differences [the relative risk [RR] of PB < 34 weeks of gestation was 0.8 [95 % CI: 0.31–2.09, p = 0.888]. The rates of obstetric and perinatal complications were similar for both devices [15 cases in both groups, 50 % of cases [RR; 0.6–1.68; p = 1]. Cervical pessary had fewer secondary effects than the cerclage [less bleeding at insertion in the pessary group compared with cerclage, 1 case vs 14 cases, p < 0.001; less pain at removal in the pessary group compared with cerclage, 14 vs 22 cases. p = 0.042 and less bleeding, 2 cases vs. 10 cases, p = 0.027].

Conclusions: Pessary does not seem less effective than cerclage, although these findings need to be confirmed in a larger randomised controlled trial. Pessary had fewer secondary effects than cerclage both at insertion and removal.

Sinopsis: Cervical pessary does not seem to be less effective than cerclage. Cervical pessary had fewer secondary effects than cerclage.

Introduction

Preterm birth [PB], defined as delivery before 37 weeks of gestation, occurs in 5–14 % of all pregnancies. PB complications account for approximately 35 % of annual neonatal deaths worldwide [1,2]. Improvements in prematurity rates may only be achieved with a more

Abbreviations: CI, cervical insufficiency; PB, preterm birth; CL, cervical length.

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accurate identification of women at risk of spontaneous preterm birth [SPB] and with the development of preventive interventions [3]. A history of SPB is the main risk factor for recurrence and risk increases the higher the number of previous PB and the lower the gestational age at the time of PB [4–6].

Cervical insufficiency, which occurs in approximately 0.15–1 % of pregnancies [7], is characterized by a progressive shortening of the cervix with painless dilation that leads to recurrent second-trimester pregnancy losses/PB in otherwise normal pregnancies. Diagnosing cervical insufficiency remains a significant challenge in obstetric practice due to its typically silent and asymptomatic course until cervical dilation occurs prematurely, often without contractions or other warning signs. This condition represents a spectrum of cervical disorders that can result in various adverse outcomes, ranging from recurrent mid-trimester pregnancy losses to spontaneous preterm births, depending on the severity of cervical dysfunction. The lack of universally agreed-upon diagnostic criteria and the wide variability in clinical presentation further complicate its identification, often leading to underestimating its true prevalence. Moreover, cervical insufficiency is frequently diagnosed retrospectively after an adverse event, limiting opportunities for early intervention. This spectrum of clinical manifestations—from subtle cervical shortening detectable by transvaginal ultrasound to overt painless dilation—underscores the need for improved diagnostic tools and strategies to identify at-risk pregnancies more accurately and manage them effectively, thereby potentially reducing the rate of preterm birth. (ref).

Cervical cerclage is the routine treatment for cervical insufficiency and reduces the rate of PB before 34 weeks of gestation with no associated reduction in neonatal morbidity and mortality [8]. Women with multiple second-trimester pregnancy losses/PB [three or more, or two of them being consecutive] may benefit from early placement of a cerclage based on their obstetric history alone [9,10]. Sonographic measurements of cervical length [CL] in women with a previous second-trimester pregnancy loss/PB can identify patients with a short cervix who may benefit from having a cerclage [secondary cerclage, ultrasound-indicated cerclage before 24 weeks of gestation]. The effectiveness of a secondary cerclage was studied in a meta-analysis where the rate of PB before 32 weeks of gestation was reduced from 30 % to 19 % using a cervical cerclage [11].

In a randomised controlled trial published in 2012, the Arabin cervical pessary lowered the rate of PB before 34 weeks of gestation and reduced the rate of neonatal adverse events [12]. The results of the largest study published to date on pessary use for preventing SPB differed from the results obtained in the previous study, with no reduction in PB rate being observed [13]. Few studies have been designed to evaluate the effect of the cervical pessary in pregnant women with CI, and their results show a PB rate reduction in women who received this intervention [14–16].

The main outcome of our pilot study was to assess the feasibility of conducting a future randomised controlled trial for evaluating the potential effectiveness of the cervical pessary and cervical cerclage in pregnant women with CI, in terms of reducing the rate of SPB before 34 weeks of gestation. The secondary outcomes were assessing the morbidity rate with both devices and their financial impact.

Material and methods

We conducted a prospective, multicentric, open-label, randomised controlled pilot trial [the CEPEIC Trial, "***CE**rclaje* vs. ***PE**sario en las pacientes con **I**nsuficiencia **C**ervical*"]. This trial was designed to compare the cervical pessary with the cervical cerclage in patients with CI, based on a significant obstetric history or minor obstetric history with CL shortening [≤ 25 mm]. The CEPEIC trial was conducted from 28/04/2015 until 01/06/2020.

Pregnant women with cervical insufficiency based on obstetric history alone -significant obstetrical history- [3 or more second-trimester pregnancy losses/PB, or with 2 of them being consecutive] were eligible for a primary cerclage or history-indicated cerclage before 16 weeks of gestation [minor obstetric history] and therefore, were eligible to participate in the trial. Additionally, women with CI based on a CL ≤ 25 mm with prior second-trimester pregnancy losses/PB [one or two non-consecutive] were eligible for a secondary cerclage or ultrasound-indicated cerclage before 24 weeks of gestation and therefore, were also eligible to participate.

Women with placenta praevia, vasa praevia, preterm premature rupture of membranes [PPROM], premature labour, cervical dilation, fetal death, identified major congenital or chromosomal fetal abnormalities, or signs of intrauterine infection were excluded.

The Research Ethics Committees from both sites approved the study [PR[AMI]284/2013, 24/01/2014]. Informed consent was obtained of all participants. After obtaining written informed consent, women were randomly allocated in a 1:1 ratio to receive a cervical cerclage or a pessary [Arabin® pessary]. Due to the type of intervention, this study was not blinded.

Microbiological vaginal and endocervical cultures were performed before the intervention. If there was evidence of vaginal infection, the appropriate treatment was prescribed. Placement of the pessary or cerclage was not deferred. If patients had vaginal infections at consecutive visits, the corresponding treatment was prescribed without removing the device. Trained research team members fitted the pessary or the cerclage on the day of randomization. Transvaginal ultrasound was performed before and after fitting the device to evaluate cervical length [total and effective cervical length].

Both devices were placed before 24 or before 16 weeks in cases of a primary intervention [cerclage or pessary]. According to the local protocol, women allocated to a cervical cerclage underwent the intervention. Both devices were kept in place until 37 weeks of gestation or until delivery, whichever occurred first. Further management was in accordance with national guidelines and local protocols for preventing preterm birth.

The primary outcome was to assess the feasibility of conducting a future randomised controlled trial evaluating the potential effectiveness of the cervical pessary and cervical cerclage in pregnant women with CI to reduce the rate of SPB before 34 weeks of gestation.

Secondary outcomes were time from intervention to delivery, gestational age at birth, rate of preterm birth before 28 and 37 weeks of gestation [overall and stratified by spontaneous or indicated delivery], premature rupture of membranes, use of tocolysis and/or corticosteroids during pregnancy, mode of delivery, maternal infections, maternal side effects, and both neonatal and maternal hospital admissions. Perinatal outcomes included newborn respiratory distress syndrome [NDPS], bronchopulmonary dysplasia [BPD], intraventricular haemorrhage [IVH], necrotising enterocolitis [NE], retinopathy of prematurity, early and late-onset sepsis, stillbirth, and death before discharge from maternity unit or neonatal intensive care unit [NICU] admission, and follow-up until 2 years of life. Secondary effects associated with the insertion and removal of the devices, such as pain, haemorrhage, or organ injury, were also evaluated. Finally, each intervention's financial impact was another outcome we assessed.

We performed a pilot study to know the acceptance rate and estimate the pessary effect in patients with cervical insufficiency compared to cerclage. The sample size was calculated based on the estimated population we could potentially recruit during the study period: 60 women, 30 for each group [cerclage and pessary]. Assuming a reduction in the rate of preterm birth below 34 weeks of gestation from 34 % to 27 % in pregnant women diagnosed with cervical insufficiency [8], to evaluate the cervical pessary as compared with the cerclage, in terms of preterm birth rate before 34 weeks of gestation.

Statistical analysis

Analysis was performed on an intention-to-treat basis, as a

randomised controlled trial. Comparisons of continuous variables were performed using the Mann-Whitney test. Secondary dichotomous outcome measures were assessed using the absolute and relative risks [RR], along with the 95 % confidence intervals. The risk of preterm delivery was assessed using the Kaplan–Meier analysis, where gestational age was the time scale and delivery was the event.

The R software [R Foundation for Statistical Computing, Vienna, Austria] was used for statistical analysis. The significance level was set at 0.05.

Ethics statement

The study was registered on 16 April 2015 on clinicaltrials.gov: NCT02405455 [clinicaltrials.gov/ct2/show/nct02405455?term=cepeic&rank= 1]. The CEPEIC trial was conducted from 28/04/2015 until 01/06/2020.

We planned this trial and estimated the sample size required at our site, Hospital Universitari Vall d'Hebron, Barcelona, Spain. In addition, Hospital de Torrejón, Madrid, Spain, also collaborated in the recruitment.

Results

The CEPEIC trial was conducted from 28/04/2015 until 01/06/2020. During the study, 94 pregnant women were invited to participate; 61 [65 %] provided written informed consent and were randomly assigned to the pessary or cervical cerclage groups (Fig. 1). Fifty-eight pregnant women were finally included, 30 in the pessary group and 28 in the cerclage group.

Table 1 shows the baseline characteristics of the participants. No differences between groups were found. According to the type of CI, 4 [7 %] women in the pessary group and 11 [19 %] women in the cerclage group met the criteria for CI based on obstetric history alone; 26 [45 %] women in the pessary group and 17 [29 %] women in the cerclage group met the criteria for CI based on ultrasound findings (Table 2). No women were following progesterone treatment at the time of fitting the devices.

Primary and secondary outcomes

No differences in prematurity rates < 37, 34 and 28 weeks of gestation were found between groups (Table 3 and Fig. 2). The relative risk of PB at various gestational ages were as follows: < 37 weeks of gestation was 0.62 [95 % CI: 0.3–1.29, p = 0.308], < 34 weeks of gestation was 0.8 [95 % CI: 0.31–2.09, p = 0.888], and < 28 weeks of gestation was 1.87 [95 % CI: 0.37–9.41, p = 0.671]. No differences were found in caesarean section rates [p = 0.287].

No differences were observed in obstetric outcomes between both groups, regarding the need for tocolytic treatment, lung maturation or fetal neuroprotection [RR: 1, 95 % CI: 0.6–1.68, p = 1] (Table 3). Regarding perinatal outcomes, no differences were found for birth weight, Apgar test or arterial and venous cord pH. Likewise, no

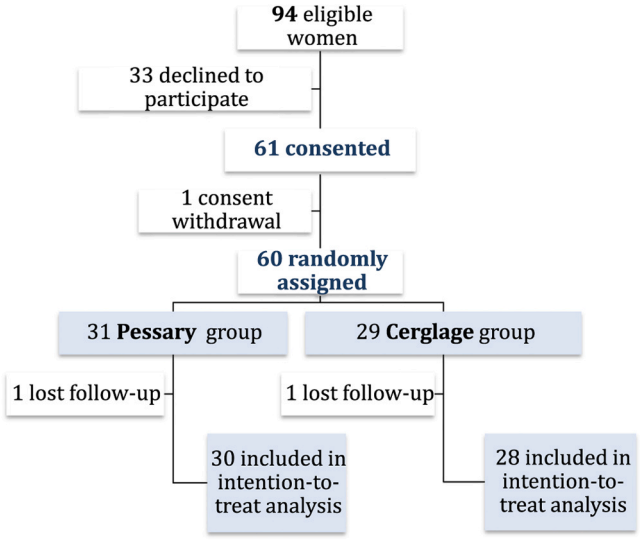

Fig. 1. Trial profile.

Table 1
Baseline characteristics of study participants.*.

	Pessary group	Cerclage group
Maternal age [years]	34 [28.3 – 37.8]	36 [31.75 – 37]
Ethnic group		
White	19 [63.3 %]	20 [71.4 %]
Latin American	8 [26.7 %]	5 [17.9 %]
Afro American	3 [10 %]	2 [7.1 %]
Asiatic	0	1 [3.6 %]
Body mass index [Kg/m^2]	23.5 [20.75 – 26.4]	25.75 [23.13 – 30]
Tobacco		
Ex-smokers	0	2 [7.1 %]
Active smoker during pregnancy	6 [20 %]	4 [14.3 %]
Other toxics		
Sporadic alcohol consumption during pregnancy	0	1 [3.6 %]
Others	1 [3.3 %]	1 [3.6 %]
Assisted reproduction techniques	1 [3.3 %]	1 [3.6 %]
Obstetric background		
Term deliveries	10 [33.3 %]	16 [57.1 %]
Preterm deliveries	16 [53.3 %]	13 [46.4 %]
1rst trimester miscarriage	8 [26.7 %]	10 [35.7 %]
2nd trimester miscarriage	15 [50 %]	12 [42.9 %]
Termination of pregnancy	8 [26.6 %]	7 [25.0 %]
Uterine malformation	1 [3.3 %]	0
Conization	2 [6.7 %]	3 [10.7 %]
Hysteroscopy	6 [20 %]	1 [3.6 %]
Mode of previous uterine evacuation		
Medical treatment	2 [6.7 %]	2 [7.1 %]
Curetage	7 [23.3 %]	4 [14.3 %]
Curetage + medical treatment	3 [10 %]	3 [10.7 %]
Previous deliveries		
Vaginal delivery	24 [85.7 %]	24 [85.7 %]
Cesarean section	5 [17.2 %]	7 [28 %]
Instrumented delivery	0	2 [8.3 %]
History of short cervix in previous pregnancies	9 [30 %]	16 [57.1 %]
PB preventive previous treatments		
Progesterone	0	1 [3.6 %]
Cerclage	4 [13.3 %]	10 [35.7 %]
Pessary	3 [10 %]	3 [10.7 %]
Distribution of pregnant women depending on the type of CI		
CI by obstetric history	4 [7 %]	11 [19 %]
CI by short CL	26 [45 %]	17 [29 %]

PB = Preterm birth; CI = Cervical insufficiency; CL = cervical length
* No differences were observed in these demographic variables between groups.

Table 2
Cervical length, effective and total, before and after fitting each device. Time required for insertion.

	Pessary	Cerclage	p
Effective cervical length pre fitting [mm]	20[12–23]	22.5 [19 – 28.5]	0.057
Total cervical length pre fitting [mm]	24.5 [19.25 – 30]	29 [24.25 – 37.5]	0.04
Effective cervical length post fitting [mm]	30.5 [27–35]	21 [17 – 26.5]	< 0.001
Total cervical length post fitting [mm]	33.5 [27.5 – 36]	40 [33.5 – 42]	0.001
Time required [min]	1[1,2]	40 [30–45]	< 0.001

Table 3
Pregnancy, obstetric and perinatal outcomes.

	Pessary	Cerclage	RR [95 % CI]	p
Pregnancy outcomes				
Delivery < 37 weeks of gestation	8 [26.7 %]	12 [42.9 %]	0.62 [0.3 – 1.29]	0.308
Delivery < 34 weeks of gestation	6 [20 %]	7 [25 %]	0.8 [0.31 – 2.09]	0.888
Delivery < 28 weeks of gestation	4 [13.3 %]	2 [7.1 %]	1.87 [0.37 – 9.41]	0.671
Spontaneous deliveries < 37 weeks	6/28 [21.4 %]	6/22 [27.3 %]	0.79 [0.29 –2.10]	0.883
Spontaneous deliveries < 34 weeks	4/28 [14.3 %]	4/25 [16.0 %]	0.89 [0.25 – 3.20]	1
Spontaneous deliveries < 28 weeks	3/29 [10.3 %]	2/28 [7.1 %]	1.45 [0.26 – 8.02]	1
Tocolytic treatment	12 [40 %]	12 [42.9 %]	0.93 [0.51 – 1.72]	1
Corticosteroid treatment for fetal lung maturation [completed dosage]	15 [50 %]	13 [46.4 %]	1.08 [0.63 – 1.84]	0.993
Neuroprotection	15 [50 %]	12 [42.9 %]	1.17 [0.67 - 2.04]	0.778
Obstetric outcomes	15 [50 %]	14 [50 %]	1 [0.6 - 1.68]	1
Preterm labour	15 [50 %]	13 [46.4 %]	1.07 [0.63 - 1.84]	0.993
Premature preterm rupture of membranes	0	2 [7.1 %]	-	0.229
Chorioamnionitis	2 [6.7 %]	2 [7.1 %]	0.47 [0.05 – 4.87]	0.605
Rescue treatment	5 [16.7 %]	3 [10.7 %]	1.56 [0.41, 5.91]	0.707
Type of delivery				0.287
Vaginal delivery	19 [63.3]	19 [67.9 %]		
Instrumental delivery	5 [16.7 %]	1 [3.6 %]		
Caesarean delivery	6 [20 %]	8 [28.6 %]		
Perinatal outcomes				
Birth weight [grams]	3045 [1769 –3216]	3040 [1930 –3235]		0.656
1-minute Apgar test	9	9		0.069
5-minute Apgar test	10	10		0.820
10-minute Apgar test	10	10		0.891
Umbilical artery pH	7.25	7.25		0.899
Umbilical vein pH	7.32	7.29		0.815
Perinatal complications	1 [3.7]	3 [11.1]	0.33 [0.04 - 3.01]	0.610
Intraventricular haemorrhage	0	1 [3.6 %]	-	0.491
Neonatal sepsis	0	1 [3.6 %]	-	0.491
Respiratory distress syndrome	1 [3.4 %]	1 [3.6 %]	0.97 [0.06 –14.7]	1
Necrotising enterocolitis	0	0		
NICU admission	4 [14.8 %]	10 [38.5 %]	0.38 [0.14 –1.08]	0.066
Alive without disease at 2 years old	25 [83.3 %]	25 [89.3 %]		
Alive with disease at 2 years old	2 [6.7 %]	1 [3.6 %]		
Neonatal death within 30 days of birth	3 [10 %]	2 [7.1 %]		

RR = Relative risk; CI = Confidence interval; NICU= Neonatal Intensive Care Unit

differences were observed for perinatal adverse outcomes [RR: 0.33, 95 % CI: 0.04–3.01, p = 0.610] or the number of days admitted to the NICU [RR: 0.38, 95 % CI: 0.14–1.08, p = 0.066] [Table 3]. Although no differences were found, the pessary group showed a trend towards a lower rate of perinatal adverse outcomes, being 11.1 % in the cerclage group and 3.7 % in the pessary group [RR: 0.33, 95 % CI: 0.04–3.01, p = 0.61] and NICU admission rates were lower [14.8 %] as compared to the cerclage group [38.5 %] [RR: 0.38, 95 % CI: 0.14–1.08, p = 0.066].

Side effects reported at the time of insertion are shown in Table 4. No differences were found for side effects at the time of insertion or removal. However, significant differences were found for vaginal discharge rates: 35.7 % in the cerclage group vs 66.7 % in the pessary group [p = 0.036]. No differences were found for vaginal infection rates.

Rescue treatment rate was similar between groups: 3 cases in the cerclage group and 5 cases in the pessary group, all of them with cerclage or pessary [the other] as alternative. No differences were found in this rate [RR: 1.56; 95 % CI: 0.41, 5.91; P = 0.707].

The average cost per patient to place a cerclage was 1183 euros, representing a total of 33124 euros, whereas the average cost per patient to place a pessary was 45 euros, representing a total of 1350 euros [p < 0.001].

In order to assess potential differences in the effectiveness of the cerclage and the pessary taking into account other characteristics that may be related to the pathophysiology of CI, we performed a subanalysis of the results classifying women into two groups based on their type of CI diagnosis [obstetric history or ultrasound findings]. Some differences were observed in terms of NICU admission rates in the subgroup with CI by ultrasound findings: 7 [46.7 %] neonates in the cerclage group and 3 [13 %] neonates in the pessary group required NICU admission [RR: 0.28, 95 % CI: 0.09–0.92, p = 0.03] (Table 5). The differences were in preterm newborns after 28 weeks.

Discussion

The CEPEIC study shows that a cervical pessary may be a beneficial intervention for preventing premature birth in pregnant women diagnosed with CI. The rates of PB< 37 weeks of gestation were 42.9 % in the cerclage group and 26.7 % in the pessary group [p = 0.308]. The rates of PB < 34 weeks of gestation were 25 % in the cerclage group and 20 % in the pessary group [p = 0.888]. Below 28 weeks of gestation, this trend was not maintained, and the rate of PB< 28 weeks of gestation was 7.1 % in the cerclage group and 13.3 % in the pessary group [p = 0.671]. Although these results were inconclusive, we could assume that the effect of the pessary on our population of pregnant women is, at the very least, similar to that of the usual treatment, the cervical cerclage.

Regarding obstetric outcomes, our study showed no statistically significant differences between the cerclage group and the pessary group, with a composite of 50 % in each group [p = 1]. Likewise, no differences were found in the need for tocolytic treatment or pulmonary maturation.

Similarly, no differences were observed in perinatal outcome rates, being 11.1 % in the cerclage group and 3.7 % in the pessary group [p = 0.61]. The pessary group required lower NICU admission [14.8 %] as compared to the cerclage group [38.5 %] [p = 0.066]. This difference was statistically significant in the subgroup of pregnant women with CI by ultrasound findings, being the NICU admission rates 46.7 % in the cerclage group and 13 % in the pessary group [p = 0.03]. In women with CI by ultrasound findings, the rate of perinatal complications was lower in the pessary group as compared to the cerclage group [p = 0.061].

Another sub-analysis of the results was performed classifying pregnant women according to the gestational age at the time of device placement [12 + 0–15 + 6 weeks of gestation, 16 + 0–19 + 6 weeks of

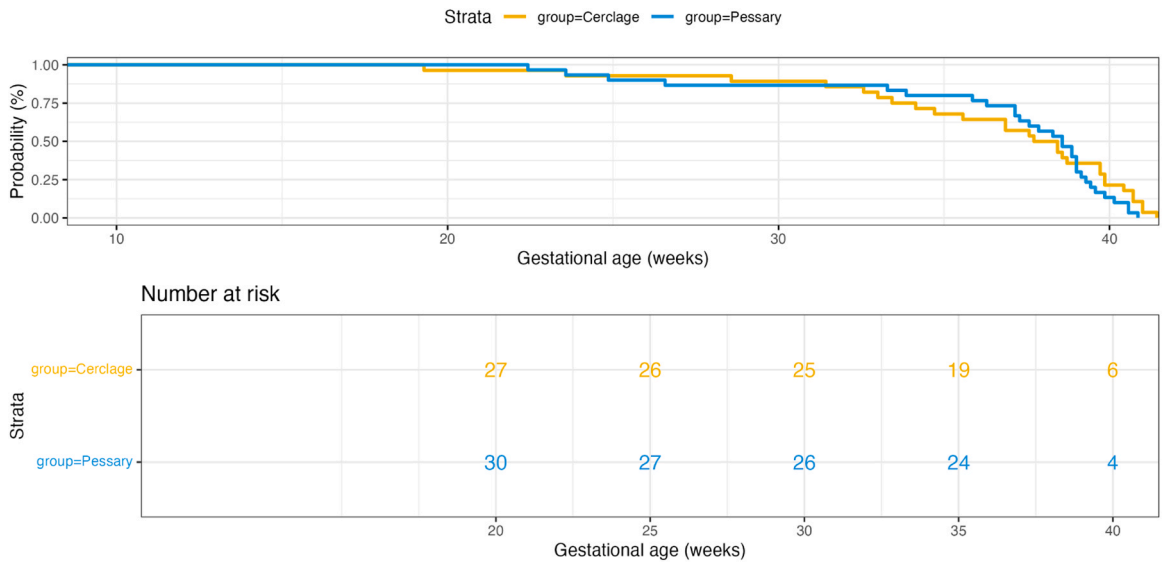

Fig. 2. Kaplan-Meier plot for probability of continued pregnancy without preterm delivery among patients receiving cervical pessary as compared with cervical cerclage.

Table 4
Side effect rates at the time of insertion, during the pregnancy and during the removal of the device. Global cost of cerclage and pessary.

	Pessary	Cerclage	p
Side effects at the time of insertion			
Pain	10 [33.3 %]	3 [10.7 %]	0.059
Bleeding	1 [3.3 %]	14 [50 %]	< 0.001
Immediate PROM	0	1 [3.6 %]	1
Injury of other organs	0	0	
Hospitalization required	3 [10 %]	24 [85.7 %]	< 0.001
Side effects during removal			
Pain	14 [51.9 %]	22 [81.5 %]	0.042
Bleeding	2 [11.1 %]	10 [38.5 %]	0.027
Injury of other organs	0	2 [7.7 %]	0.236
Side effects during pregnancy			
Pain	6 [20 %]	8 [28.6 %]	0.649
Vaginal discharge	20 [66.7 %]	10 [35.7 %]	0.036
Vaginal infection	7 [23.3 %]	10 [35.7 %]	0.455
Cost [euros]	45	1183	< 0.001

PROM = Premature rupture of membranes

gestation, 20 + 0–25 + 6 weeks of gestation]. The results did not provide a sufficient level of significance as to allow any conclusions.

The etiopathogenesis of CI is likely to be different in the different subgroups of pregnant women. We must bear in mind that the definition of CI is broad and includes three types of pregnant women with different characteristics [women with a history of repeated gestational losses or PB, women with a history of gestational losses or PB and a short CL, and women with cervical dilation]. These patients receive the cerclage intervention at different gestational periods. These different clinical features and circumstances may be relevant in relation to the effectiveness of the suggested preventive treatment. It would not be surprising if each subtype of pregnant woman diagnosed with CI benefited more from one intervention than the other.

Major side effects were reported at the time of cervical cerclage placement [metrorrhagia, 50 % vs 3.3 %, $p < 0.001$] and removal [pain, 81.5 % vs 51.9 %, $p = 0.042$; metrorrhagia, 38.5 % vs 11.1 %, $p = 0.027$; cervical lacerations, 7.7 % vs 0, $p = 0.236$]. No cases of cervical necrosis were reported with any device. Finally, as reported by virtually all studies on the cervical pessary [20], we found a significant increase in vaginal discharge: 33.7 % of pregnant women in the cerclage group and 66.7 % in the pessary group [$p = 0.036$]. This did not result in a higher vaginal infection rate.

In order to understand the effect of these two devices we need reliable data. The cervical pessary increased effective cervical length [ECL] more than the cerclage [$p < 0.001$]. The cervical cerclage increased total cervical length more than the pessary [$p = 0.001$]. There were no differences between groups in terms of ECL before and after removing the device. In both groups, ECL significantly shortened with gestational age, which is in agreement with previous studies [21]. In addition, and also significantly, ECL during the follow-up of pregnant women was higher in the pessary group and cervical shortening was more pronounced in this group as compared to the cerclage group. These findings may be explained by the fact that the pessary and the cerclage have different mechanisms of action.

As Mendoza et al. observed, cervical edema and the mechanical support provided by the pessary increased cervical consistency. Similarly, Cannie et al. reported that immediately after pessary placement, 4.5 % of pregnant women showed cervical edema, which increased to an average of 20.5 % at three weeks and 38.6 % at seven weeks ($p < 0.01$). This suggests that prolonged use of the pessary causes more significant changes at the cervical level, potentially resulting in a more substantial impact on prolonging pregnancy.

Few observational studies have evaluated the cervical pessary in patients diagnosed with CI, and their results show a potential reduction in PB rates among patients carrying a pessary [14–16,18,19]. A recent study by Konkov [17] has shown a significant reduction in PB rates when using a perforated pessary [manufactured by CJSC "Medical enterprise Simurg" [Vitebsk, Belarus]] as compared with a control group in pregnant women diagnosed with CI. The results of our study and Korkov's study support the feasibility of conducting a randomised study of similar characteristics, but with a larger sample size, which will increase the reliability of the results.

Our results support the design of a larger randomised study with the initial peace of mind of not having observed any significant adverse effects of the cervical pessary in women with CI. The main limitation of our trial was the reduced number of patients included.

Conclusions

In the CEPEIC trial, there were no differences in the rates of preterm birth < 34 weeks of gestation, the rates of obstetric and perinatal complications were similar, and there were no differences in terms of rescue treatment rate. On the other hand, there were fewer secondary effects in the pessary group than in the cerclage group. Also, given the

Table 5
Pregnancy and perinatal outcomes in the cervical insufficiency subgroup by ultrasound findings. Adverse outcomes.

	Pessary N = 26	Cerclage N = 17	RR [95 % CI]	p
Pregnancy outcomes				
Delivery < 37 weeks of gestation	7 [26 %]	9 [52.9 %]	0.50 [0.23 – 1.11]	0.161
Delivery < 34 weeks of gestation	5 [19.2 %]	5 [29.4 %]	0.65 [0.22 – 1.92]	0.687
Delivery < 28 weeks of gestation	3 [11.5 %]	2 [11.8 %]	0.98 [0.18 – 5.27]	1
Spontaneous delivery < 37 weeks of gestation	5/24 [20.8 %]	5/13 [38.5 %]	0.54 [0.19 –1.53]	0.443
Delivery < 34 weeks of gestation	3/24 [12.5 %]	4/16 [25.0 %]	0.50 [0.13 –1.94]	0.407
Delivery < 28 weeks of gestation	2/25 [8.0 %]	2/17 [11.8 %]	0.68 [0.11 –4.37]	1
Tocolytic treatment	11 [42 %]	7 [41 %]	1.03 [0.5 – 2.12]	1
Corticosteroid treatment for fetal lung maturation [complete dosage]	11 [42 %]	8 [47 %]	1.03 [0.5 – 2.12]	1
Neuroprotection	11 [42 %]	7 [41 %]	1.03 [0.5 - 2.12]	1
Obstetric complications	11 [42 %]	8 [47 %]	0.9 [0.46 - 1.77]	1
Preterm labour	11 [42 %]	7 [41 %]	1.03 [0.5 - 2.12]	1
Premature preterm rupture of membranes	0	1 [5.9 %]	-	0.395
Chorioamnionitis	1 [3.8 %]	1 [5.9 %]	0.65 [0.04 - 9.76]	1
Rescue treatment				
Perinatal outcomes				
Birth weight [grams]	3045 [2769 –3216]	3010 [1850 –3205]		0.423
1-minute Apgar test	9	9		1
5-minute Apgar test	10	10		1
10-minute Apgar test	10	10		1
Umbilical artery pH	7.25	7.26		0.485
Umbilical vein pH	7.32	7.31		0.982
Perinatal complications	0	3 [18.8]		0.061
Intraventricular haemorrhage	0	1 [5.9 %]	-	0.405
Neonatal sepsis	0	1 [5.9 %]	-	0.405
Respiratory distress syndrome	1 [3.4 %]	1 [5.9 %]	-	0.405
Necrotising enterocolitis	0	0		
NICU admission	3 [13 %]	7 [46.7 %]	0.28 [0.09 - 0.92]	0.03
Alive without disease at 2 years old	22 [84.6 %]	14 [82.4 %]		
Alive with disease at 2 years old	1 [3.8 %]	1 [5.9 %]		
Neonatal death within 30 days of birth	3 [11.5 %]	2 [11.8 %]		

NICU = Neonatal intensive care unit; RR = Relative risk; CI = Confidence interval

fact that the cervical pessary is cheaper, it is worth considering the pessary as a new intervention for pregnant women with cervical insufficiency. These findings need to be confirmed in a larger randomised controlled trial. Our study shows that a RCT to compare the effect of pessary vs. cerclage in women with cervical insufficiency is feasible.

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CRediT authorship contribution statement

Andrea Gascón: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Maria Goya:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elena Carreras:** Writing – review & editing, Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Nerea Maiz:** Writing – review & editing, Writing – original draft, Software, Methodology. **Ester del Barco:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Manel Mendoza:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **Maia Brik:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

AGP and MGC conducted the trial. AGP was the principal investigator. MGC was the coordinating investigator. AGP, MGC and MMC undertook participant inclusion at HVH. MB included patients in HT. AGP and MGC wrote the manuscript. All authors read and approved the final manuscript.

References

[1] Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7(1):e37–46.
[2] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371(9606):75–84.
[3] Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008; 371(9607):164–75.
[4] McManemy J, Cooke E, Amon E, Leet T. Recurrence risk for preterm delivery. Am J Obstet Gynecol 2007;196(6):576. discussion 576.e6-7.
[5] Iams JD, Berghella V. Care for women with prior preterm birth. Am J Obstet Gynecol 2010;203(2):89–100.
[6] Phillips C, Velji Z, Hanly C, Metcalfe A. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis. BMJ Open 2017;7(6):e015402.
[7] Mönckeberg M, Valdés R, Kusanovic JP, Schepeler M, Nien JK, Pertossi E, et al. Patients with acute cervical insufficiency without intra-amniotic infection/ inflammation treated with cerclage have a good prognosis. J Perinat Med 2019;47 (5):500–9.
[8] Alfirevic Z, Stampalija T, Medley N. Cervical stitch [cerclage] for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev 2017;06(6): CD008991.
[9] Berghella V, Mackeen AD. Cervical length screening with ultrasound-indicated cerclage compared with history-indicated cerclage for prevention of preterm birth: a meta-analysis. Obstet Gynecol 2011;118(1):148–55.
[10] Bachmann LM, Coomarasamy A, Honest H, Khan KS. Elective cervical cerclage for prevention of preterm birth: a systematic review. Acta Obstet Gynecol Scand 2003; 82(5):398–404.

[11] Berghella V, Ciardulli A, Rust OA, To M, Otsuki K, Althuisius S, et al. Cerclage for sonographic short cervix in singleton gestations without prior spontaneous preterm birth: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol 2017;50(5):569–77.
[12] Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, et al. Cervical pessary in pregnant women with a short cervix [PECEP]: an open-label randomised controlled trial. Lancet 2012;379(9828):1800–6.
[13] Nicolaides KH, Syngelaki A, Poon LC, Picciarelli G, Tul N, Zamprakou A, et al. A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. N Engl J Med 2016;374(11):1044–52.
[14] Sieroszewski P, Jasiński A, Perenc M, Banach R, Oszukowski P. The Arabin pessary for the treatment of threatened mid-trimester miscarriage or premature labour and miscarriage: a case series. J Matern Fetal Neonatal Med 2009;22(6):469–72.
[15] Ting YH, Lao TT, Wa Law L, Hui SYA, Chor CM, Lau TK, et al. Arabin cerclage pessary in the management of cervical insufficiency. J Matern Fetal Neonatal Med 2012;25(12):2693–5.
[16] Acharya G, Eschler B, Grønberg M, Hentemann M, Ottersen T, Maltau JM. Noninvasive cerclage for the management of cervical incompetence: a prospective study. Arch Gynecol Obstet 2006;273(5):283–7.
[17] Konkov DG, Zhurauleu AY, Honcharenko OM, Lobastova TV, Shevchuk TV. The clinical assessment of the cervical perforated pessary for the prevention of preterm labor in women with prior preterm births. Wiad Lek 2022;75(1 pt 2):191–6.
[18] Newcomer J. Pessaries for the treatment of incompetent cervix and premature delivery. Obstet Gynecol Surv 2000;55(7):443–8.
[19] Quaas L, Hillemanns HG, du Bois A, Schillinger H. The Arabin cerclage pessary–an alternative to surgical cerclage. Geburtshilfe Frau 1990;50(6):429–33.
[20] Conde-Agudelo A, Romero R, Nicolaides KH. Cervical pessary to prevent preterm birth in asymptomatic high-risk women: a systematic review and meta-analysis. Am J Obstet Gynecol 2020;223(1):42–65.e2.
[21] Papastefanou I, Pilalis A, Kappou D, Souka AP. Cervical length at 11-40 weeks: unconditional and conditional longitudinal reference ranges. Acta Obstet Gynecol Scand 2016;95(12):1376–82.