Cerclage Pessary for Preventing Preterm Birth in Women with a Singleton Pregnancy and a Short Cervix at 20 to 24 Weeks: A Randomized Controlled Trial

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Abstract

Objective To determine the effectiveness of cerclage pessary in the prevention of preterm birth in asymptomatic Chinese women with a short cervix at 20 to 24 weeks.

Methods Low-risk women carrying singleton pregnancies were screened with transvaginal ultrasound, and those with a cervical length <25 mm at 20 to 24 weeks were recruited into a randomized controlled trial, comparing the prophylactic use of cerclage pessary with expectant management. The analysis was by intent-to-treat. The primary outcome measure was preterm delivery before 34 weeks.

Results Among 4438 screened women, 203 women (4.6%) met the inclusion criteria and 108 (58%) consented for the study. A total of 53 and 55 women were allocated to pessary and control groups, respectively. There was no difference in background demographics, including the mean cervical length (19.6 mm versus 20.5 mm) and the mean gestational age at randomization (both 21.9 weeks). Delivery before 34 weeks occurred in 9.4% and 5.5% ($p = 0.46$) in the pessary and the control groups, respectively. No differences in major side effects were noted between the groups.

Conclusion In our population, <5% had a cervical length of less than 25 mm at 20 to 24 weeks' gestation. The prophylactic use of cerclage pessary did not reduce the rate of preterm delivery before 34 weeks.

Keywords
- cerclage pessary
- short cervix
- preterm birth

Although cerclage pessary was proposed as a treatment option for cervical incompetence as early as 1959,[1] there are only limited data from small observational case series on its effectiveness in reducing preterm birth in high-risk groups of patients.[2–8] The majority of these studies have used the Arabin pessary, which is a flexible, ringlike silicone pessary that is available in various sizes. Dharan and Ludmir summarized those case series and reported that among 121 women with prior history of preterm birth or high-risk factors, 63% achieved a term delivery in their subsequent pregnancy when treated with the pessary.[9] The pessary is thought to act by changing the inclination of the cervical canal,[2] and it may be a safer alternative to surgical cerclage.[9]

However, evidence to support the use of cervical pessary from randomized controlled studies is limited. In 2010, the Cochrane Library performed a systematic review to evaluate the efficacy of cerclage pessary for prevention of preterm birth. Two randomized trials[10,11] were found, but both were

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excluded because the criteria for inclusion in the review were not met. The review concluded that there is a need for well-designed randomized controlled trials with clear selection criteria.[12]

In view of the paucity of data, we designed this randomized controlled trial to examine the use of the Arabin pessary for preventing preterm birth in asymptomatic women who were found to have a short cervix of less than 25 mm.

Methods

This was a randomized controlled trial conducted at the Department of Obstetrics and Gynecology of Prince of Wales Hospital, the Chinese University of Hong Kong (CUHK) starting in October 2008. Approval was obtained from the CUHK-New Territories East Cluster Joint Clinical Research Ethics Committee of Hong Kong (reference number: CRE-2008.375-T). The study followed the Declaration of Helsinki. The trial was registered with http://www.controlled-trials.com, number: ISRCTN18185477. The cerclage pessaries were purchased from Dr. Arabin GmbH & Co. (Witte, Germany), which was not involved in any part of the study. The cerclage pessary is CE marked (CE0482, MED/CERT ISO 9003/EN 46003) for the use as cerclage pessary.

Chinese women with a viable singleton pregnancy undergoing routine fetal morphology ultrasonography at 20 to 24 weeks of gestation received in addition a routine transvaginal measurement of cervical length as a predictor of spontaneous early preterm delivery. The sonographers were certified by the Fetal Medicine Foundation, United Kingdom, to be competent in cervical assessment and followed its guidelines (http://www.fetalmedicine.com/). Women with cervical length less than 25 mm were invited to participate in the trial. Before randomization, the women underwent a speculum examination to check for cervical dilatation.

The exclusion criteria were known history of cervical incompetence, surgical cerclage in current or previous pregnancy, multiple gestation, known major fetal abnormalities, presence of cervical dilatation (any dilated cervical os discovered during speculum examination), painful uterine contractions, or ruptured membranes.

After written informed consent was obtained, the women were randomized into the pessary group or control group. Randomization was performed using a computer-generated sequence, and the allocation results were concealed in sequentially numbered, identical, opaque, sealed envelopes and kept away from the clinic where patients were being assessed. The treatment allocation was only revealed to the obstetrician in charge after the patient was consented. The patient was blinded to the allocation. Depending on the parity and the baseline cervical length, the appropriate-size cerclage pessary was inserted in the woman allocated to the pessary group. Patients in the control group received a vaginal digital examination in an attempt to simulate the insertion of a pessary. All participants received a speculum examination and a high vaginal swab was taken for culture and sensitivity at baseline.

Both groups were followed with ultrasound for fetal growth and cervical length every 4 weeks till 34 weeks of gestation. If the cervical length became less than 10 mm, four doses of intramuscular injection of dexamethasone 6 mg 12 hours apart were given. High vaginal swabs were performed at each follow-up visit. The patients were asked to report any vaginal or pelvic discomfort. Appropriate treatment was given if the patient was symptomatic with abnormal swab results. The pessary was removed by a simple vaginal examination at 37 weeks, or earlier if the patient presented with rupture of membranes, vaginal bleeding, or painful uterine contractions.

Outcome Measures

The primary outcome measure was preterm delivery before 34 weeks of gestation. The determination of gestational age was based on the date of last menstrual period (confirmed by the second-trimester ultrasound) and/or crown-rump length measured during early dating ultrasound. The secondary outcome measures were gestational age at delivery, interval from randomization to delivery, new-onset vaginal infections, birth weight, miscarriage rate, neonatal death, major adverse outcomes before discharge from the hospital including neonatal jaundice, sepsis, intraventricular hemorrhage, and respiratory distress syndrome.

Information on the characteristics of the patients, including demographic data, obstetrics history, medical history, and body mass index, were obtained from the patients at first visit. Data on pregnancy outcomes were obtained from the hospital records.

Statistical Analysis

The sample-size calculation was based on a reduction in spontaneous delivery before 34 weeks from 8% in the control group to 4% in the pessary group,[13–15] with a power of 80% and significance level of 5%. A total of 1120 patients with cervical length less than 25 mm were needed.

Analysis was performed by intent-to-treat. Continuous data were compared using independent Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical data were compared using chi-square test or Fisher's exact test, as appropriate. The *p* values were two-sided. A *p* value of 0.05 or less was used to indicate statistical significance. The risks of preterm birth were quantified by relative risk and 95% confidence interval. Kaplan-Meier analysis using interval from randomization to delivery as the time scale was performed, both for overall delivery without censoring as well as for spontaneous delivery with induced or elective deliveries censored.

Results

From October 2008 to February 2011, only 100 women were enrolled in the trial. Because of a slow accrual rate, it was felt that the target sample size was not going to be achieved in a single center. To determine whether to reevaluate the sample size or extend the study to other centers, the investigators decided to perform a first interim analysis when the outcome

data became available for the first 100 women. By the time this decision was made in November 2011, a further eight cases had been recruited. In the interim analysis, the frequency of preterm delivery before 34 weeks was lower than expected in the control group (actual 5.5% versus expected 8%) and higher than estimated in the pessary group (actual 9.4% versus estimated 4%). Around the same time, the Pesario Cervical para Evitar Prematuridad (PECEP) group in Spain had published the result of a randomized controlled trial on the use of cervical pessary.[16] With a sample size of 385, the PECEP study found that the use of cervical pessary significantly reduced the rate of spontaneous preterm delivery before 34 weeks from 27% in the control group to 6% in the treatment group ($p < 0.001$). Our study design shared many similarities with the PECEP study, yet the results were surprisingly different. With this emerging data, we decided to stop our study and publish the results of our interim analysis.

From October 2008 to November 2011, 4438 women with singleton pregnancies underwent a transvaginal ultrasound for cervical length measurement at 20 to 24 weeks' gestation. Two hundred three women (4.6%) had cervical length less than 25 mm. Seventeen cases were not eligible due to exclusion criteria, and 78 eligible patients refused to participate. A total of 108 (58%) patients consented and were recruited into the study, with 53 and 55 randomized into the pessary and control groups, respectively. All 108 women were included in this analysis. There were no significant differences in the baseline characteristics between the control and pessary groups (►**Table 1**). The mean gestational age and the mean baseline cervical length at time of randomization were similar between the two groups (21.9 weeks in both groups; 19.6 mm and 20.5 mm in the pessary and control groups, respectively).

The outcomes are presented in ►**Table 2**. The primary outcome, preterm delivery rate before 34 weeks, occurred in 9.4% in the pessary group and 5.5% in control group ($p = 0.46$). All of them were spontaneous preterm births. The interval from randomization to delivery was 113.6 days in the pessary group and 111.9 days in the control group ($p = 0.72$). The gestational age and birth weight at delivery were not significantly different between the groups. No difference was observed in the rate of preterm prelabor rupture of membrane, with 8 of 55 (14.5%) in the control group and 6 of 53 (11.3%) in the pessary group, respectively ($p = 0.62$; ►**Table 2**). Additional maternal and perinatal outcomes including miscarriage, malpresentation, new-onset vaginal infection, neonatal morbidities (clinical sepsis, neonatal jaundice, respiratory distress syndrome, intraventricular hemorrhage, admission to neonatal intensive care unit), and neonatal mortality were not significantly different.

Table 1 Baseline Demographics in the Pessary and Control Groups

Baseline Demographics	Pessary Group ($n = 53$)	Control Group ($n = 55$)	p Value
Maternal age (y)			0.87
Mean (SD)	31.6 (4.7)	31.8 (5.3)	
Range	22–42	22–44	
Parity			0.12
Median	0	0	
Range	0–2	0–2	
Obstetric history, *n* (%)			
Nulliparous women	38 (71.7)	31 (56.4)	0.11
Women with history of preterm delivery	3 (5.7)	6 (10.9)	0.49
Body mass index (kg/m^2)			0.72
Mean (SD)	21.9 (3.5)	21.7 (3.3)	
Range	17.2–32.9	16.0–32.6	
Smoking during pregnancy, *n* (%)	1 (1.9)	3 (5.5)	0.62
History of cervical surgery, *n* (%)	0 (0)	1 (1.8)	1.00
Gestation at randomization (wk)			0.82
Mean (SD)	21.9 (0.8)	21.9 (0.8)	
Range	20.6–24.0	20.0–23.9	
Cervical length at randomization (mm)			0.32
Mean (SD)	19.6 (0.5)	20.5 (0.4)	
Range	4.4–24.7	5.4–24.9	
Preexisting vaginal infections, *n* (%)	13 (24.5)	14 (25.5)	0.91

SD, standard deviation.

Table 2 Primary and Secondary Outcomes in the Pessary and Control Groups

Outcomes	Pessary Group ($n = 53$)	Control Group ($n = 55$)	RR (95% CI)	p Value
Delivery rate (wk), *n* (%)				
<37	8 (15.1)	10 (18.2)	0.96 (0.81–1.14)	0.67
<34	5 (9.4)	3 (5.5)	1.04 (0.94–1.12)	0.46
<30	3 (5.7)	3 (5.5)	1.00 (0.92–1.10)	1.00
<28	2 (3.8)	3 (5.5)	0.98 (0.90–1.07)	1.00
<26	1 (1.9)	3 (5.5)	0.96 (0.90–1.04)	0.62
<24 (miscarriage)	0 (0)	2 (3.6)	0.96 (0.92–1.01)	0.50
Interval to delivery (d)				0.72
Mean (SD)	113.6 (24.0)	111.9 (28.1)		
Range	31–140	4–137		
Gestational age at delivery (wk)				0.68
Mean (SD)	38.1 (3.4)	37.8 (3.9)		
Range	25.3–41.2	22.1–41.3		
Birth weight (kg)				0.38
Mean (SD)	2.840 (0.59)	2.953 (0.74)		
Range	0.795–3.725	0.445–4.145		
Neonatal morbidity, *n* (%)				
Clinical sepsis	3 (5.7)	5 (9.4)	0.96 (0.86–1.07)	0.72
Neonatal jaundice	15 (28.3)	14 (26.4)	1.03 (0.81–1.23)	0.91
Respiratory distress	5 (9.4)	2 (3.8)	1.06 (0.96–1.18)	0.44
Intraventricular hemorrhage	0 (0)	1 (1.9)	0.98 (0.95–1.02)	1.00
Admission to neonatal intensive care unit	21 (39.6)	17 (32.1)	1.13 (0.85–1.50)	0.54
Neonatal mortality, *n* (%)	1 (1.9)	0 (0)	1.02 (0.98–1.06)	0.49
Dexamethasone injection, *n* (%)	9 (17.0)	8 (14.5)	1.03 (0.87–1.21)	0.73
New vaginal infections, *n* (%)	11 (20.8)	11 (20.0)	1.01 (0.83–1.22)	0.92
Candida	5	5		
Bacterial vaginosis	1	2		
Group B streptococcus	4	4		
Escherichia coli	1	0		
Malpresentation, *n* (%)	4 (7.5)	4 (7.3)	1.00 (0.90–1.12)	1.00
Preterm prelabor rupture of membrane, *n* (%)	6 (11.3)	8 (14.5)	0.96 (0.83–1.11)	0.62

CI, confidence interval; RR, relative risk; SD, standard deviation.

The risk of preterm birth in the two groups was assessed by Kaplan-Meier survival analysis (►**Fig. 1A**). There was no significant difference in the interval between randomization to delivery in the pessary group compared with the control group (113.6 days versus 111.9 days, $p = 0.159$).

The Kaplan-Meier survival analysis was also performed after censoring (►**Fig. 1B**). Twenty-one women did not have spontaneous labor and required either induction of labor or cesarean delivery. Reasons for induction of labor included oligohydramnios ($n = 2$), prolonged pregnancy ($n = 2$), preeclampsia ($n = 2$), and premature rupture of the membranes at term ($n = 2$). Indications for prelabor cesarean delivery included previous cesarean ($n = 4$), breech presentation ($n = 3$), maternal request ($n = 3$), macrosomia ($n = 1$), placenta abruption at 36 weeks ($n = 1$), and fetal umbilical vein varix at 35 weeks ($n = 1$). All except the latter two cases were delivered after 37 weeks. After censoring these 21 iatrogenic births, the interval between randomization to delivery was longer by 3.3 days in the pessary group compared with the control group, and this did not reach statistical significance as well (116.7 days versus 113.4 days, $p = 0.083$)

Delivery outcomes were also obtained from 65 of the 78 (83%) patients in whom the cervical length was less than

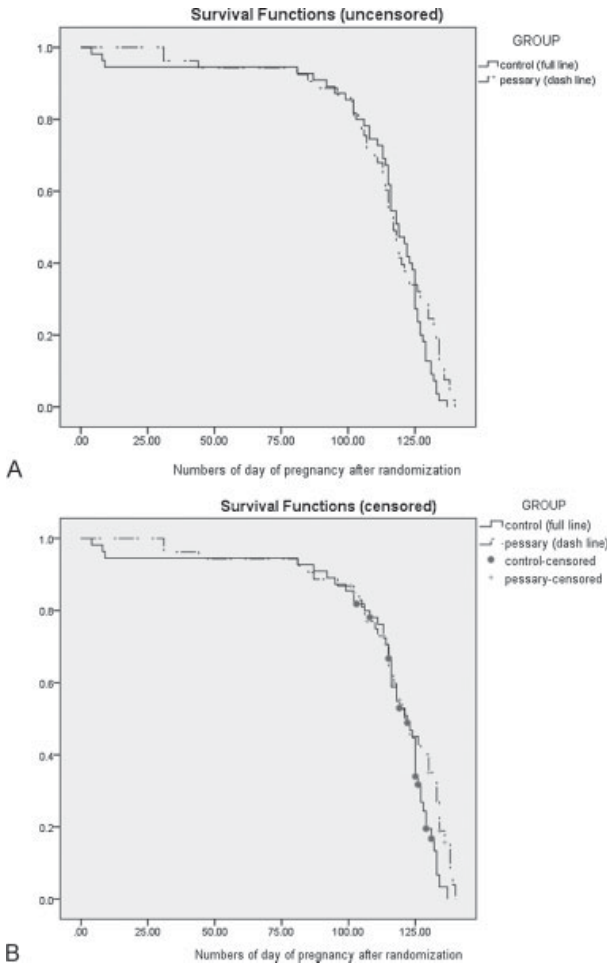

Figure 1 (A, B) Survival analysis with respect to interval from randomization to delivery.

25 mm (mean 20.8 mm) but refused to participate in the trial. Four of 65 (6.2%) patients delivered before 34 weeks.

Significantly more side effects were experienced by the patients in the pessary group (56.6% versus 27.3%, $p = 0.0038$). For the pessary group, 25 patients complained of increased vaginal discharge, 4 had pressure sensations, the pessary dislodged in 2 patients and required replacement, 1 patient had vaginal bleeding, 1 had vaginal pain, and 1 developed urinary retention. In the control group, 12 patients complained of vaginal discharge, 2 had pressure sensations, and 1 developed urinary retention.

Discussion

Our study shared many similarities with the PECEP study in terms of study design, baseline cervical length for inclusion, exclusion criteria, interventions and monitoring, analytic methods, and outcomes parameters.[16] In particular, both ours and PECEP study enrolled women with short cervix (<25 mm) from a general population, and the mean cervical length of the recruited women were similarly around 19 mm to 20 mm. However, although the PECEP study showed a significant reduction of preterm delivery rate before 34 weeks from 27 to 6% with the use of cerclage pessary, ours failed to demonstrate any difference (9.4% in the pessary group versus 5.5% in the control group). More interestingly, the preterm rates in our control group (5.5%) were close to their treatment group (6%). The differences in the outcomes between our findings and that of the PECEP study are worthy of further evaluation before concluding that the favorable result of the PECEP study is generalizable.

The preterm delivery rate before 34 weeks was similar in the control group and the pessary group as well as the group that declined enrollment, with percentages of 5.5%, 9.4%, and 6.2%, respectively. These figures were close to our previous observational study published in 2005, in which we found an early preterm delivery rate of 9.4% among women with cervical length less than 25 mm.[17] Moreover, our previously published epidemiological study showed that the overall preterm delivery rate before 37 weeks was ~7% among Hong Kong Chinese women, 4% of which due to spontaneous preterm delivery, and early preterm delivery occurred in only 2%.[18] Furthermore, when we compared our epidemiological data with that published by the Euro-PeriStat project, we found that our background preterm delivery rate is very similar to that in Spain, which is ~0.8% before 32 weeks and 8% before 37 weeks.[19] Given that a short cervix of less than 25 mm increases the risk of preterm delivery by around three- to sixfold,[14,15] the rates in our current study are consistent with the epidemiological data. Therefore, we believe that the low preterm rate in our cohort is genuine and not related to any selection bias, and the 27% rate of early preterm birth in the PECEP study is unusually high and unlikely generalizable. It is unlikely that we would have ever been able to demonstrate a beneficial effect as good as the one seen in PECEP study, even if we were able to reach the planned sample size.

Further evaluation is required to clarify whether the PECEP study recruited women with additional risk factors that could account for such a high baseline preterm rate compared with ours. Compared with our purely Chinese cohort, the Spanish cohort members were heavier (body mass index 24 to 25 versus 21 to 22), had a higher prevalence of smoking (20% versus <5%), and were mostly white and Latin American (90%). These differences in baseline characteristics may partially explain the differences in the baseline preterm rate. Even so, further research is essential to investigate whether the effect of cervical pessary is reproducible in low-risk women and whether the result is generalizable to other ethnic groups.

Similar to the PECEP study, we showed that the use of pessary was not associated with any harmful effects. Although significantly more patients in the pessary group reported side effects, especially increase in vaginal discharge, no significant difference was identified in the rate of vaginal infection. Therefore, if its efficacy in preventing preterm birth is confirmed, the pessary may become a safe alternative to traditional surgical cerclage. In view of the differences in the outcomes between our findings and that of the PECEP study, further researches are urgently needed to confirm the efficacy of cerclage pessary in prevention of preterm birth.

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