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Cervical pessary for preterm birth prevention after an episode of arrested preterm labor: a retrospective cohort study with targeted maximum likelihood estimation of the average treatment effect

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Abstract. – OBJECTIVE: To evaluate whether cervical pessary effectively reduces the preterm birth < 37 weeks rate in patients who have not delivered after an episode of arrested preterm labor.

PATIENTS AND METHODS: Retrospective cohort study was conducted on singleton pregnant patients admitted to our institution between January 2016 and June 2021 for threatened preterm labor and who had a cervical length < 25 mm. Women in whom a cervical pessary was placed were considered as exposed, while women in whom expectant management was preferred were considered as unexposed. The primary outcome was the rate of preterm birth before 37 weeks. A targeted maximum likelihood estimation was used to estimate the average treatment effect of cervical pessary by adjusting for a-priori-defined confounders.

RESULTS: A cervical pessary was placed in 152 (36.6%) patients (exposed), while the remaining 263 (63.4%) were managed expectantly (unexposed). The adjusted average treatment effect was -14% (-18 to -11%), -17% (-20 to -13%), and -16% (-20 to -12%) for preterm birth < 37 weeks, < 34 weeks, and < 32 weeks, respectively. The average treatment effect for adverse neonatal outcomes was -7% (-8 to -5%). No difference in gestational weeks at delivery between exposed and unexposed emerged when gestational age at first admission was > 30.1 gestational weeks.

CONCLUSIONS: The positioning of a cervical pessary placement may be evaluated to reduce the risk of a subsequent preterm birth after an episode of arrested preterm labor in pregnant patients with onset of symptoms before 30 gestational weeks.

Key Words:
Preterm birth, Cervical pessary, Arrested preterm labor, Cervical length, Preterm birth prevention.

Introduction

Preterm birth is defined as any birth before 37 completed gestational weeks[1]. It is estimated that preterm birth is responsible for more than 70% of all neonatal and infant deaths and hospitalization[2]. Preterm labor preceded approximately 50% of preterm births[1], and it presents with frequent uterine contractions leading to cervical changes or preterm premature rupture of the membranes. Approximately 10% of all pregnant patients may experience an episode of threatened preterm labor requiring hospital admission[1], and patients who have had an episode of threatened preterm labor with a short cervix remaining (also defined arrested preterm labor) represent a high-risk group for subsequent spontaneous preterm birth[1]. To date, there are few evidence-based therapeutic strategies for this high-risk group of patients, apart from clinical procedures focused on adverse neonatal outcomes prevention. Indeed, randomized controlled trials have shown unsatisfactory results regarding the effect of progesterone administration in lowering the rate of preterm delivery in symptomatic patients after an episode of threatened preterm labor[3-5], and strong evidence recommends tocolysis only for the duration of antenatal steroids administration[2,6]. Alternative treatments are emergency cervical cerclage or cervical pessary.

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Emergency cervical cerclage may be performed only in the absence of treatment-resistant uterine contractions, and its therapeutic effect is therefore limited in case of threatened preterm labor[7]. A cervical pessary made of silicone or plastic is thought to support the cervix mechanically by bending the cervix posteriorly and might protect the cervical mucus plug, which plays an essential role in pregnancy maintenance[8]. To date, evidence about the role of cervical pessary to prevent preterm birth after an episode of threatened preterm labor is still limited[9-12]. Therefore, the primary aim of our study was to evaluate whether cervical pessary placement effectively reduces preterm birth < 37 gestational weeks in women who did not deliver after an episode of threatened preterm labor and short cervix remaining. The secondary aim was to evaluate the effect of cervical pessary placement on adverse obstetric and neonatal outcomes related to preterm birth.

Patients and Methods

Study Design

This was a retrospective cohort study conducted on all pregnant patients admitted to our institution, a tertiary care center with a neonatal intensive care unit, from January 2016 to June 2021 for threatened preterm labor with intact membranes between 23+1 and 34+0 gestational weeks. The STROBE checklist was used to design the study (**Supplementary Table I**).

Inclusion and Exclusion Criteria

Patients were eligible in case of diagnosis of threatened preterm labor (at least four 30-seconds lasting painful regular uterine contractions in 20 minutes with cervical length < 25 mm) and no delivery within 48 hours since admission, with the resolution of uterine contractions and a short cervix remaining (arrested preterm labor).

Patients were excluded in case of: multiple pregnancy, ruptured membranes, cervical dilatation > 3 cm, a residual cervical length that made it impossible to place a cervical pessary, cervical length > 25 mm, signs of intrauterine infection (maternal fever >38°, maternal tachycardia with heart rate > 100 bpm, uterine tenderness, foul-smelling amniotic fluid), major fetal anomalies, fetal death, placenta previa or accreta, active vaginal bleeding, evidence of protruding membranes through the external cervical os, or cervical cerclage.

Description of Procedures

According to our local protocols and available national guidelines, all patients admitted to our institution for threatened preterm labor with intact membranes between 23+1 and 34+0 gestational weeks were submitted at admission to a speculum examination to determine if there was any protrusion of the membranes or any evidence of preterm premature rupture of the membranes; a digital examination which reported the cervical condition and the cervical dilatation expressed in centimeters; a complete physical examination to accurately compile all other signs and symptoms.

An ultrasound examination was performed to determine fetal number and viability, evident fetal abnormalities incompatible with life, and cervical length. Cervical length was measured with the probe in the anterior vaginal fornix; measurements were obtained *via* a sagittal view of the cervix with the calipers at the internal and the external cervical os; the shortest of three measurements was recorded.

A blood sample was taken to determine a complete blood count and measure C-reactive protein (CRP) levels.

The standard treatment for threatened preterm labor according to our local protocols and national guidelines[13] was: tocolysis for 48 hours (intravenous Atosiban), antenatal steroids (two doses of betamethasone 12 mg intramuscular 24 hours apart), and magnesium sulfate administration for fetal neuroprotection when the gestational age was under 32 weeks.

Clinical management in terms of cervical pessary placement was made case by case, after an informed discussion between a senior obstetrician and the patient, after verifying the resolution of uterine contractions and the episode of preterm labor, in the third or fourth day after admission. Patients in whom a cervical pessary was placed were considered as exposed, while those in whom expectant management was preferred were considered as unexposed.

The cervical pessary (Dr. Arabin GmbH&Co KG im FEZ, Alfred-Herrhausen-Str. 44, 58455 Witten; CE0482, MED/CERT ISO 2003/EN 13485) is a double ring-shaped pessary made of non-allergic, soft, and flexible silicone, available in different sizes. It is approved for use in pregnant patients at risk of preterm birth with a shortened or dilated cervix. During a simple vaginal examination, the pessary size which best suited the uterine cervix was assessed, and subsequent-

ly, the pessary was folded and placed around the cervix.

The pessary was retained until 37 weeks gestational age or delivery. Date of pessary removal, reason of removal, and reinsertion of a new pessary were recorded. Apart from pessary placement, all patients received care according to protocol, with follow-up visits scheduled approximately every four weeks until delivery. The onset of pessary-related adverse events was also recorded (increase in vaginal discharge, pelvic pain, blood loss, or pessary displacement).

Variables

All data were retrieved from clinical charts and entered into an electronic database. The collected variables were: maternal age in years, ethnicity, education, nulliparity, previous cesarean section, previous spontaneous miscarriage or previous stillbirth, gestational weeks at admission (both as continuous variable and with the following five classes: 23.1-26.0 weeks, 26.1-28.0 weeks, 28.1-30.0 weeks, 30.1-32.0 weeks, and 32.1-34.0 weeks), cervical length at admission in mm (both as continuous variable and with the following four classes: ≤ 10.0 mm, 10.1-15.0 mm, 15.1-20.0 mm, and 20.1-25 mm), pregnancy obtained with *in vitro* fertilization (IVF), body mass index (BMI) (pre-pregnancy), smoking, drug abuse, history of preterm birth, history of late spontaneous miscarriage, history of cervical cerclage, history of cervical excisions, history of cervical surgery (e.g., uterine curettage, conization, cervical canal dilatation), diagnosis of uterine malformations, diagnosis of uterine fibromatosis, diagnosis in the current pregnancy of hypertensive disorders of pregnancy, gestational diabetes, or polyhydramnios, hemoglobin (Hb) levels at admission (g/dl), white blood cell count (WBC) at admission (cell/mcL), CRP levels at admission (mg/dl). Those variables were considered a priori as confounders with regard to preterm birth[14].

Outcomes

The primary outcome was the rate of preterm birth before 37 gestational weeks. The secondary outcomes were the rate of preterm birth before 34, 32, and 28 gestational weeks, the interval from admission to delivery in weeks (≤ 6.0, 6.1-12.0, and ≥12.1 weeks), the rate of re-hospitalizations, the neonatal weight at delivery in gr (≤ 1500, 1501-2500, ≥ 2501 gr), the Apgar score at 1 minute and 5 minutes (Apgar 0-6, 7-8, and 9-10), and the rate of adverse neonatal outcomes (neonatal death, necrotizing enterocolitis, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy, treatment for sepsis, phototherapy, or mechanical ventilation). We also collected any adverse events related to cervical pessary (vaginal discharge, pelvic discomfort, pelvic pain, or bleeding).

Statistical Analysis

The statistical software used was RStudio (2022.02.3 Build 492© 2009-2022 RStudio, PBC; https://www.rstudio.com/products/rstudio/release-notes/). The normality of each variable was evaluated by the D'Agostino-Pearson test. Normally distributed variables were expressed as arithmetic mean ± standard deviation (SD), while not-normally distributed variables were reported as median and interquartile range (IQR). Qualitative variables were expressed as numbers and percentages. The chi-square test, the *t*-test, or the Mann-Whitney test were used for variables comparison, as appropriate.

The average treatment effect (ATE) of cervical pessary placement with 95% CI was reported both for the primary and secondary outcomes as the risk difference between exposed and unexposed. Targeted Maximum Likelihood Estimation (TMLE) was used to estimate the adjusted ATE of cervical pessary on the primary outcome (rate of preterm birth < 37 weeks) and on the secondary outcomes considering as confounders all the available variables[14-16]. TMLE presents advantage over traditional regression models. Indeed, it combines a propensity score model for the exposure (cervical pessary placement) and a model for the outcome. If either of these models is correctly specified, the estimate of association is considered unbiased; this characteristic defines TMLE as a "doubly robust estimator"[17]. TMLE naturally integrates loss-based super learning, which increases the chance to reduce bias due to model misspecification[15]. All results are presented with 95% confidence intervals (CI).

As subgroup analysis, we evaluated the following correlations between continuous variables with the Pearson's correlation coefficient (r with 95% CI) and a scatter diagram according to cervical pessary placement: gestational weeks at admission – gestational weeks at delivery; gestational weeks at admission – interval from admission to delivery; cervical length at admission – gestational weeks at delivery; cervical length at admission – interval from admission to delivery. We also compared the mean ± SD gestational

weeks at delivery and the mean ± SD interval from admission to delivery according to classes of gestational weeks at admission and to classes of cervical length at admission.

A Kaplan-Meier analysis was performed to compare the probability of preterm birth < 37, < 34, < 32, and < 28 weeks between exposed and unexposed with Log-rank test and determination of the HR with 95% CI, considering the interval between admission and delivery in weeks. A *p*-value <0.05 was regarded as statistically significant.

The sample size for the present study was determined for the primary outcome, the rate of preterm birth before 37 gestational weeks. According to previous literature[9,18-20], the preterm birth rate after an episode of threatened preterm labor varies between 19.9% and 50%. Considering a mean value of 31.5%, we assume that a significant clinical benefit could be provided by cervical pessary if the preterm birth rate drops by 15% in patients with cervical pessary placement.

The G*Power version 3.1.9 software was used to determine the required sample size using a Chi-square test to compare preterm birth rate between patients in whom a cervical pessary was placed and patients managed without cervical pessary placement. Based on an alpha of 0.05, a power of 0.80, an effect size w of 0.32, a total sample size of 194 subjects was required (97 for each group). In order to reach the required sample size, we included patients from January 2016 to June 2021. The research was conducted according to the Declaration of Helsinki. According to Italian legislation, the local ethical committee of our institution (Comitato Etico Regionale Marche) took notice of the study protocol (No. CERM 2021/51).

Results

A total of 415 patients admitted to our institution from January 2016 to June 2021 with a diagnosis of threatened preterm labor and no delivery within 48 hours, who fulfilled the inclusion and exclusion criteria, were included in the study analysis (Figure 1). A cervical pessary was placed in 152 (36.6%) patients (exposed), while the remaining 263 (63.4%) were considered as unexposed. No serious adverse event was recorded in

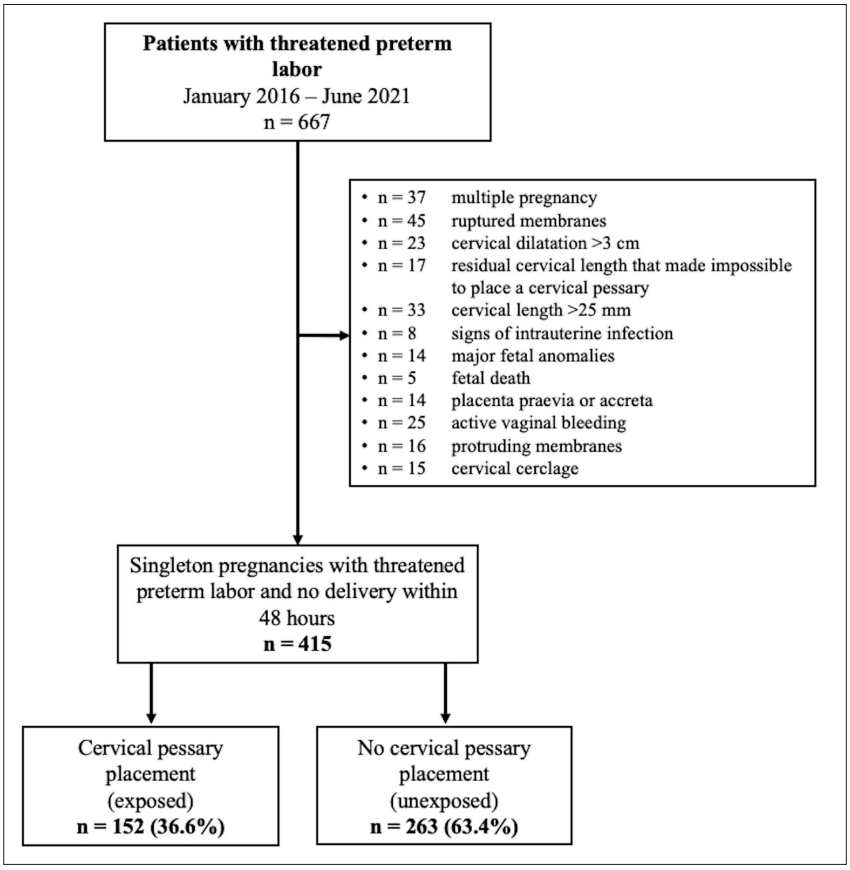

Figure 1. Flow-chart of the study population.

patients in whom a cervical pessary was placed; 58/152 (38.2%) of them reported an increase in vaginal discharges, which did not impact their quality of life. The comparison of background and clinical characteristics between the exposed and unexposed group is reported in Table I. No difference in the age at admission (32.1 ± 6.0 years *vs.* 32.0 ± 6.0 years, $p = 0.8701$) or in the rate of pregnancies obtained by IVF (5.3% *vs.* 2.3%, $p = 0.1046$) emerged between exposed and unexposed.

Patients of the exposed group presented a reduced gestational age at admission (27.1 ± 2.9 *vs.* 29.9 ± 2.9 weeks, $p < 0.001$) and a shorter cervical length at admission (14.7 ± 5.4 *vs.* 18.7 ± 5.9 mm, $p < 0.001$).

The unadjusted and TMLE-adjusted ATE of cervical pessary placement are reported in Table II. The TMLE-adjusted ATE with regard to preterm birth < 37 weeks was -14% (-18% to -11%) in patients in whom a cervical pessary was placed.

The scatter diagrams and the Pearson's correlation coefficients (r with 95% CI) of the correlations between gestational weeks at admission/cervical length at admission and gestational weeks at delivery or interval admission-delivery are reported in Figure 2 and Figure 3, respectively. The r coefficient of the correlation between cervical length at admission and gestational weeks at delivery was higher for patients of the cervical pessary group (0.41 *vs.* 0.22, $p = 0.0391$).

Table III and Table IV respectively reports the comparison of gestational weeks at delivery and interval from admission to delivery between exposed and unexposed according to classes of gestational weeks at admission or cervical length

Table I. Comparison of background and clinical characteristics between exposed (n = 152) and unexposed (n = 263).

Characteristic	Cervical pessary (n = 152)	No cervical pessary (n = 263)	p*
Age (years)	32.1 ± 6.0	32.0 ± 6.0	0.8701
Ethnicity			
Caucasian	135 (88.8%)	230 (87.5%)	0.6952
African American	4 (2.6%)	16 (6.1%)	0.1091
Asian	5 (3.3%)	8 (3.0%)	0.8655
Middle East	7 (4.7%)	7 (2.7%)	0.2815
Hispanic	1 (0.7%)	2 (0.8%)	0.9103
Education			
Primary	1 (0.7%)	3 (1.1%)	0.6866
Lower secondary	15 (9.9%)	26 (9.9%)	1.000
Upper secondary	70 (46.1%)	113 (43.0%)	0.5405
University degree	66 (43.4%)	121 (46.0%)	0.6085
No previous pregnancy	61 (40.1%)	117 (44.5%)	0.3835
Previous cesarean section	16 (10.5%)	21 (8.0%)	0.3898
Previous spontaneous miscarriage	44 (28.9%)	80 (30.4%)	0.7480
Previous stillbirth	0 (0.0%)	3 (1.1%)	0.1950
Gestational weeks at admission	**27.1 ± 2.9**	**29.9 ± 2.9**	**< 0.0001**
Cervical length at admission	**14.7 ± 5.4**	**18.7 ± 5.9**	**< 0.0001**
Pregnancy obtained by IVF	8 (5.3%)	6 (2.3%)	0.1046
BMI (pre-pregnancy)	23.0 ± 4.5	22.6 ± 4.4	0.3768
Smoking	2 (1.3%)	10 (3.8%)	0.1431
Drug abuse	0 (0.0%)	1 (0.4%)	0.4355
Previous preterm birth	7 (4.6%)	7 (2.7%)	0.3038
Previous late spontaneous miscarriage	9 (5.9%)	12 (4.6%)	0.5615
Previous cervical cerclage	0 (0.0%)	1 (0.4%)	0.4355
Previous cervical excisions	7 (4.6%)	3 (1.1%)	0.0244
Previous cervical surgery	21 (13.8%)	27 (10.3%)	0.2836
Uterine malformations	5 (3.3%)	8 (3.0%)	0.8655
Uterine fibromatosis	11 (7.2%)	20 (7.6%)	0.8813
Hypertensive disorders of pregnancy	7 (4.6%)	9 (3.4%)	0.5404
Gestational diabetes	26 (17.1%)	50 (19.0%)	0.6301
Polyhydramnios	6 (3.9%)	13 (4.9%)	0.6375
Hb at admission (g/dl)	11.3 ± 1.0	11.1 ± 1.1	0.0659
WBC at admission (cell/mcL)	11,921 ± 4072	12,200 ± 3,801	0.4832
CRP at admission (mg/dl)	0.4 (0.3-1.1)	0.5 (0.3-1.3)	0.2794

Data are reported as mean ± SD, median (IQR) or n (%). *Chi-square test, *t*-test, or Mann-Whitney test, as appropriate.

Table II. Unadjusted and TMLE-adjusted average treatment effect of cervical pessary on primary and secondary outcomes.

Outcome	Cervical pessary (n = 152)	No cervical pessary (n = 263)	ATE (95% CI) (unadjusted)	*p*	ATE (95% CI) (TMLE-adjusted*)	*p*
Rate of preterm birth						
≤ 37.0 weeks	47 (30.9%)	91 (34.6%)	-0.04 (-0.15 to 0.09)	0.4413	-0.14 (-0.18 to -0.11)	0.0037
≤ 34.0 weeks	24 (15.8%)	59 (22.4%)	-0.06 (-0.15 to 0.03)	0.1057	-0.17 (-0.20 to -0.13)	< 0.001
≤ 32.0 weeks	16 (10.5%)	35 (13.3%)	-0.02 (-0.10 to 0.05)	0.4029	-0.16 (-0.20 to -0.12)	< 0.001
≤ 28.0 weeks	7 (4.6%)	14 (5.3%)	0.00 (-0.05 to 0.05)	0.7539	-0.06 (-0.08 to -0.04)	0.0010
Interval admission-delivery						
≤ 6.0 weeks	27 (17.7)	131 (49.8)	-0.32 (-0.43 to -0.21)	< 0.001	-0.34 (-0.39 to -0.29)	< 0.001
6.1-12.0 weeks	74 (48.7)	104 (39.5)	0.09 (-0.04 to 0.24)	0.0684	0.16 (0.12 to 0.20)	< 0.001
≥ 12.1 weeks	51 (33.6)	28 (10.7)	0.23 (0.13 to 0.34)	< 0.001	0.16 (0.13 to 0.19)	< 0.001
Re-hospitalizations	29 (19.1)	38 (14.4)	-0.05 (-0.11 to 0.02)	0.2102	0.03 (-0.01 to 0.08)	0.1243
Neonatal weight at delivery						
≤ 1,500 gr	10 (6.6)	30 (11.4)	-0.05 (-0.11 to 0.02)	0.1109	-0.14 (-0.17 to -0.11)	< 0.001
1,501-2,500 gr	37 (24.3)	74 (28.1)	-0.04 (-0.14 to 0.08)	0.3998	-0.08 (-0.11 to -0.04)	0.0465
≥ 2,501 gr	105 (69.1)	159 (60.5)	0.09 (-0.07 to 0.26)	0.0797	0.22 (0.17 to 0.26)	< 0.001
Apgar score at 1 minute						
0-6	8 (5.3)	28 (10.7)	-0.05 (-0.11 to 0.01)	0.0606	-0.13 (-0.16 to -0.10)	0.0068
7-8	28 (18.4)	43 (16.3)	0.02 (-0.06 to 0.12)	0.5843	-0.01 (-0.05 to 0.03)	0.6927
9-10	116 (76.3)	192 (73.0)	0.03 (-0.14 to 0.22)	0.4596	0.14 (0.10 to 0.17)	< 0.001
Apgar score at 5 minutes						
0-6	1 (0.7)	3 (1.1)	0.00 (-0.02 to 0.03)	0.6866	-0.001 (-0.002 to -0.0003)	0.0066
7-8	13 (8.6)	22 (8.4)	0.00 (-0.06 to 0.07)	0.9439	-0.06 (-0.09 to -0.04)	0.0052
9-10	138 (90.8)	238 (90.5)	0.00 (-0.06 to 0.07)	0.9197	0.08 (0.05 to 0.11)	0.0004
Adverse neonatal outcomes	8 (5.3%)	20 (7.6%)	-0.03 (-0.08 to 0.03)	0.3691	-0.07 (-0.08 to -0.05)	< 0.001

Data are reported as n (%). *Adjusted for age, ethnicity, education, obstetrical history, gestational weeks at admission, cervical length at admission, IVF, pre-pregnancy BMI, surgical history, smoking, drug abuse, uterine malformations, uterine fibromatosis, adverse obstetric outcomes, Hb, WBC, and CRP at admission.

at admission. No difference between exposed and unexposed was noted in gestational weeks at delivery in case of gestational age at admission ≥ 30.1 weeks. The interval from admission to delivery was higher in patients in whom a cervical pessary was placed and had a gestational age at admission ≤ 30.0 weeks (Table III). A higher interval from admission-delivery was noted in

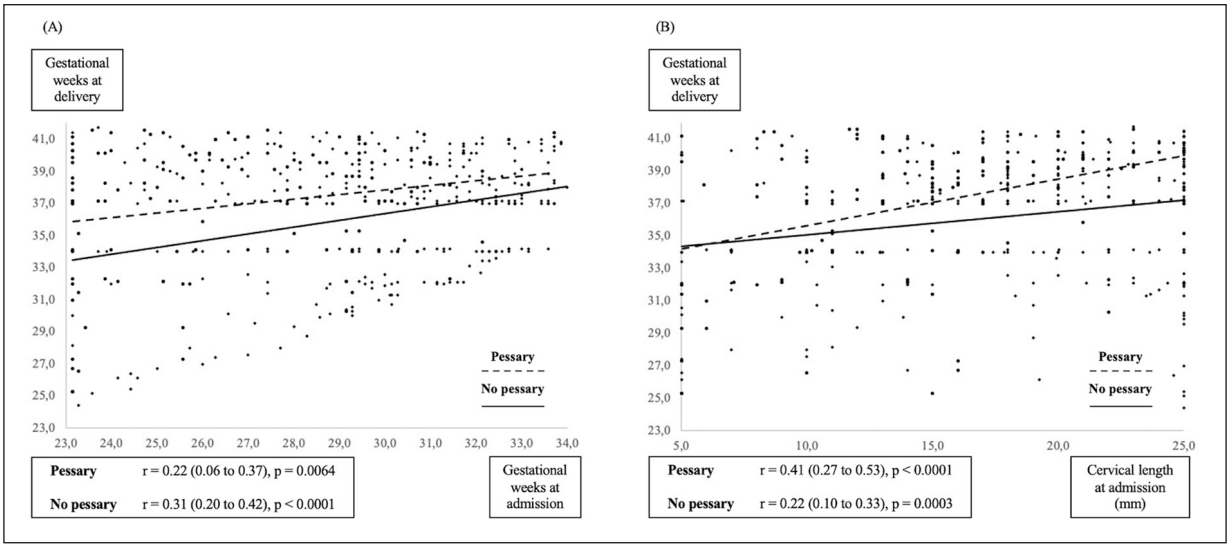

Figure 2. Scatter diagrams and regression line of the association between gestational weeks at delivery and gestational age at admission (**A**) or cervical length at admission (**B**).

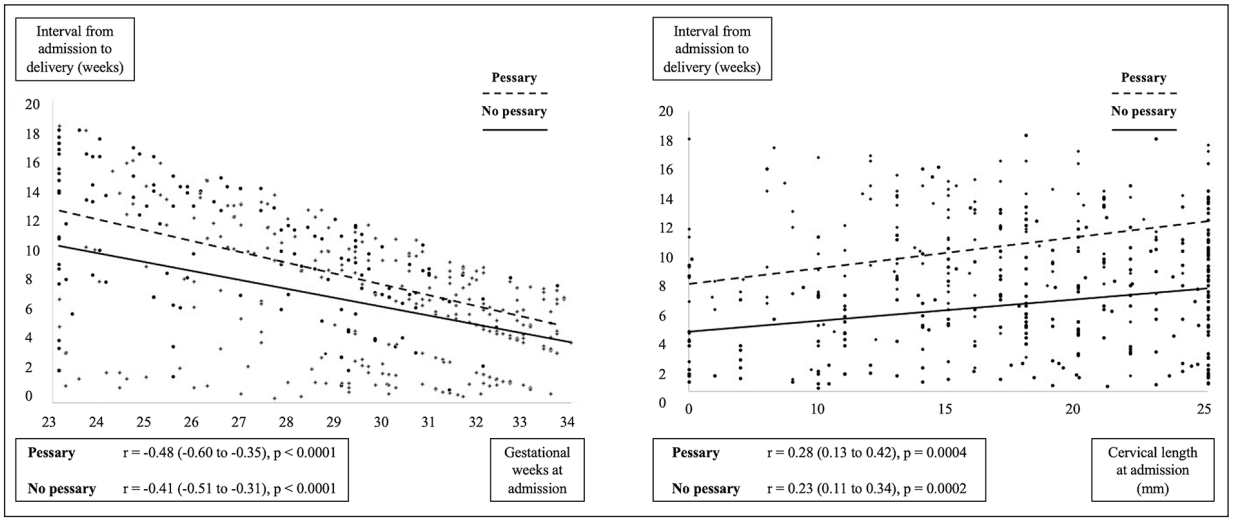

Figure 3. Scatter diagrams and regression line of the association between interval admission-delivery and gestational age at admission (**A**) or cervical length at admission (**B**).

the exposed group regardless of cervical length at admission (Table IV).

According to Kaplan-Meier analysis and Log-rank test, the HR (95% CI) in case of cervical pessary placement for preterm birth <37 weeks was 0.69 (0.49-0.98), $p = 0.0385$ and 0.60 (0.38-0.93), $p = 0.0233$ for preterm birth < 34 weeks (Figure 4).

Discussion

Results from the present study showed that cervical pessary placement seems to be associated with a 14% reduction of the rate of preterm birth < 37 weeks in patients with arrested preterm labor. The magnitude of this effect was similar when considering preterm birth < 34 weeks (-17%) and < 32 weeks (-16%) but seems to be reduced for preterm birth < 28 weeks (-6%). Patients with cervical pessary placement had a 16% higher chance of giving birth more than 6-12 weeks after the first admission for threatened preterm labor. However, these effects seem to have a limited impact on neonatal adverse outcomes reduction (-7%).

The beneficial effect of cervical pessary placement in term of higher gestational weeks at delivery and higher interval from first admission to delivery seems to decrease if patients experienced threatened preterm labor after 30.1 gestational weeks (Table III), regardless of cervical length at admission (Table IV).

These findings are partially in line with those reported in the available literature regarding cervical pessary effect in arrested preterm labor. Indeed, the randomized controlled trial (RCT) conducted by Pratcorona et al[9] reported a lower rate (14.7% *vs.* 25.1%) of late preterm birth (34-37 weeks), threatened preterm labor recurrence (4.5% *vs.* 20.0%), and preterm premature rupture of membranes rate (2.3% *vs.* 8.0%) in patients with cervical pessary placement, even if cervical pessary did not lower the rate (10.7% *vs.* 13.7%) of spontaneous preterm birth < 34 weeks after a threatened preterm labor episode.

On the other hand, the RCT of Hermans et al[10] was stopped after a planned interim analysis since 48% of the 65 patients in whom a cervical pessary was placed after an episode of threatened preterm labor had a preterm birth < 37 weeks compared to 39% of the no-treatment group (65 patients). Similarly, the RCT by Mastantuoni et al[11] was concluded before the completion of enrollment; an increased rate of preterm birth < 37 weeks in the 32 patients randomized in the pessary group was noted, even if this observation did not reach a statistical significance (risk ratio 2.98, 95% CI 0.96-9.30). In the retrospective study from Seravalli et al[12], the cervical pessary resulted less effective when applied in case of a short cervix following an episode of threatened preterm labor than in the case of asymptomatic cervical shortening in the second trimester, even if the study did not include patients managed without pessary placement as controls.

Table III. Gestational weeks at delivery and interval from admission to delivery according to classes of gestational weeks at admission.

Gestational weeks at admission	Gestational weeks at delivery					Interval admission-delivery (weeks)				
	N	Cervical pessary	N	No cervical pessary	*p**	N	Cervical pessary	N	No cervical pessary	*p**
23.1-26.0 weeks	64	35.8 ± 4.8	33	33.5 ± 5.9	0.0357	64	11.7 ± 4.7	33	8.9 ± 5.7	0.0121
26.1-28.0 weeks	21	39.2 ± 2.3	40	36.4 ± 4.1	0.0050	21	12.0 ± 2.7	40	9.3 ± 4.2	0.0080
28.1-30.0 weeks	40	37.2 ± 2.9	46	35.7 ± 4.1	0.0438	40	8.1 ± 3.0	46	6.5 ± 4.1	0.0442
30.1-32.0 weeks	21	37.6 ± 2.3	66	36.8 ± 3.3	0.2750	21	6.9 ± 2.2	66	5.7 ± 3.2	0.1150
32.1-34.0 weeks	6	37.9 ± 3.1	78	37.4 ± 2.3	0.6312	6	5.3 ± 2.8	78	4.5 ± 2.1	0.3795

Data are reported as mean ± SD. **t*-test.

Table IV. Gestational weeks at delivery and interval from admission to delivery according to classes of cervical length at admission.

Cervical length at admission (mm)	Gestational weeks at delivery					Interval admission-delivery (weeks)				
	N	Cervical pessary	N	No cervical pessary	*p**	N	Cervical pessary	N	No cervical pessary	*p**
≤ 10.0 mm	36	34.7 ± 4.8	31	33.8 ± 4.5	0.4181	36	8.0 ± 4.5	31	4.0 ± 3.8	0.0003
10.1-15.0 mm	51	37.0 ± 3.2	41	35.6 ± 3.9	0.0654	51	9.9 ± 5.8	41	5.8 ± 4.1	< 0.0001
15.1-20.0 mm	39	38.0 ± 3.3	70	37.0 ± 3.1	0.0969	39	10.6 ± 6.5	70	6.5 ± 3.8	< 0.0001
20.1-25.0 mm	26	38.7 ± 2.7	121	36.8± 4.0	0.0221	26	11.3 ± 4.1	121	7.2 ± 4.1	< 0.0001

Data are reported as mean ± SD. **t*-test.

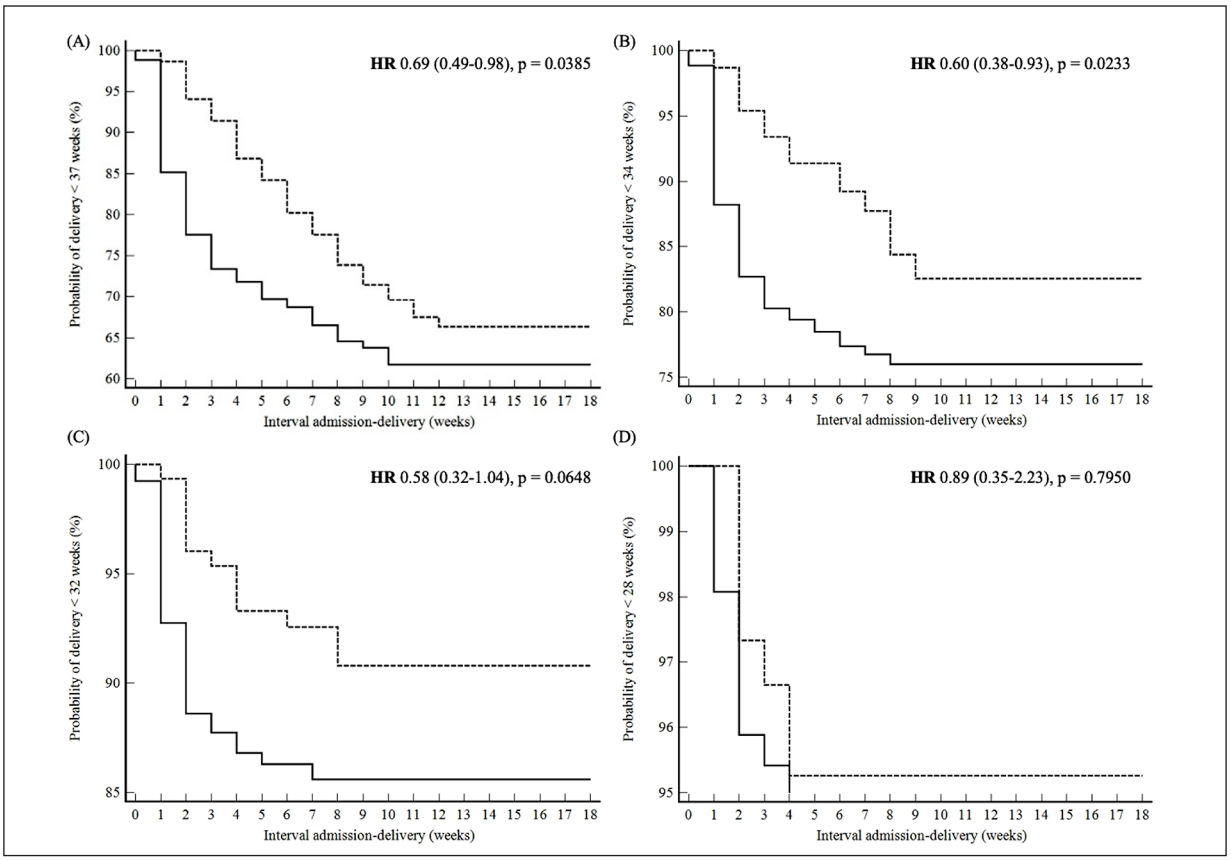

Figure 4. Kaplan-Meier analysis of the probability of preterm birth < 37 (**A**), < 34 (**B**), < 32 (**C**), and < 28 (**D**) weeks between according to cervical pessary placement.

The heterogeneity of the available data could be to the complex pathogenesis of preterm labor, with the possibility that patients may have different risk profiles and that only some of them could benefit from cervical pessary placement. In this context, obtaining information about the effectiveness of cervical pessary in different subgroups of patients with arrested preterm labor could allow to target the intervention and avoid its placement in those cases where it might be less effective. At this regard, our study showed that the efficacy of cervical pessary appears to be more evident in term of gestational weeks at delivery and interval from admission to delivery when the first admission for threatened preterm labor occurred before 30 gestational weeks. It is known that there are different pathogenetic mechanisms of preterm birth that act differently regarding the gestational age of onset of symptoms[21], and it is possible to speculate that the hypothesized mechanical action of cervical pessary may be more likely to occur when the uterine volume and weight are lower than those of a more advanced gestational age. Further research is needed to identify the relation between preterm birth pathogenesis and cervical pessary according to gestational age.

Deepening the research about preterm birth prevention would also make it possible to reduce the potential maternal and fetal complications related to preterm delivery management. Indeed, this management is made difficult by the choice of mode of delivery (cesarean section *vs.* vaginal birth)[22], by the negative recommendation about vacuum extraction in case of assisted preterm vaginal delivery[23], by the need to avoid maneuvers, such as fundal pressure[24-25], and by the risk of delivery room infections[26]. Moreover, common pathogenetic mechanisms seems to be shared by premature preterm rupture of membranes (pPROM) and amniotic fluid embolism (AFE)[27], a rare although potentially fatal obstetrical complication[28]. Since preterm birth is one the most common adverse obstetric outcome related to COVID-19 infection, an effective prevention in the current pandemic context is of crucial importance[29].

Regarding the side effects of pessary placement, we found an increase in vaginal discharges in 38.2% of patients who had no impact on quality of life and no serious adverse events. Similar findings were reported by Pratcorona et al[9], who described no pessary-use related adverse events but the presence of vaginal discharge in all patients[9], as well as in the study of Mastantuoni et al[11], where no difference in adverse events was found between study and control group[11]. On the contrary, Hermans et al[10] stated that cervical pessary placement was associated with substantial discomfort and unpleasant symptoms (vaginal discharge, blood loss, and abdominal pain).

Limitations

Limitations of this study include its retrospective nature, with the possibility of unmeasured confounders that could have influenced the exposure (cervical pessary placement), the primary outcome (preterm birth), or both. However, the reported data come from a real-world setting, with daily management by healthcare professionals, and the included variables reflect the information that is commonly available in every center that manages patients with arrested preterm labor, thus increasing the generalizability of the results.

In our study population, patients in whom a cervical pessary was placed had a reduced gestational age and cervical length at admission, conditions that may influence the risk of preterm birth. It is reasonable that clinicians may have preferred to provide an additional therapeutic tool for those women they believed to be at increased risk for preterm birth. However, the rigorous statistical analysis adopted, using TMLE as double robust estimator, allowed us to measure an ATE adjusted for confounders that could influence the risk of the exposure, of the outcome, or both. Moreover, having included a large number of patients further strengthens our conclusions.

Conclusions

After an episode of arrested preterm labor occurring before 30 gestational weeks, cervical pessary placement seems to reduce the risk of a subsequent preterm birth < 37, < 34, and < 32 gestational weeks, prolonging the pregnancy for 6-12 weeks or more. No effect was observed regarding adverse neonatal outcomes prevention. These findings should be further assessed in prospective studies focusing on gestational age of symptom onset.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Giovanni Delli Carpini: conception and design of the study; analysis and interpretation of data; drafting the article. Luca Giannella: methodology; analysis and interpretation of data; drafting the article. Martina Carboni, Mariasole Fichera, Davide Pizzagalli, Noemi Segnalini, Claudia Conti, Elisa Tafuri, Lucia Giuliani, Federica Ragno, Carlotta Mancusi: acquisition of data; analysis of data; drafting the article. Stefano Raffaele Giannubilo: analysis and interpretation of data; drafting the article; Andrea Ciavattini: conception and design of the study, supervision; critical revision of the manuscript. All authors have given approval of the submitted and final versions.

Ethics Approval

In order to reach the required sample size, we included patients from January 2016 to June 2021. The research was conducted according to the Declaration of Helsinki. According to Italian legislation, the local ethical committee of our institution (Comitato Etico Regionale Marche) took notice of the study protocol (No. CERM 2021/51).

Informed Consent

Proper informed consent was obtained from all individual participants included in the study.

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