ORIGINAL ARTICLE

THE CLINICAL ASSESSMENT OF THE CERVICAL PERFORATED PESSARY FOR THE PREVENTION OF PRETERM LABOR IN WOMEN WITH PRIOR PRETERM BIRTHS

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ABSTRACT

The aim: The assessment of clinical effectiveness the cervical perforated pessary (CPP) used for prevention of preterm labor.

Materials and methods: Caucasian women with prior SPL who were randomized to receive a CPP (clinical group) or without pessary (control group) was conducted at the Vinnytsya maternal hospital №1, from 2014 through 2018. Eligible women were those referred to the institution for a diagnosis of cervical incompetence between 16 weeks and 18 weeks +6 days. Outcomes will be PTL before 28, 32, 35, and 37 weeks of gestation; a composite of poor perinatal outcomes.

Results: The incidence of SPL at less than 37 weeks of gestation was occurred in 14,1% vs 29,3% (RR 0,48, 95% CI, 0,23-0,99), lower rate of SPL at less than 35 weeks of gestation (RR 0,30, 95% CI, 0,10-0,88), longer gestational age (Dif. -1,4, 95% CI, -2,30 to -0,50), higher birth weight (Dif. -197,9, 95% CI, -307,6 to -88,15), lower incidence of adverse composite perinatal outcome (RR 0,28, 95% CI, 0,1-0,81) from the pessary and control group respectively. The participants pessary clinical group had a higher rate than the control group of increased vaginal discharge (RR 1,31, 95% CI, 1,01-1,69), but no differences in pelvic discomfort (RR 0,54, 95% CI, 0,14-2,18), chorioamnionitis (RR 0,30, 95% CI, 0,06-1,44).

Conclusions: The women with prior SPL use of a CPP, resulted in a lower rate of SPL. The component in the successful results of preventive strategy SPL is consideration of vaginal microbiota and role of special trained staff for installation and care cervical pessary.

KEY WORDS: preterm labor, singleton pregnancy, cervical perforated pessary, Shtember scale

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INTRODUCTION

The World Health Organization (WHO) defines spontaneous preterm labor (PTL) as a live birth prior before 37 completed weeks of gestation. Very premature refers to those born between 28 and 31+6 weeks gestation and extreme prematurity refers for births at less than 27+6 weeks gestation. The problem of premature infants is medical and social. Every year, more than 20 million children are born prematurely in the world. According to statistics, PTL is the cause of almost half of all deaths of newborns in the world [1-2]. Of the 4 million neonatal deaths in a year, more than the fifth were due to premature birth. Delivery until 37 weeks of gestation occurs in 8-12% of all pregnancies in developed countries, 80% of perinatal mortalities and 50% of childhood neuro-developmental disorders occur in these populations of patients. The prognosis of premature infants directly depends on gestational age and birth weight. Children who survive may face the risk of significant disability, including cerebral palsy, intellectual impairment, chronic lung disease and vision and hearing loss for a lifetime. They are also at greater risk of developing hypertension, obesity, neuro-endocrine disorders and development problems later in their lives [3-5]. More than one million of these children die within a year of birth. In Ukraine in recent years, the frequency of premature births ranged from 3,5 to 5,2%.

PTL is a pregnancy complication that associated with multiple etiologic processes such as prior preterm delivery, vaginal infection or inflammation, endothelial dysfunction, decidual problems, uterine over-distention, hormonal misbalance (androgen / estrogen / progesterone), cervical incompetence, maternal-fetal immunological tolerance disorders, and maternal stress, among others [6,7]. Genetic and environmental factors contribute to each etiology of the PTL. Demographic factor such as the modern trend toward higher maternal age for pregnancy in large part to known reasons for development of preterm labor too [8].

Different strategies have been adopted for prevention of spontaneous PTL. Although vaginal progesterone, cervical cerclage and cervical pessary have been used in clinical practice to prevent PTL, evidence regarding the effectiveness of these interventions is still inconclusive [9, 10].

A meta-analysis of randomized clinical trials (RCTs) suggested that progesterone potentially reduced PTL and neonatal complications in women with twin pregnancies and a short cervix. However, a recent meta-analysis showed that progesterone could only improve some secondary outcomes, regardless of cervical length (CL) [11, 12].

For cervical cerclage, a meta-analysis of three trials in 49 women with twins and a CL <25 mm could not demonstrate a benefit of cerclage in this population. Moreover, cerclage group had higher rates of very low birth weight and of respiratory distress syndrome than control group. In contrast, a recent systematic review and meta-analysis, which includes RCTs and cohort studies, indicate that cerclage placement is beneficial for the reduction of PTL only in twin pregnancies with a CL <15 mm or dilated cervix of >10 mm [13].

An alternative approach for prevention of preterm birth is transvaginal placement of a round silicone cervical perforated pessary (CPP) around the cervix. The main functions of CPP are support of the cervix, helps keep the cervix closed and changes the inclination of the cervical canal and returned its direction toward the sacrum, thereby reducing the direct pressure from the uterine contents on the cervical canal [14].

The prevention of spontaneous preterm birth with CPP in asymptomatic pregnant women with short cervical length midtrimester remains controversial. The prominent problems, in the first line, were associated with limited number of well-trained, certified staffs were involved in the pessary installation; used an open design, which is unavoidable due to the nature of the interventions, could introduced bias; for the majority of women involving in the prior trials microbial (infection) factor was not excluded before CPP placement and during current pregnancy [15]. Therefore, the external validity of the previous studies might be compromised.

THE AIM

The assessment of clinical effectiveness the cervical perforated pessary used with singleton pregnancy and history preterm labor.

MATERIALS AND METHODS

A prospective open randomized clinical trial of Caucasian women (region Podilia) with asymptomatic singleton pregnancies with prior spontaneous preterm birth who were randomized to receive a CPP (intervention group (64 pregnant women)) or without pessary (control group (58 pregnant women)) was conducted at the maternal hospital №1, Vinnytsya, (clinical base department Obstetrics & Gynaecology №1, National Pirogov Memorial Medical University) from 2014 through 2018.

The trial was approved by the biological and medical ethics committee of the National Pirogov Memorial Medical University, Vinnytsya and was carried out strictly in accordance with the code of ethics of the World Medical Association (declaration of Helsinki) for experiments involving humans. All participants in the trial provided written informed consent.

Eligible women were those referred to the institution for a diagnosis of cervical incompetence during the assessment by Shtember scale between 16 weeks and 18 weeks +6 days. Gestational age was determined from menstrual history and confirmed by fetal crown-rump length measurement at a first-trimester scan. The pregnant women with previous PL found to have a 6 point or more by Shtember scale were approached by the research staff and consented.

Inclusion criteria were age 21 to 35 years, history of spontaneous preterm birth, singleton pregnancy, experienced medical personal for CPP placement and care (certificate), 6 point or more by Shtember scale, and gestational age at randomization between 16 weeks and 18 weeks +6 days.

Exclusion criteria were multiple pregnancies, fetal structural abnormality, cerclage in situ, vaginal bleeding at the time of randomization, colpitis, vaginal dysbiosis, placenta previa or accreta, prolapsed amnion membranes through the cervix into the vagina, cervical length less than 15 mm.

The cervical perforated pessary made of flexible silicone manufactured by CJSC "Medical enterprise Simurg" (Vitebsk, Belarus). Speculum examination was carried out to inspect the cervix for any pathology and obtain a high vaginal swab for bacteriological examination. If there was offensive vaginal discharge (dysbiosis) therapy and vaginal probiotics was given and insertion of the CPP was delayed until the discharge subsided. The CPP was inserted through the vagina with the woman in the recumbent position and placed upward around the cervix [16]. We introducing the cervical pessaries received instruction on selecting the appropriate size and introducing the device.

Pregnant women from control group received the same obstetrical care as those in the pessary group. Follow-up visits for ultrasound assessment of fetal growth and cervical length, were carried out every 4 weeks until 34 weeks' gestation. pH of vaginal discharge we studded every 3 weeks until 37 weeks' gestation. Bacteriological examination we performed when women were offensive vaginal discharge.

In the intervention group, the cervical pessary was placed at the time of randomization and was removed during the 37th week (37weeks –37 weeks + 6 days) or earlier if clinically indicated.

The primary outcome will be PTL <37 weeks' gestation for any indication.

Secondary outcomes will be delivery before 28, 32 and 35 weeks of gestation; tocolytic drugs, antenatal corticosteroids or $MgSO_4$ for neuroprotection use; preterm premature rupture of membrane; chorioamnionitis; maternal side effects (including vaginal discharge, fever, vaginal infection or pain, pessary repositioning and necrosis or rupture of the cervix); maternal morbidity (urinary tract infection, endometritis); birth weight; 5 min APGAR score; perinatal death, neonatal intensive care unit (NICU) admission; days of admission to the NICU; intraventricular hemorrhage; respiratory distress syndrome; necrotizing enterocolitis; neonatal infection and a composite of poor perinatal outcomes.

Adverse events were defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigators were recorded.

Table I. Demographic and clinical participants characteristics

Characteristics	Pessary group (n = 64)	Control group (n = 58)	*p*
Age, mean (SD), y	26,78 (3,80)	27,48 (4,01)	*0,32*
Body mass index, mean (SD), kg/m^2	22,2 (2,94)	21,2 (2,73)	*0,06*
Smoking, n (%)	26 (40,6)	23 (39,6)	*0,91*
Gestation time at randomization,mean (SD), wk	17,08 (0,63)	17,18 (0,72)	*0,41*
Parity 2, n (%)	48 (75,0)	46 (79,3)	*0,57*
Parity 3, n (%)	12 (18,75)	10 (17,2)	*0,83*
Parity 4, n (%)	4 (6,25)	2 (3,5)	*0,48*
Cervical length, mean (SD), mm	19,1 (2,2)	19,6 (2,5)	*0,24*
≤25 mm, n (%)	12 (18,75)	12 (20,7)	*0,79*
≤20 mm, n (%)	52 (81,25)	46 (79,3)	*0,79*
Positive vaginal swab culture atrandomization, n (%)	18 (28,1)	12 (20,7)	*0,35*
Cardio-vascular pathology, n (%)	6 (9,4)	5 (8,6)	*0,89*
Chronic pulmonary disease, n (%)	4 (6,25)	2 (3,5)	*0,48*
Chronic kidney disease, n (%)	24 (37,5)	16 (27,6)	*0,25*
Asymptomatic bacteriuria, n (%)	17 (26,6)	14 (24,1)	*0,76*
Pelvic inflammatory disease, n (%)	18 (28,1)	14 (24,1)	*0,62*
Prior cervical surgery, n (%)	7 (10,9)	6 (10,3)	*0,92*
Prior infertility, n (%)	12 (18,75)	10 (17,2)	*0,83*
Prior hyperandrogenia, n (%)	21 (32,8)	15 (25,9)	*0,40*
Current pregnancy due to ART, n (%)	4 (6,25)	2 (3,5)	*0,48*
Prior miscarriage, n (%)	23 (35,9)	17 (29,3)	*0,44*
Prior abortion (eg, dilation and curettage), n (%)	42 (65,6)	39 (67,2)	*0,85*

The values are expressed as mean (SD) or n (%).Student's t test for continuous variables or chi-squared test for categorical variables was applied for comparison with control women.

Table II. Primary and secondary outcomes among participants in the pessary and control groups

Outcomes	Pessary group (n = 64)	Control group (n = 58)	RR or Between-Group Difference
SPL<37wk, n (%)	9 (14,1)	17 (29.3)	*0,48, 95% CI, 0,23-0,99, p=0,047*
SPL <35wk, n (%)	4 (6,25)	12 (20,7)	*0,30, 95% CI, 0,10-0,88, p=0,029*
SPL <32 wk, n (%)	1 (1,6)	7 (12,1)	*0,13, 95% CI, 0,02-1,02, p=0,052*
SPL <28 wk, n (%)	-	3 (5,2)	-
Gestational age at delivery, mean (SD), wk	37,8 (1,8)	36,4 (3,1)	*Difference -1,4, 95% CI, -2,30 to -0,50, p=0,002*
Intrauterine growth restriction, n (%)	5 (7,8)	7 (12,1)	0,65, 95% CI, 0,22-1,93, p=0,43
Preterm premature rupture of membranes <37 wk, n (%)	14 (21,9)	18 (31,0)	*0,71, 95% CI, 0,39-1,29, p=0,25*
Cesarean delivery, n (%)	4 (6,25)	5 (8,6)	*0,72, 95% CI, 0,20-2,57, p=0,62*
Spontaneous vaginal delivery, n (%)	60 (93,75)	53 (91,4)	*1,03, 95% CI, 0,93-1,13, p=0,62*
Vaginal discharge, n (%)	49 (76,6)	34 (58,6)	*1,31, 95% CI, 1,01-1,69, p=0,04*
Pelvic discomfort, n (%)	3 (4,7)	5 (8,6)	0,54, 95% CI, 0,14-2,18, p=0,39
Chorioamnionitis, n (%)	2 (3,1)	6 (9,4)	*0,30, 95% CI, 0,06-1,44, p=0,13*
Endometritis, n (%)	3 (4,7)	4 (6,25)	*0,68, 95% CI, 0,16-2,91, p=0,60*
Birth weight, mean (SD), g	3360,0 (260,5)	3162,1 (349,0)	*Difference -197,9, 95% CI, -307,6 to -88,15, p=0,0005*
5 min APGAR score, mean (SD), p	8,5 (1,04)	7,87 (1,78)	*Difference -0,63, 95% CI, -1,15to -0,11, p=0,02*
Neonatal intensive care unit, n (%)	6 (9,4)	13 (22,4)	*0,42, 95% CI, 0,17-1,03, p=0,06*
Perinatal death, n (%)	-	3 (5,2)	-
Composite perinatal outcome, n (%)	4 (6,25)	13 (22,4)	*0,28, 95% CI, 0,1-0,81, p=0,02*

Data are shown as means or as numbers and percentages. Comparisons between groups were performed with the use of the t test to test group means by assuming equal within-group variances. Statistical data were calculated and compared using the MedCalc software, developed by "MedCalc Software" (Ostend, Belgium).

The primary analysis was an intention-to-treat comparison of the treatment assigned at randomization. The effect of pessary use on the cumulative incidence of each outcome was quantified in 2 ways: first as the difference between treatment groups in cumulative incidence of the outcome with 95% confidence intervals and second as the unadjusted relative risk (RR) and its 95% confidence interval. The between-group difference calculated the difference between the observed means in two independent samples. A significance value (P-value) and 95% Confidence Interval (CI) of the difference is reported. The P-value is the probability of obtaining the observed difference between the samples if the null hypothesis were true. The null hypothesis is the hypothesis that the difference is 0. Original prespecified analysis included the use of the odds ratio instead of the unadjusted RR. However, given that RR is easier to interpret, we decided to quantified the incidence of the primary outcome by using the unadjusted relative risk.

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

RESULTS

From April 2014 to October 2018, 122 asymptomatic pregnant women agreed to take part in our prospective trial. Patients with singleton pregnancies with prior spontaneous preterm birth with more the 6 points by Shtember scale (the sonographic evaluation considered the cervical length of 25 mm less) between 16 weeks and 18 weeks +6 days of gestation were enrolled and followed up. Of the pregnant women, 64 (52,5%) were randomized to the carriers group of silicone cervical perforated pessary and 58 (47,5%) to the control group. No pregnant women were excluded after randomization or lost to follow-up. No women in the intervention group had the pessary removed by request or for severe discomfort.

In the table I we showed the baseline demographic and clinical characteristics for pregnant women in each group. There were 52 women (81,25%) in the pessary group and 46 (79,3%) pregnant women in the control group who had a cervical length of 20 mm or less. There were 18 (28,1%) patients in the group carriers of CPP and 12 (20,7%) women in the control group received preceding complex treatment because of vaginal dysbiosis at the time of randomization.

The mean gestational age at randomization was 17,08 ± 0,63 weeks versus 17,18 ± 0,72 weeks for our patients in the CPP and control groups, respectively. Among pregnant women our clinical trial the mean cervical length was 19,1 ± 2,2 mm) in pessary group and 19,6 ± 2,5 mm in the control group were obtained. We found also that enough rate of prior of incidents dilation and curettage was associated with risk of cervical incompetence, 42 (65,6%) for pessary group and 39 (67,2%) for the women from control group. There were spreading cases of prior hyperandrogenia among women who had 6 and more points by Shtember scale, 21 (32,8%) for participants from pessary group and 15 (25,9%) for the control group.

According to the primary outcome, in Table II shows the incidence of spontaneous preterm labor at less than 37 weeks of gestation was occurred in 9 patients (14,1%) from the pessary group and 17 participants (29,3%) in the control group (RR 0,48, 95% CI, 0,23-0,99, p=0,047).

In generally, in the group of participants-carriers of CPP we found a significantly lower rate of spontaneous preterm birth at less than 35 weeks of gestation (p=0,029), longer gestational age at delivery (p=0,002), higher birth weight (p=0,0005), higher rate by points APGAR score on 5 minutes (p=0,02), and lower incidence of adverse composite perinatal outcome (p=0,02) compared with patients from control group. In women-carriers of CPP also were established significantly lower rates of respiratory distress syndrome (p=0,02).

According to the adverse events follow-up, the participants pessary clinical group had a higher rate than the control group of increased vaginal discharge (RR 1,31, 95% CI, 1,01-1,69, p=0,04), but no significant differences in pelvic discomfort (RR 0,54, 95% CI, 0,14-2,18, p=0,39), chorioamnionitis (RR 0,30, 95% CI, 0,06-1,44, p=0,13), and endometritis (RR 0,68, 95% CI, 0,16-2,91, p=0,60) were reported. The incidents of perinatal deaths among participants from the control group were associated with placental abruption (2 cases) and sudden umbilical vein thrombosis (1 case). In our clinical prospective trial any cases of serious injuries cervix during removal of the CPP were reported.

DISCUSSION

In the results of the current study are consistent with those of the trial by Goya et al. which concluded that a cervical pessary could prevent preterm birth in a population of appropriately selected at-risk women previously screened for cervical length assessment on transvaginal ultrasound at the midtrimester visit [17]. There were more participants with prior preterm birth in the trial by C. Nicolaides et al. (16,5%) compared with the trial by Goya et al. (10,8%). This raises the question of whether a can be effective only in women with a short cervix but without prior preterm birth [18].

But, the main controversies of previous trial s were ignoring the influences of states vaginal microbiota and role of special trained staff for installation and care cervical pessary.

More than half of the women included in the meta-analysis (932/1420) came from trial by C. Nicolaides et al., which drives the summary statistics [18]. This trial was methodologically very different from our study. Nicolaides et al included both women without prior preterm birth and those with prior preterm birth, and the study

included multiple sites, some of which did not enroll many participants, raising the possibility of lesser experience with pessary placement and management. The current study's trial protocol included hands-on certificated training and a requirement for all staff to demonstrate pessary insertion competence on a special simulated model, while C. Nicolaides et al. did not include this type of training. The median cervical length at randomization was lower in this study compared with the trial by C. Nicolaides et al (approximately 15 mm vs 20 mm). The current trial was included not only measurement length of cervix but other signs of the cervical incompetence, such as opening of the internal os and/or cervical canal, cervical angle, cervical position and consistency, serum androgen level, history of preterm labor or late miscarriage, respectively. For preventive strategy by CPP, clinical experience related to technique of operation or insertion, clinical surveillance and mode and timing of removal should not be neglected as an essential factor contributing to a successful or unsuccessful strategy [11, 18]. The different results between the trials raise the question of whether a cervical pessary can be effective only at very low cervical length cut offs, although there was no effect modification by cervical length in the current study.

According to opinion of Conde-Agudelo A at al., among patients with a singleton gestation and a short cervix who receive vaginal progesterone, a cervical pessary should not be placed given that the device does not offer any additional benefits over administration of vaginal progesterone alone in reducing preterm birth and adverse perinatal outcomes [6].

Multicenter Spanish study PECEP of 2012 with 385 women with cervix ≤25mm between week 18-22 of gestation in a not selected group of general population. The obstetricians who participated carried out sonographic training in the placement of the CPP. The primary outcome was spontaneous preterm labor before week 34. This rate was significantly lower in the pessary group, and also in gestations shorter than 28 and 37 weeks. The need for tocolysis or use of glucocorticoids was lower. Neonatal results were also significantly better in the pessary group. The main adverse effect was an increase in vaginal discharge. The limitation is that it is an open trial and that the rate of premature delivery in the expectant management group was 27%, much higher than the one published previously. They conclude that the cervical pessary is an affordable alternative, safe and effective for the prevention of spontaneous preterm birth in a population of women adequately selected for cervical length of the second trimester [19].

According to the single-center, non-blinded study Saccone et al. among women without prior spontaneous preterm birth who had asymptomatic singleton pregnancies and short transvaginal cervical length, use of a cervical pessary, compared with no pessary use, resulted in a lower rate of spontaneous preterm birth at less than 34 weeks of gestation [20].

In the study of Pratcorona L et al. was obtained that pessary use did not significantly lower the spontaneous preterm birth rate <34 weeks in women with a short cervix remaining after a threatened preterm labor episode but did significantly reduce the spontaneous preterm birth rate <37 weeks, threatened preterm labor recurrence, and the preterm premature rupture of membranes rate [21].

Since it is a less invasive preventive method than cerclage, not dependent on hormonal supplementation, the cervical perforated pessary is assuming an important role in the medical practice among clinicians. The placement of cervical pessary is relatively non invasive procedure is easy to use, does not require anesthesia, can be used in an outpatient clinic setting. The silicone cervical pessary is easily removed when necessary. A cervical pessary would change the inclination of the cervical canal, directing it more posteriorly [22]. In doing so, the weight of the pregnancy would be more on the anterior lower segment. As our opinion, interesting proposed mechanism is that the pessary could strengthen the immunological barrier between the chorioamnion-extraovular space and the vaginal microbiological flora, as cerclage has been postulated to do.

The results of our clinical trial among pregnant women with prior preterm labor require confirmation in future multicenter clinical trials.

CONCLUSIONS

1. The participants with prior spontaneous preterm labor who had asymptomatic singleton pregnancies and combine signs of cervical incompetence, use of a CPP, compared with no pessary use, resulted in a lower rate of SPL at less than 37 and 35 weeks of gestation.
2. The pregnant women as carriers CPP with prior SPL and signs of cervical incompetence had also more longer gestational age at delivery (p=0,002), higher birth weight (p=0,0005), higher rate by points APGAR score on 5 minutes (p=0,02), and significant lower incidence of adverse composite perinatal outcome (p=0,02).
3. The main component in the successful results of preventive strategy SPL is consideration of function the vaginal microbiota and role of special trained staff for installation and care cervical pessary.
4. The results of our prospective clinical study among pregnant women with prior preterm labor require confirmation in follow-up multicenter clinical trials.

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