Efficacy of cervical pessary versus cervical cerclage in preventing spontaneous preterm birth: a meta-analysis

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Abstract

Backgroud: The clinical efficacy and safety of cervical pessary versus cervical cerclage in preventing spontaneous preterm birth remain uncertain. Objectives: To systematically review the clinical efficacy of cervical pessary versus transvaginal cervical cerclage in preventing spontaneous preterm birth caused by cervical shortening. Search Strategy: The Cochrane Library, PubMed, EMbase, WanFang Data, CNKI, VIP Data and CBM Data were electronically searched. Selection Criteria: Randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs, including cohort studies) comparing cervical pessary and transvaginal cervical cerclage in preventing spontaneous preterm birth from the inception of the database to August 2020. Main Results: A total of 9 studies (2 RCTs and 7 non-RCTs) were included, involving 1174 patients with a short cervix in the second trimester (cervical length <25mm), 693 in the cervical pessary group and 481 in the cervical cerclage group. The results of meta-analysis showed that the incidence of preterm premature rupture of the membranes (PPROM) in the cervical pessary group was significantly lower than that in the cervical cerclage group (RR=0.48, 95% CI: 0.35 to 0.67, P<0.00001), and the premature birth rate before 34 weeks in the cervical pessary group was also significantly lower than that in the cervical cerclage group (RR=0.68, 95%CI: 0.51 to 0.89, P<0.006). Conclusion: Compared with transvaginal cervical cerclage, use of a cervical pessary may decrease the risks of PPROM and premature birth before 34 weeks. Given its advantages of easy-to-use and minimal damage, cervical pessary may become a useful preventive intervention that deserves widespread clinical application.

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Conclusion: Compared with transvaginal cervical cerclage, use of a cervical pessary may decrease the risks of PPROM and premature birth before 34 weeks. Given its advantages of easy-to-use and minimal damage, cervical pessary may become a useful preventive intervention that deserves widespread clinical application.

Keywords: Pessary; Cervical cerclage; Preterm birth; Meta-analysis; Systematic review; Randomized controlled trial; Non-randomized controlled trial

1. Introduction

Since the late 1970s, placement of a cervical pessary as a novel intervention has been introduced into clinical practice. In Europe, Arabin cervical pessary has been approved for use in the prevention of preterm birth, while in the US and Canada, cervical pessary has been approved for use in scientific research [1]. In addition to its benefits in reducing the incidence of preterm birth[2-4], the insertion of a cervical pessary is a non-invasive and simple procedure associated with few adverse effects, minimal maternal injury and short hospital stay[5].However, its clinical efficacy and safety versus cervical cerclage remain uncertain. Based on a systematic search of published literatures, we performed a meta-analysis of studies on the clinical efficacy of cervical pessary versus cervical cerclage in preventing spontaneous preterm birth, so as to provide more evidence for decision-making in real-world clinical practice.

2. Materials and methods

2.1 Study sample

2.1.1 Literature search

The Cochrane Library, PubMed, EMbase, WanFang Data, CNKI, VIP Data and CBM Data were electronically searched to collect randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs, including cohort studies) comparing cervical pessary and transvaginal cervical cerclage in preventing spontaneous preterm birth. According to the PRISMA Guidelines and the Cochrane Handbook for Systematic Reviews of Interventions[6-7], the literature search was conducted using MeSH terms combined with entry terms (e.g., pessaries, pessary, cervical cerclage, cerclage, cervical, premature birth, preterm birth, etc.). Taking PubMed for example, the detailed search strategy is provided in Box 1-1. All electronic databases were searched from their inception to August 31, 2020.

2.1.2 Inclusion criteria

Study type: RCTs and non-RCTs (including cohort studies).

Study subjects: pregnant women with a short cervical length (CL) <25mm in the second trimester who received cervical pessary or transvaginal cervical cerclage to prevent spontaneous preterm birth.

Interventions: cervical pessary of any type in the trial group, and transvaginal cervical cerclage of any technique in the control group.

Outcome measures: 1) abortion rate before 28 weeks; 2) premature birth rate before 32 weeks; 3) premature birth rate before 34 weeks; 4) premature birth rate before 37 weeks; 5) mean gestational weeks at delivery; 6) incidence of preterm premature rupture of the membranes (PPROM); 7) neonatal survival rate; 8) neonatal birth weight; and 9) cesarean section rate.

2.1.3 Exclusion criteria

1) Non-English or Chinese literatures; 2) only the most recent article was included when two or more articles reporting a same study; 3) studies unavailable in full-text; 4) studies whose data were inadequate or insufficient to estimate the outcomes; 5) studies involving patients at risk for premature rupture of membranes, intrauterine infection, monochorionic twin-twin transfusion syndrome, fetal anomalies or chromosomal abnormalities, or those who had regular contractions and unexplained active vaginal bleeding; and 6) studies involving patients who had allergy or contraindications to the cervical interventions used.

2.2 Study selection and data extraction

Study selection and data extraction was conducted by two reviewers independently. First, they screened the title and abstract for potentially relevant studies. Next, they read through the entire study to evaluate its eligibility for inclusion. Then, resultant studies from the two reviewers were compared; any discrepancies between the two reviewers were resolved through discussion with a third reviewer. Data were extracted from each study according to the data extraction table. If there was any missing data, the corresponding author was contacted via email or telephone call to obtain the required information. The data extracted comprised the following: 1) basic information such as article title, study type, name of the first author and year of publication; 2) subject baseline characteristics and different interventions; 3) study design and essential parameters for risk of bias assessment; and 4) outcome data.

2.3 Assessment of risk of bias

Two reviewers independently assessed the quality of each included study, and any disagreements between the two reviewers were resolved by consensus. The Cochrane risk-of-bias tool [6]was utilized to evaluate the included RCTs. For non-RCTs, the methodological index for non-randomized studies (MINORS) [8]was used to assess risk of bias.

2.4 Statistical analysis

We used Review Manager 5.3 (The Cochrane Collaboration, Oxford, United Kingdom) to perform meta-analysis. Continuous variables were presented as mean differences (MD), while categorical variables were reported as relative risks (RR). For each outcome measure, point estimates and 95% confidence intervals (95% CI) were also calculated. Heterogeneity across studies was evaluated using the I^2 statistic. Statistical significance was set at $\alpha = 0.1$. If $P > 0.1$ and $I^2 < 50\%$, the heterogeneity among studies was not significant, so that a fixed effect model was used; otherwise, a random-effect model was applied. Sensitivity analysis was used to detect the source of heterogeneity by excluding each study based on the leave-one-out method. In all meta-analyses, figures with a p-value less than 0.05 were considered statistically significant.

3. Results

3.1 Study selection

A total of 322 relevant studies were initially retrieved. After careful screening, 9 studies [9-17] met the eligibility criteria including 2 RCTs [9,11] and 7 non-RCTs[10, 12-17] .Totally 1174 patients with the threat of preterm birth were included for analysis, 693 in the cervical pessary group and 481 in the cervical cerclage group. The search process and the number of studies obtained in each step were presented in a flow chart in Figure 1-1.

3.2 Basic characteristics and quality assessment

Table 1-1 presented the basic characteristics of the included studies. The methodological quality assessment of non-RCTs (including cohort studies) was presented in Table 1-2. And Table 1-3 presented the assessment of risk of bias for the included RCTs.

3.3 Results of meta-analysis

3.3.1 Abortion rate before 28 weeks

Five studies were included for this analysis[9-11, 14, 15]. Due to statistical homogeneity across studies (P =0.97, I^2=0%), a fixed-effect model was applied. Results showed that the abortion rate before 28 weeks was comparable between the cervical pessary group and the cervical cerclage group *(*RR =0.57, 95%CI : 0.29 to 1.09, P =0.97) (Figure 1-2).

3.3.2 Premature birth rate before 32 weeks

Four studies were included for this analysis[10,13,15,17]. Due to statistical homogeneity across studies (P =0.22,I^2=31%), a fixed-effect model was applied. No significant difference in premature birth rate before 32 weeks was found between the two groups (RR =0.99, 95%CI : 0.59 to 1.66,P =0.96) (Figure 1-3).

3.3.3 Premature birth rate before 34 weeks

Eight studies were included for this analysis[9-15,17]. Given the significant heterogeneity across studies (P =0.08, I^2=45%), sensitivity analysis was performed to detect the source of heterogeneity. Fichera 2019 *et al.* was found to be the most influential study. After excluding this study, no significant heterogeneity was noted (P =0.58,I^2=0%), and a fixed-effect model was used for analysis. Results revealed that the premature birth rate before 34 weeks in the cervical pessary group was significantly lower than that in the cervical cerclage group (RR =0.68, 95%CI : 0.51 to 0.89,P <0.006). Sensitivity analyses did not significantly alter the results, suggesting that the results were predominantly stable (Figure 1-4).

3.3.4 Premature birth rate before 37 weeks

Six studies were included for this analysis [9, 11, 12, 15-17]. Due to statistical homogeneity across studies (P =0.81, I^2=0%), a fixed-effect model was utilized. Meta-analysis did not find any significant difference in the rate of premature birth before 37 weeks between the two groups (RR =0.94, 95%CI : 0.76-1.15, P =0.52) (Figure 1-5).

3.3.5 Mean gestational weeks at delivery

Five studies were included for this analysis [12, 13, 15-17]. A fixed-effect model was used because of sufficient homogeneity across studies (P =0.17,I^2=37%). Results showed that the mean gestational weeks at delivery was similar between the cervical pessary group and the cervical cerclage group (MD =- 0.24, 95%CI : -0.87 to 0.39, P =0.45) (Figure 1-6).

3.3.6 Incidence of preterm premature rupture of the membranes

Four studies were included for this analysis[12,13,15,16]. Given the significant heterogeneity across studies (P =0.01, I^2=73%), sensitivity analysis was performed to detect the source of heterogeneity. After excluding the most influential study by Fichera 2019 *et al.* , heterogeneity was no longer significant (P =0.37, I^2=1%), and a fixed-effect model was used for analysis. A significant lower incidence of PPROM was found in the cervical pessary group compared with that in the cervical cerclage group (RR =0.48, 95%CI : 0.35 to 0.67,P <0.00001). Sensitivity analyses did not significantly alter the results, suggesting that the results were stable (Figure 1-7).

3.3.7 Neonatal survival rate

Four studies were included for this analysis[12,13,15,16]. Due to statistical homogeneity across studies (P =0.68,I^2=0%), a fixed-effect model was applied. No significant difference was found in neonatal survival rate between the two groups (RR =1.70, 95%CI : 0.66 to 4.41, P =0.28) (Figure 1-8).

3.3.8 Neonatal birth weight

Four studies were included for this analysis[10,11,16,17]. Due to sufficient homogeneity across studies (P=0.74, I^2=0%), a fixed-effect model was used. No significant difference was found in neonatal birth weight between the two groups (MD =36.89, 95%CI: -72.54 to 146.32,P =0.51) (Figure 1-9).

3.3.9 Cesarean section rate

Four studies were included for this analysis[10,11,16,17]. Due to significant heterogeneity across studies (P =0.33, I^2=66%), a random-effect model was used. Meta-analysis did not find any significant difference in cesarean section rate between the two groups (RR =1.02, 95%CI : 0.72 to 1.44, P =0.93) (Figure 1-10).

3.4 Publication bias

A funnel plot was used to detect potential publication bias for the outcome of premature birth rate before 34 weeks. As pictorially shown in Figure 2, the funnel plot was symmetric on visual inspection, indicating a low risk of publication bias.

4. Discussion

Preterm birth is one of the most important determinants of perinatal and infant mortality and morbidity worldwide, which is among the most complex challenges to modern obstetrics. Spontaneous preterm birth is estimated to be responsible for roughly 28% of the world's 4 million annual neonatal deaths[18]. Decreasing the incidence of spontaneous preterm birth is critical to reduce perinatal and neonatal mortality and morbidity. The onset and delivery of preterm labor is similar to that of full term, but the exact mechanism remains unknown. Short cervix syndrome, also known as cervical shortening, is considered as a strong predictor of preterm birth[19]. For pregnant women with a prior history of preterm birth or shortened cervix, secondary prevention based on proper management of a short cervix has been shown to reduce the risk of preterm birth[19].

However, the published studies on the use of cervical pessary versus cervical cerclage to prevent short cervix-related preterm birth are limited by their small sample size, and these studies reported conflicting findings. There is a lack of meta-analysis comparing cervical pessary with cervical cerclage in the management of preterm birth associated with a short cervix. Therefore, this study systematically reviewed the published RCTs and non-RCTs on the efficacy and safety of cervical pessary versus cervical cerclage in preventing spontaneous preterm birth, in order to offer more effective options for pregnant women with a short cervix who are at a risk for preterm birth. Our results indicated that compared with cervical cerclage, use of a cervical pessary significantly decreased the incidence of PPROM and premature birth rate before 34 weeks. But other endpoints including premature birth rates before 28, 32 or 37 weeks, cesarean section rate as well as neonatal outcomes were similar between the two groups.

We acknowledge that this study has several limitations: 1) Only 2 non-blinded RCTs were included, which are subject to potential selection bias and measurement bias. 2) One study was conducted in twin pregnancies while others were performed in singleton pregnancies. 3) Seven of the included studies used Arabin cervical pessary, while other studies did not specify the type of cervical pessary used; four studies used McDonald cervical cerclage, two used McDonald or Shirodkar cerclage, one used Lyubimova technique, one used Lyubimova or Mammadaliyeva technique, while other studies did not mention the specific technique used for cervical cerclage. The use of variable pessary types or cerclage techniques may influence outcome data. 4) Few studies reported all of these outcome measures and the quality of included studies varied, which may affect the reliability of our findings. 5) Few studies reported the potential complications (e.g. vaginal drainage, infection, bleeding, intrauterine infection, neonatal complications) or economic parameters (e.g. length of hospital stay, cost) associated with cervical cerclage and cervical pessary. Only one study reported the endpoint of mean gestational weeks extended. And thus, it is not possible to analyze these outcomes in this study.

In conclusion, compared with transvaginal cervical cerclage, use of a cervical pessary may decrease the risks of PPROM and premature birth before 34 weeks. Given its advantages of easy-to-use and minimal damage, cervical pessary may become a useful preventive intervention that deserves widespread clinical application. However, due to the limitations in the available evidence, more high-quality, large-scale, multicenter studies are needed to further clarify its role in preterm birth prevention.

Author contributions

Shu Zhou designed the research study. Yana Liu and Zhiwei Xue performed the research and collected the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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