Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Comparing the Efficacy of Pessary as an Adjunctive Therapy after Cerclage, and Cerclage Alone in Prevention of Spontaneous Preterm Birth: A Randomized Controlled Trial

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Article Info

10.30699/jogcr.7.5.382

Received: 2021/09/22;
Accepted: 2022/01/29;
Published Online: 07 July 2022;

Use your device to scan and read the article online

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ABSTRACT

Background & Objective: The aim of this study was to evaluate the effectiveness of adjunctive pessary therapy after cerclage in increasing the gestational age (GA) to 37 weeks in women with cervical insufficiency (CI).

Materials & Methods: This randomized controlled trial (RCT) was conducted at the infertility department of Royan Institute, Tehran, Iran. A total of 170 singleton pregnant women aged 18-42 years old, diagnosed with CI by GA 14-24weeks, who had intact membrane with no signs of intrauterine infection, vaginal bleeding, or uterine contraction, were enrolled. Patients were randomized 1:1 to receive either cervical cerclage or pessary after cerclage. The primary outcome was spontaneous preterm birth (SPB) (<37weeks). The secondary outcomes were GA at the time of delivery, SPB (less than 34, 32 & 28 weeks), delivery method, neonatal outcomes, maternal adverse events, and maternal satisfaction with the intervention.

Results: The incidence of SPB (<37, 34, 32 & 28weeks), method of delivery, GA at time of delivery, and neonatal outcomes were not significantly different between the two groups. The incidence of vaginal bleeding (P=0.007) and pelvic pain (P=0.03) significantly was less in the intervention group. The mean score of satisfaction in the intervention group was significantly higher than the control group (P=0.01).

Conclusion: The placement of an adjunctive pessary for pregnant women with singleton pregnancy and CI, did not result in a lower rate of SPB (<37weeks) compared to cerclage alone. However, pregnancy complications after the intervention until delivery were less in these women, while the level of satisfaction was higher.

Keywords: Cervical insufficiency, Cerclage, Pessary, Preterm delivery, Adjunctive therapy

Introduction

Preterm labor is defined as delivery before the 37th week of pregnancy. The prevalence of preterm labor is 5-9% of pregnancies in developed countries **(1)** and 9.2% in Iran **(2)**. Prematurity is associated with increased mortality, disability, and developmental impairment **(3, 4)**. CI (a painless cervical dilatation in the second trimester of pregnancy) is seen in 1% of pregnancies **(5)** and is the responsible factor for 8% of recurrent miscarriages and 15-25% of pregnancy loss in the second trimester **(5, 6)**.

Cervical cerclage is a choice treatment for CI **(7)**. According to the American College of Obstetrics and Gynecology, in singleton pregnant women with a history of preterm labor (less than 34 weeks) and cervical length less than 25 mm (measured by transvaginal ultrasound before the 24th week), cervical cerclage was recommended. Cerclage is recommended in women without a previous history of preterm delivery based on an ultrasonographic diagnosis of asymptomatic cervical shortening. Emergency

cerclage must be done for patients with acute cervical shortening **(8)**.

Obstetricians prefer to use adjunctive therapy combined with cerclage surgery to increase GA and reduce neonatal complications. GA at birth, especially between 22-32 weeks, is related to mortality and neonatal complications. Infants born at 32-37 weeks also have increased rates of adverse outcomes. Rates of cognitive impairment and cerebral palsy at 5 years old also decrease with advancing GA at birth **(9)**. The rate of neonatal intensive care unit (NICU) hospitalization is 5% in infants born at 34 weeks, compared with 2% of infants born at 35 weeks, 1.1% at 36 weeks, 0.6% at 37 weeks, and 0.5% at 39 weeks **(10)**.

Adjunctive therapies that are used after cerclage include progesterone, tocolytics, antibiotics, bed rest, and pessary. Some of these agents, such as 17 alpha-hydroxyprogesterone **(11-13)**, and indomethacin **(14, 15)**, have already been studied. Some methods, such as bed rest and long-term antibiotics, may be harmful when used as adjunctive therapy after cerclage **(16-18)**.

The use of a pessary for preventing preterm delivery or loss of pregnancy was first published in 1959 by Cross **(19)**. A pessary used to treat CI is a silicone-shaped ring. It can be used in the clinic (without anesthesia) and is simply expelled at delivery time. This method is easy-to-use, cheap, and causes few side effects; the only side effect is increased vaginal discharge **(20)**. The pessary may be able to adjust the angle of the cervical canal anteriorly or posteriorly and reduce the pressure on the internal os, preventing premature rupture of the membranes. Furthermore, the pessary may prevent the fetus presenting part from moving downward, transfer the resulting forces from the fetal weight to the pubis or sacrum, press the internal os, and protect the mucus plug **(21)**.

The first RCT about pessary placement in CI was published in 2012, where 385 women between 18-22 weeks with a singleton pregnancy and a short cervical length < 25 mm, with routine second-trimester ultrasonography, were enrolled. The study showed that the use of a pessary reduces the rate of preterm labor before 34th weeks of gestation compared to the control group. Neonatal complications also decreased in the pessary group **(22)**. In another RCT, researchers showed that the use of a cervical pessary in women with singleton pregnancies without prior spontaneous preterm birth but with a transvaginal ultrasound cervical length of 25 mm or less significantly lowered preterm birth (<34 weeks) compared to the control group without pessary **(23)**. Recently, studies have been conducted in this regard in Iran. In a study, researchers showed that the insert of cervical pessary for pregnant women between 24 and 34 weeks of gestational age with signs of threatened preterm labor and cervix length shorter than 25 mm in the ultrasound examination significantly increased gestational age and improved neonatal outcomes **(24, 25)**. A study which was conducted in China had different results. In this RCT, 203 women with less than 25 mm cervical length in 20-24 weeks were analyzed. Delivery before 34 weeks was not significantly different between the pessary and control groups. This study was not strong, and analysis was performed before setting targets **(26)**.

Until now, no published observational studies or clinical trials reported the application of a vaginal pessary as an adjunct to cervical cerclage in comparison to cerclage alone. Only one retrospective study addressed this point. Based on their report, 15 women were treated with pessary in addition to cerclage, and 17 women were treated with cerclage alone. Both groups also received vaginal progesterone until 34 weeks. The researchers concluded that adjunctive pessary therapy allows delaying delivery in women treated with emergency cervical cerclage due to CI with bulging fetal membranes **(27)**. Therefore, we decided to evaluate the effectiveness of a pessary as adjunctive therapy after cerclage in increasing the GA to 37 weeks in women with singleton pregnancy and CI.

Methods

We adhered CONSORT guidelines in our study.

Study Design and Participants

This concurrent RCT was conducted from May 2018 to May 2020 at the infertility department of Royan Institute, Tehran, Iran. The Institutional Review Boards and the Ethics Committees of Royan Institute, Tehran, Iran, approved this study (Ethics approval No. IR.ACECR.ROYAN.REC.1395.81. date:2017-03-07). All procedures performed in studies involving human participants were in accordance with the ethical standards of Royan institute and the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Eligible women were those referred to the institution with a diagnosis of a short cervix. The inclusion criteria were having a singleton pregnancy, being 18-42 years old, being diagnosed with CI, GA 14-24 weeks, and having an intact membrane, with no signs of vaginal bleeding, uterine contraction, or intrauterine infection (maternal fever and leukocytosis, uterine tenderness, fetal tachycardia). Exclusion criteria were multiple pregnancies, uterine contractions, fatal structural abnormalities in the fetus, intrauterine infection, active vaginal bleeding, premature rupture of the membranes, and fetal demise.

Randomization and Intervention

After obtaining written informed agreement, subjects were randomly allocated to the intervention or control group in a 1:1 ratio. We used simple randomization and the Cards Shuffling method. Simple randomization is based on a single sequence of random assignments and is one of the most common methods for performing a randomization process **(28)**. Opaque envelopes contained cerclage or cerclage-pessary

cards, and they were sealed and marked with numbers from 1 to 170. This randomization was performed by the statistician colleague. A midwife outside of the research team allocated these women to two groups. This study was open-label since masking of intervention was not possible.

After randomization, patients were divided into two groups: the control group received cerclage surgical treatment. In contrast, for the intervention group, cerclage was performed, and then the pessary was used as an adjunctive method. Both groups were monitored until delivery and compared in terms of maternal and neonatal complications and delivery time. Detection of CI in women was carried out using either the obstetrical background (a history of more than three premature delivery or abortion in the second trimester) **(29)**, or ultrasound-based diagnosis (cervical length less than 25 mm on transvaginal ultrasound before 24 weeks) **(30)**. Vaginal ultrasound was used for those referred to the institution with a diagnosis of a short cervix. Cervical length cases less than 25 mm with or without funneling were selected for cerclage. At first, the demographic information and medical history questionnaire were completed. Then, the patients were examined by a perinatologist who also performed all interventions. At the time of randomization and prior to cerclage, vaginal swabs were performed for all women in both groups; If the results showed an infection, appropriate treatment was given. The McDonald's cervical cerclage surgical method was used for both groups. Seven to 14 days after the cerclage, a pessary (Hodge Folding) certified by American company manufacturing (cooper surgical) was inserted through the vagina for women in the intervention group. All participants were visited one week after the intervention and received routine prenatal care. Also, 200 mg/d vaginal progesterone was administered to all subjects after cerclage until 36 weeks. Women in both groups were asked about increased vaginal discharge, pelvic pain, and vaginal bleeding at each routine prenatal visit. If the mother complained of these symptoms, conservative and appropriate treatment by the perinatologist was performed. The pessary and cerclage were removed electively at 36-37 weeks in the perinatology clinic in Royan Institute or immediately upon the beginning of preterm labor by obstetricians in other hospitals. The data collection form was comprised of 3 parts that covered demographic information, information on recent pregnancies, and the outcomes. The last section of the third part was about the assessment of the satisfaction of the pregnant women with the intervention; participants were asked three questions: "Are you satisfied with your treatment?", "Would you recommend this treatment to others?" and "would you choose this treatment again?" The response options were: "not at all"; "to a low degree," and "to a great extent". The scores were between 0 and 6. Information about maternal satisfaction was collected at 36 weeks in a routine prenatal care visit or after delivery through phone calls.

Outcomes

The primary outcome was SPB before 37 weeks. Spontaneous beginning of preterm labor or preterm premature rupture of membranes were considered an SPB. Induction of preterm labor due to medical conditions (fetal or maternal) was not included in the primary outcome as the use of a cerclage cannot modify them. The secondary outcomes were GA at the time of delivery, SPB (less than 34, 32, and 28 weeks), the method of delivery, neonatal outcomes (birth weight, neonatal death, intrauterine fetal death, and NICU hospitalization), maternal adverse events (vaginal discharge, vaginal bleeding, and pelvic pain) and maternal satisfaction of the intervention. Maternity information such as time of delivery, method of delivery, and neonatal outcomes were collected and recorded through retrieval from hospital records.

Ethical Considerations

All eligible pregnant women entered the study after providing them with full explanations about the purpose of the study and obtaining written consent from them. The authors affirmed and supported the principle of the participant's right to privacy.

Sample Size Calculation

To determine the sample size, we used the statistical software G * Power version 1/3. The sample size was calculated using an independent t-test to compare the mean of the studied variables between the two groups with type I error of 0.05, type II error of 0.2 (power 0.8), and effect size 0.4 (average), 78 people in each group. Considering a sample loss of 10%, the sample size was 85 subjects in each group.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences; SPSS V.16.0 (SPSS Inc., Chicago, Ill., USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequencies (percentage). The normality of the variables was checked by the Kolmogorov-Smirnov test. Independent sample t-test and Chi-square test were used to evaluate the difference between cerclage and cerclage-pessary groups. The effect of pessary as an adjunctive therapy on the incidence of each outcome was calculated in 2 ways: either as the difference between groups in cumulative incidence of the outcome with 95% confidence intervals or as the unadjusted relative risk (RR) and its 95% confidence interval. Because RRs are easily interpreted, we calculated the incidence of outcomes by using an unadjusted RR. RRs were estimated using the Cox proportional hazards model. A P-value<0.05 was considered statistically significant.

Results

From May 2018 to May 2020, of the 283 women referred for CI, 170 women with singleton pregnancies between 14-24 weeks agreed to participate in the study, underwent randomization, and were registered and followed up. Of 170 enrolled women, 85 (50%) were randomized to the cervical-pessary group and 85 (50%) to the control group. Six women were excluded after randomization and did not receive any intervention: 3 in the cerclage-pessary group (declined to participate) and 3 in the cerclage group (declined to participate) (Figure.1). No participants in the intervention group requested the removal of the pessary due to severe pain or discomfort. Table 1 shows that there is no statistically significant difference between the two groups in terms of demographic and clinical characteristics. The mean GA at the time of randomization was 17.87 (SD, 1.62) weeks vs. 17.73 (SD, 1.60) weeks in the cerclage-pessary and control groups, respectively.

Primary Outcome

SPB at less than 37weeks of gestation occurred in 16 women (19.51%) in the cerclage-pessary group and 17 women (20.73%) in the control group. In the survival analysis to 37 weeks of gestation, the incidence of preterm birth was not significantly different between the cerclage-pessary and the control group (RR, 1; 95%CI, 0.161-6.202, Table 2).

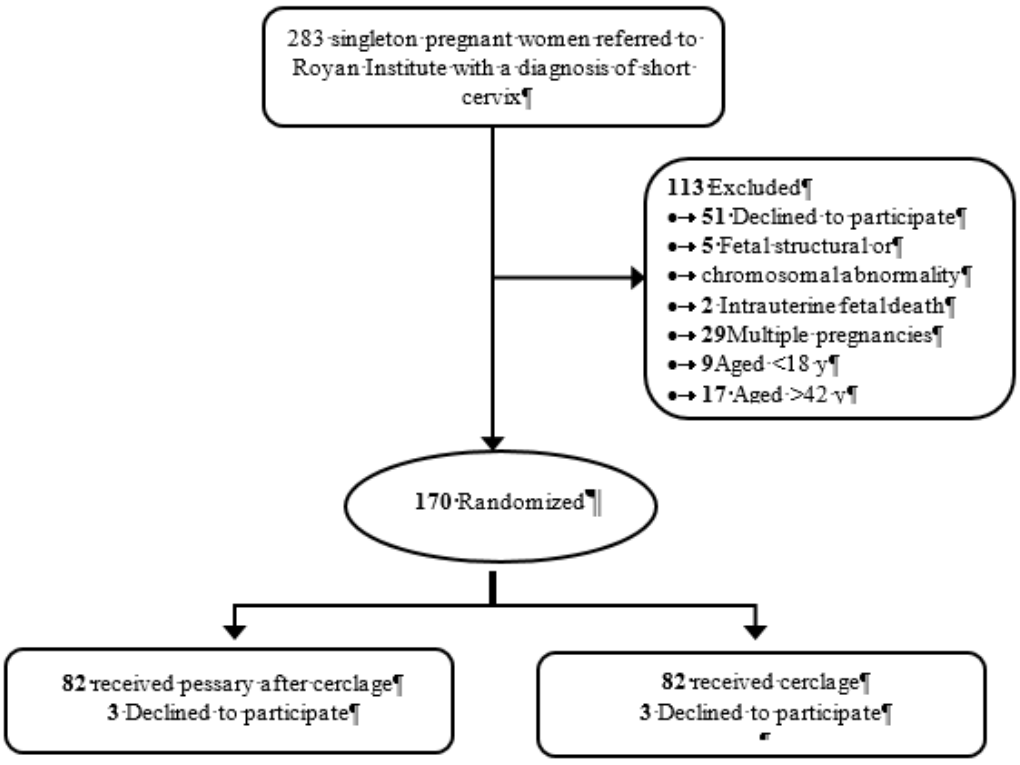

Figure 1. Flow chart of the population

Table 1. Demographic and clinical characteristics of the study groups

Characteristics	Cerclage-Pessary Group (n=82)	Control Group (n=82)	*P*
Age			
Age, mean (SD), y	31.44(5.01)	32.08(4.86)	0.407
18≤Age≤ 35 y, No. (%)	62(75.61)	58(70.73)	0.118
35<Age ≤42y, No. (%)	20(24.39)	24(29.27)	
Education			
Under diploma/Diploma	48(58.54)	43(52.44)	0.429
Academic	34(41.46)	39(47.56)	
Body mass index, mean (SD)[a]	26.51(3.66)	25.49(3.71)	0.071

Characteristics	Cerclage-Pessary Group (n=82)	Control Group (n=82)	*P*
Gravidity			
Primigravida, No. (%)	30(36.58)	34(41.46)	0.581
1<multigravida≤3, No. (%)	42(51.21)	37(45.12)	
Multigravida>3, No. (%)	10(12.19)	11(13.41)	
Parity			
Nulliparous, No. (%)	56(68.29)	54(65.85)	0.229
Multiparous=1, No. (%)	20(24.39)	26(31.70)	
1<multiparous≤3, No. (%)	5(6.10)	2(2.44)	
Multiparous>3, No. (%)	1(1.22)	0(0)	
Abortion			
Abortion=0, No. (%)	44(53.65)	46(56.10)	0.906
Abortion=1, No. (%)	25(30.48)	23(28.05)	
1<Abortion≤3, No. (%)	12(14.63)	12(14.63)	
Abortion>3, No. (%)	1(1.22)	1(1.22)	
Indication of Cerclage			
[b] Obstetrical background, No. (%)	1(1.22)	2(2.44)	0.946
[c] Ultrasound-based diagnosis, No. (%)	59(71.95)	56(68.29)	
[d] Both, No. (%)	22(26.83)	24(29.27)	
Prior gynecology surgery, No. (%)	34(41.46)	28(34.14)	0.616
Hysteroscopic Septoplasty, No. (%)	2(2.44)	0(0)	
Hysteroscopic Polypectomy, No (%)	7(8.53)	6(7.32)	
Laparotomy, No. (%)	1(1.22)	3(3.66)	
Diagnostic laparoscopy, No. (%)	6(7.32)	5(6.10)	
Dilation and curettage (D&C), No. (%)	18(21.95)	14(17.07)	
Prior cervical cerclage, No. (%)	7(8.53)	10(12.19)	0.452
Prior preterm delivery, No. (%)	18(21.95)	25(30.48)	0.30
Gestation age at randomization, Mean (SD), w	17.87(1.62)	17.73(1.60)	0.584
14≤GA≤16, w, No. (%)	19(23.17)	21(25.61)	0.900
17≤GA≤19, w, No. (%)	51(62.19)	50(60.98)	
20≤GA≤24, w, No. (%)	12(14.63)	11(13.41)	

[a] Calculated as weight in kilograms divided by height in meters squared.
[b] A history of more than three premature delivery or abortion in the second trimester
[c] Cervical length less than 25 mm on transvaginal ultrasound before 24 weeks
[d] History of premature delivery or abortion in the second trimester and cervical length less than 25 mm on transvaginal ultrasound before 24 weeks in this pregnancy.

Table 2. Primary and secondary outcomes in the cerclage-pessary and control groups

Outcomes	Cerclage-Pessary Group	Control Group	Between-Group Difference in Mean (95% CI)	Relative Risk (95% CI)	*P*
Primary Outcome					
SPB<37 w, No. (%)	16(19.51)	17(20.73)		1(0.161-6.202)	0.47
Secondary Outcomes					
GA at delivery, Mean (95% CI), w	37.35(35.2-39.5)	37.09(34.78-39.4)	0.26(-0.43-0.95)		0.44
SPB<34 w, No. (%)	5(6.09)	6(7.31)		1(0.006-156.83)	0.76
SPB<32 w, No. (%)	3(3.65)	3(3.65)		0.976(0.203-4.69)	0.648

Outcomes	Cerclage-Pessary Group	Control Group	Between-Group Difference in Mean (95% CI)	Relative Risk (95% CI)	*P*
SPB<28 w, No (%)	0(0)	2(2.43)		0(0-Na)	0.242
Method of delivery					
Spontaneous Vaginal delivery, No. (%)	16(19.51)	7(8.53)		2.2306(0.9690-5.1349)	0.05
Cesarean delivery, No. (%)	66(80.48)	75(91.46)		1.8(0.98-6.51)	0.31
Maternal Adverse Effects					
Vaginal discharge, No. (%)	9(10.97)	5(6.09)		0.76(0.30-1.90)	0.56
Pelvic Pain, No. (%)	6(7.31)	21(25.60)		1.73(1.04-2.87) [a]	0.03
Vaginal Bleeding, No. (%)	0(0%)	9(10.97)		2.68(1.31-5.46) [a]	0.007
Neonatal Outcomes					
Birth weight, mean (95% CI), g	2968.5(2412.48-3524.52)	2954.07(2349.31-3558.83)	14.42(-164.65-193.49)		0.87
NICU, No. (%)	13(15.85)	15(18.29)		1(0.32-3.06)	0.68
NICU (Days), mean (95% CI)	2.91(0-12)	2.42(0-9)	0.49(-2.04-3.03)		0.70
[b] Neonatal death, No. (%)	0	0	-	-	-
[c] Intrauterine fetal death, No. (%)	0	0	-	-	-
Maternal Satisfaction					
mean (95% CI) (Min-Max)	5.73(0-6)	5.25(0-6)	0.47(0.10-0.84)[a]		0.01

[a] Statistically significant. [b] death of a live-born infant within the first 28 days of life. [c] fetal death after 20 weeks of gestation.

Secondary Outcomes

The cervical pessary as adjunctive therapy after cerclage was associated with a lower rate of SPB at less than 28 and 34 weeks, longer GA at delivery, higher birth weight, higher vaginal deliveries, and a lower rate of admission to NICU compared to the cerclage alone, but these differences were not significant. There were no neonatal death and intrauterine fetal death in both groups.

Evaluation of maternal complications after randomization to delivery showed that the rate of vaginal bleeding and pelvic pain (at least once) in the intervention group was significantly lower compared to the control group. No women in the cerclage-pessary group but 9 women (10.97%) in the control group had vaginal bleeding after randomization. In the survival analysis, the incidence of vaginal bleeding in the cerclage-pessary group was significantly different from that of the control group (RR, 2.68; 95%CI 1.31-5.46, *P*=0.007). Six women (7.31%) in the cerclage-pessary group and 21 women (25.6%) in the control group had pelvic pain after randomization. In the survival analysis, the incidence of pelvic pain was significantly different between the two groups (RR, 1.73; 95%CI 1.04-2.87, *P*=0.03). The mean score of satisfaction in the intervention group (5.73) was significantly higher than that of the control group (5.25) (between-group difference, 0.47; 95%CI 0.10-0.84, *P*=0.01; Table 2).

Adverse Occurrences

No cases of maternal death or serious damages during insertion or removal of the pessary, were reported.

Discussion

Information about the use of a pessary as an adjunctive method in CI treatment is limited. The present study is the first RCT on the use of pessary as an adjunctive method after a cervical cerclage to prevent preterm delivery. Based on systematic reviews published in 2013 **(31)** and 2016 **(32)** and the available literature, no observational studies or RCTs reported vaginal pessary as an adjunct to standard cerclage compared to cerclage alone. The findings of our trial showed that among women with singleton pregnancies

who had a placement of a cervical pessary as an adjunctive method after routine cerclage, preterm delivery (< 37 weeks) was no less than those who received the cerclage alone.

Katarzyna *et al.* retrospectively analyzed the medical records of singleton pregnancy patients with CI treated with emergency cervical cerclage due to cervical dilatation of up to 4 cm accompanied by bulging of fetal membranes into the vagina, diagnosed in the second trimester of pregnancy. They found significantly higher GA at delivery **(26)**. Consistent with Katarzyna study, in our study, there were no significant differences between both groups regarding birth weight, NICU hospitalization rates, and the number of admission days in NICU. Secondary outcomes of the present study, namely, complications after the intervention and participants' satisfaction, were not assessed in the Katarzyna study. Their study was limited by its retrospective nature, lack of randomization, small sample size, and selected study group.

Pessary has the following advantages: low-cost, easy-to-use, non-invasive, and no requirement of surgery (operating room) and anesthesia **(33)**. In our study, pessary had an acceptable side-effect profile in most participants; No person requested to stop the use of a pessary before 36 weeks; after the intervention, the rate of vaginal bleeding and pelvic pain in the pessary group was significantly lower compared to the control group; full satisfaction with the intervention in the cerclage-pessary group (90.36%) was greater than that of the control group (74.07%).

There are few side effects reported following the use of a pessary. Goya *et al.* used a questionnaire to examine patients' adverse effects and the maternal satisfaction in two groups (pessary and expectant management); only 1 patient asked for pessary removal due to discomfort, and the mean pain score was 4 when a pessary was applied, and 7 (0-10) when it was removed. Also, 95% of pregnant women would recommend the vaginal pessary to others **(22)**. Arabin *et al.* showed that all patients who were treated with a pessary and delivered at their center had a positive opinion about the treatment; one patient was indifferent, but all others would undergo the same treatment in a future pregnancy or recommend it to a friend, there might be some increased of vaginal discharge **(33)**.

Strengths and Limitations

The study's strengths are: first, being an RCT with central randomization and the recruitment of the anticipated number of patients with approximately complete follow-up; second, no changes were made to the protocol after initiation of the trial.

This study has two limitations. First, the single-center nature of the trial raises the question of the external generalizability of the findings. Second, the unavoidable open-label nature of the trial could have affected medical decision-making.

Conclusion

In conclusion, this RCT showed that the placement of an adjunctive pessary for pregnant women with singleton pregnancy and a CI at 14-24 weeks did not result in a lower rate of preterm delivery before 37 weeks than cerclage alone. However, pregnancy complications after the intervention until delivery were less in these women, while the level of satisfaction was higher. The use of a pessary is non-invasive and inexpensive, so its use could be considered for pregnant women who need a cerclage. Further studies are needed to determine the role of pessary as an adjunct therapy in CI treatment.

Acknowledgments

The authors would like to thank patients for their invaluable contributions to this research performance.

Funding

No financial support has been granted.

Author's Contributions

MMoshfeghi, MAF, and MMohammadi contributed to the conception and design of the study. MMoshfeghi, MAF, KRK, and ME contributed to the literature search, patient selection, data collection, and interpretation of data. MAF wrote the first version of the manuscript. MMoshfeghi, KRK and ME revised the manuscript. The statistical analysis of the data was proposed by MMohammadi. All authors read and approved the final manuscript.

Conflict of Interest

The authors declared no conflict of interests.

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How to Cite This Article:

Moshfeghi M, Arjmandifar M, Mohammadi M, Eftekhari M, Rezaie Keikhaie KH. Comparing the Efficacy of Pessary as an Adjunctive Therapy after Cerclage, and Cerclage Alone in Prevention of Spontaneous Preterm Birth: A Randomized Controlled Trial. J Obstet Gynecol Cancer Res. 2022; 7(5):382-90.

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