Comparing Efficacy of Cerclage and Adjunctive Therapy (Cerclage & Pessary) in Prevention of Preterm Birth in Pregnant Women with Cervical Insufficiency: A Randomized Clinical Trial.

Mitra Arjmandifar
Department of reproductive health, school of nursing midwifery,Tehran University of Medical Sciences
Maryam Moshfeghi (Moshfeghimaryam@royan-rc.ac.ir)
Royan Institute https://orcid.org/0000-0003-4870-5475
Maryam Mohammadi
faculty of paramedicine sciences, shahid beheshti university of medical scienses
Mahya Eftekhari
Shahid Beheshti University of Medical Sciences: Shaheed school of medicine,shahid Beheshti University of Medical Sciences

Research article

Keywords: Cervical insufficiency, Cerclage, Pessary, Pregnant women, Preterm delivery, Satisfaction

Posted Date: September 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-80050/v1

Abstract

Background: Cervical insufficiency is the responsible factor for 15-25% of pregnancy loss in the second trimester. Midwifery specialists sometimes prefer to use adjunctive therapy in combination with cerclage surgery for management of cervical insufficiency. The aim of this study was to evaluate the effectiveness of adjunctive pessary therapy after cerclage in improving perinatal and neonatal outcome and increasing satisfaction in women with cervical insufficiency.

Methods: This concurrent randomized clinical trial was conducted at the infertility department of Royan Institute, Tehran, Iran from May 2018 to May 2020. In this trial, 170 singleton pregnant women, diagnosed with cervical insufficiency, of gestational age 14 to 26 weeks, were enrolled. Patients were randomized 1:1 to receive either cervical cerclage or pessary after cerclage. The primary outcomes were gestational age at the time of delivery and the percentage of preterm labor (<37 weeks). The secondary outcomes were the method of delivery, neonatal outcomes, maternal adverse events and maternal satisfaction of interventions.

Results: Preterm birth before 37 weeks of gestation occurred in 16 women (19.3%) in the pessary group and 17 women (21%) in the control group (between-group difference, 1.11%; 95%CI 0.518–2.388%). In the survival analysis to 37 WK of gestation, the incidence of preterm birth was not significantly different between the two groups (Relative Risk (RR), 1; 95%CI, 0.161-6.202). Based on survival analysis, the incidence of vaginal bleeding and pelvic pain significantly differed between the two groups (RR, 2.68; 95%CI (1.31-5.46)) and (RR, 1.73; 95%CI (1.04-2.87), respectively. The mean score of satisfaction in the intervention group (5.73) was significantly higher than the control group (5.25), (between-group difference, 0.47; 95%CI (0.10-0.84).

Conclusions: The placement of an adjunctive pessary for pregnant women with singleton pregnancy and a cervical insufficiency, did not result in a lower rate of preterm delivery before 37 weeks of gestation compared to cerclage alone. However, the complications of pregnancy after the intervention until delivery, were less in these women, while the level of satisfaction was higher.

Trial registration: Iranian Registry of Clinical Trials (IRCT20180302038914N1), May 5,2018.

Background

Preterm labor is defined as delivery before the 37th week of pregnancy. The prevalence of preterm labor is 5–12% of pregnancies [1, 2]. Prematurity is associated with increased mortality, disability and developmental impairment [3, 4]. Cervical insufficiency is a painless cervical dilatation in the second trimester of pregnancy [5], is seen in 0.05 to 1% of pregnancies and is the responsible factor for 15–25% of pregnancy loss in the second trimester [6, 7].

Cervical cerclage is a surgical technique that mechanically closes the cervical canal [8]. The usefulness of cerclage was shown by a meta-analysis of 5 randomized clinical trials including 504 women with 250

cerclage [9]. In this study, in women with singleton pregnancy, a history of preterm delivery and ultrasound diagnosis of cervical insufficiency, cerclage reduced the rate of preterm labor (< 37 weeks of pregnancy) by up to 30% and decreased morbidity and mortality by 36%. According to the American College of Obstetrics and Gynecology (2014), in singleton pregnant women with a history of preterm labor (less than 34 weeks of gestation) and cervical length less than 25 mm (measured by ultrasound before the 24th week of gestation), cervical cerclage was recommended. In people without a previous history of preterm delivery, cerclage depends on the time of ultrasonographic diagnosis of cervical asymptomatic shortening. Patients with acute cervical failure (painless dilatation and effacement) emergency cerclage must be done [10].

The use of a pessary for preventing preterm delivery or loss of pregnancy, was first published in 1959 by Cross [11]. A pessary used for the treatment of cervical insufficiency is a silicone-shaped ring. It can be used in the clinic (without anesthesia) and is simply expelled at the time of delivery. This method is easy-to-use, cheap and causes little side effects; the only side effect is increased vaginal discharge [12]. Pessary changes the tendency of the cervical canal to the front in the vaginal angle. It relieves the direct pressure on the internal cervical OS by distributing the weight of the pregnant uterus on the vaginal floor, retro symphyseal osteo-muscular structures, and Douglas cavity; so, it may prevent premature rupture of the membranes. Furthermore, it blocks the fetal head from descending towards and pressing the internal steam and protects the mucus plug [13]. In a pilot study (without randomization) that was conducted by Arabin et al in 2003, 12 singleton pregnant women with high risk of pregnancy (i.e. with a history of preterm labor, pre-term labor symptoms in the recent pregnancy or cervical length of 15 mm or less) between 22–24 weeks of pregnancy, were offered treatment with an Arabin pessary. The researchers performed a retrospective matched-pair analysis with 12 controls selected from the database with a cervical length < 10th percentile. In pregnancies treated with the pessary, there were no cases of spontaneous preterm birth, compared with the controls with a 25% delivery before 32 weeks [14]. The first randomized clinical trial (RCT) about pessary placement in cervical insufficiency was published by Goya et al in 2012, where approximately 12,000 women between 18 and 22 weeks, were screened with routine second-trimester ultrasonography; researchers randomized 385 women with a singleton pregnancy and a short cervical length < 25 mm for a pessary (n = 192) or expectant management (n = 193) delivery before 34 weeks. Results showed a significant reduction in the pessary group (6% compared to 27% in the control group) with odds ratio, 0.18 95% CI, 0.08–0.37. Neonatal complications also decreased in the pessary group [15].

A study which was conducted in China by Hui et al., had different results. In this RCT, 4400 women were screened, 203 people with cervical length less than 25 mm in 20–24 weeks of pregnancy were found. 108 women with a singleton pregnancy (53 pessary / 55 control) were followed. Delivery before 34 weeks of gestation was not significantly different between the pessary group (9.4%) and control group (5.5%). This study was poor and analysis was carried out prior to setting targets [16].

Midwifery specialists sometimes prefer to use adjunctive therapy in combination with cerclage surgery to increase gestational age and reduce neonatal complications. Adjunctive therapies that are used after

cerclage include progesterone, secondary cerclage, tocolytics, antibiotics, bed rest and pessary. Some of these agents such as 17 alpha-hydroxyprogesterone [17] and indomethacin [18, 19] have already been studied. Other methods such as cervical pessary, rest on the bed and use of antibiotics, were not enough studied. Treatments such as pessary [12–16, 20, 21], and vaginal progesterone [22, 23] do not seem to be harmful, but scarce studies recommended them as an adjunctive therapy after cerclage. Some methods, such as bed rest and long-term antibiotics, may be potentially harmful when used as adjunctive therapy after cerclage [24–26].

Until now, no published observational studies or clinical trials reported the application of vaginal pessary as an adjunct to cervical cerclage in comparison to cerclage alone. Only one retrospective study addressed this point (Katarzyna et al., 2015). In this study, the researchers concluded that adjunctive pessary therapy allows delaying delivery in women treated with emergency cervical cerclage due to cervical insufficiency with bulging fetal membranes [27].

The aim of this study was to evaluate the effectiveness of adjunctive pessary therapy after cerclage in improving perinatal and neonatal outcome, increasing the gestational age to 37 weeks and enhancing patient satisfaction in women with cervical insufficiency.

Methods

Study design and participants

This concurrent randomized clinical trial was conducted at the infertility department of Royan Institute, Tehran, Iran, from May 2018 to May 2020. Eligible women were chosen among those referred to the institution for treatment of cervical insufficiency. The inclusion criteria were having singleton pregnancy, being 18 to 42 years old, being diagnosed with cervical insufficiency, gestational age 14 to 26 weeks, and having an intact membrane, with no signs of vaginal bleeding, uterine contraction or intrauterine infection (maternal fever, maternal leukocytosis, uterine tenderness, fetal tachycardia). Exclusion criteria were multiple pregnancies, cervical dilatation more than 4 cm at the time of randomization, uterine contractions at the time of randomization, fatal structural abnormality in the fetus, or contraindication of cerclage.

We adhered CONSORT guidelines in our study.

Randomization and intervention

After obtaining written informed agreement from women, subjects were randomly allocated to the intervention group or the control group in a 1:1 ratio. We used simple randomization and Cards or Envelops 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 were filled with cards indicating the allocation to cerclage or pessary arms and sealed. This

study was open label since masking of intervention was not possible, however, data analysts were blinded to allocations.

After simple randomization, patients are divided into two groups: One group (control group) received cerclage surgical treatment, while for the other group (intervention group), cerclage was performed and then the pessary was used as an adjunctive method. The two groups were monitored until delivery and compared in terms of maternal and neonatal complications and delivery time. Detection of cervical insufficiency in women was carried out using either 1-the background (more than 3 times premature delivery or abortion in the second trimester), 2-physical examination (a dilatation greater than or equal to 1 cm or prolapse of the membranes) or 3-ultrasonography diagnosis (cervical length less than 25 mm before 24 weeks in singleton pregnancy with a history of premature labor)[29]. At first, the demographic information and medical history questionnaire were completed. Then, the patients were examined by a perinatologist who also performed all interventions. 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 from week 16 to 36 of pregnancy. At each routine prenatal visit, women in both groups were asked about increased vaginal discharge, pelvic pain and vaginal bleeding. Women reporting increased vaginal discharge were examined by the perinatalogist for signs of infection and if needed, antibiotic therapy was given. The cervical pessary was removed by the perinatologist at the time of delivery. The data collection form was comprised of 3 sections that covered demographic information, information on recent pregnancy and the outcomes. The questionnaire concerning outcomes section of this form was about satisfaction of 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 chose this treatment again”? The response options were: (i) not at all; (ii) to a low degree; and (iii) to a great extent. The scores were between 0 and 6.

Outcomes

The primary outcomes were gestational age at the time of delivery and the percentage of preterm labor (before 37 weeks of gestation). The secondary outcomes were the method of delivery, neonatal outcomes (birth weight, and neonatal intensive care unit hospitalization), maternal adverse events (vaginal discharge, vaginal bleeding and pelvic pain) and maternal satisfaction of interventions. The delivery information was gathered through phone calls and recorded.

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 supports the

principle of the participant's right to privacy. The study approval number was IR.ACECR.ROYAN.REC.1395.81. approved by Ethics Committee of Royan Institute, Tehran, Iran. The trial was registered in the Iranian Registry of Clinical Trials (IRCT20180302038914N1).

Sample size calculation

The sample size was calculated using the statistical software G * Power version 1/3. Due to the fact that the main purpose of the design was to compare the mean of the studied variables between the two groups (cerclage and pessary), independent t-test was used. To determine the sample size, the error of the first type was considered 0.05 and the error of the second type was considered 0.2 (power of 0.8); Also, according to previous research and the researchers' expectation of practical (or clinical) difference, the size of the effect size was considered 0.4 (average). According to the above information, the sample size was calculated 78 people. To compensate for data loss, we considered a 10% larger sample size (i.e. 85 subjects in each group).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences; SPSS V.22.0 for Windows (IBM SPSS V.22.0.0). Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as frequencies (percentage). The normality of the variables was checked by Kolmogorov-Smirnov test. Independent sample t-test and chi square test was used to evaluate the difference between cerclage and pessary groups. The primary analysis was an intention-to-treat comparison of the treatment allocated at randomization. The effect of pessary use on the cumulative incidence of each outcome was calculated in 2 ways: either as the difference between treatment groups in cumulative incidence of the outcome with 95%confidence intervals or as the unadjusted relative risk and its 95% confidence interval. Because relative hazards are easily interpreted, we decided to calculate the incidence of the primary outcome by using an unadjusted relative risk. Hazard ratios were estimated using the Cox proportional hazards model. No temporary analyses were planned. No adjustment for multiple comparisons was made, so, the findings of the secondary outcomes should be considered exploratory. A P-value < 0.05 was considered statistically significant.

Results

From July 2016 to August 2019, of the 485 women referred for cervical insufficiency, 170 women with singleton pregnancies between 14 and 26 weeks of gestation agreed to participate in the study, underwent randomization, and they 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 lost to follow-up: 2 in the pessary group (declined to participate) and 4 in the cerclage group (2 intrauterine fetal death and 2 missed abortion)

(Fig. 1). No participant in the intervention group had the pessary removed by request or for severe pain or discomfort.

Table 1 shows the demographic and clinical characteristics of each group. There were 83 women (50.6%) in the pessary group and 81 (49.4%) in the control group and they received vaginal progesterone. The mean gestational age at randomization was 17.09 (SD, 2.2) weeks vs 16.96 (SD, 2.2) weeks in the pessary and control groups, respectively.

Primary Outcome

Preterm birth at less than 37weeks of gestation occurred in 16 women (19.3%) in the pessary group and 17 women (21%) in the control group (between-group difference, 1.11%; 95%CI 0.518 − 2.388%, Table 2). In the survival analysis to 37 weeks of gestation, the incidence of preterm birth was not significantly different between the pessary and the control group (RR, 1; 95%CI, 0.161–6.202, Table 2).

Secondary Outcomes

The cervical pessary as an adjunctive therapy after cerclage was associated with lower rate of spontaneous preterm birth at less than 37weeks of gestation, longer gestational age at delivery, higher birth weight, and lower rate of admission to a neonatal intensive care unit compared to the cerclage alone, but these differences were not significant.

The number of vaginal delivery was higher in the pessary group 16(19.28%) than the cerclage group 7(8.65%), (between-group difference, 0.1; 95%CI -0.01-0.21). In the survival analysis, the incidence of vaginal delivery was different between the two groups (RR, 2.23; 95%CI 0.96–5.13, $P = 0.05$). If the sample size was higher, this difference would have been significant.

Evaluation of maternal complications showed that the rate of vaginal bleeding and pelvic pain in the intervention group was significantly lower compared to the control group. No women in the pessary group but 9 women (11.1%) in the control group had vaginal bleeding after randomization (between-group difference, 1.12; 95%CI 1.04–1.21,). In the survival analysis, the incidence of vaginal bleeding in the 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 (7.2%) in the pessary group and 21 women (25.9%) in the control group had pelvic pain after randomization (between-group difference, 4.5; 95%CI 1.70-11.82). 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 treatment of cervical insufficiency 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[30] and 2016[31] and the available literature, no observational studies or RCTs reported vaginal pessary as an adjunct to standard cerclage in comparison 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 of gestation) was no less than those received the cerclage alone.

Katarzyna et al. retrospectively analyzed the medical records of singleton pregnancy patients with cervical insufficiency treated with emergency cervical cerclage (ECC) 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. 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 week 34. They found a significantly greater gestational age at delivery, and a longer period between cerclage insertion and delivery following the use of adjunct pessary [27]. Consistent with Katarzyna et al study, in our study, there were no significant differences between the two groups regarding birth weight, NICU hospitalization rates, the number of admission days in NICU and vaginal delivery, although the difference in the rate of normal delivery between the two groups was greater in our study. Secondary outcomes of the present study namely, complications after the intervention and participants satisfactions were not assessed in the Katarzyna et al. study. The Katarzyna et al. study was the first report that evaluated the impact of adjunctive pessary therapy on perinatal outcomes in women with ECC. This study was limited by its retrospective nature, lack of randomization, a small sample size, and selected study group.

Pessary has the following advantages: low-cost, easy-to-use, non-invasive and no requirement of surgery and anesthesia [14]. In our study, pessary as an adjunctive method after cerclage had an acceptable side-effect profile in most participants; No person requested to stop the use of pessary before 34 weeks of gestation; 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 pessary group (90.36%) was greater than that of the control group (74.07%).

There are few side effects reported following the use of 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 (0–10) when a pessary was applied and 7 (0–10) when it was removed. Also, 95% of pregnant women would recommend the vaginal pessary to other people [15]. Arabin et al. showed that all patients who were treated 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 [14]. In another study, 200 pregnant women

treated with pessary were compared with women with normal pregnancies, for infections and pregnancy complications; there was no higher infection morbidity in pessary-treated subjects compared to the control group [32].

The strengths of the study are: first, being an RCT with central randomization and 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; and third, blinding of the data analysts.

This study has several limitations. First, since the study was conducted at an infertility center, it may have influenced the decision to undergo cerclage surgery (overdiagnosis of cervical insufficiency). Second, the single-center nature of the trial raises the question of the external generalizability of the findings. Third, the unavoidable open-label nature of the trial could have affected medical decision making.

Conclusions

In conclusion, this randomized trial showed that the placement of an adjunctive pessary for pregnant women with singleton pregnancy and a cervical insufficiency at 20 to 24 weeks of gestation, did not result in a lower rate of preterm delivery before 37 weeks of gestation than cerclage alone. However, the complications of pregnancy after the intervention until delivery, were less in these women, while the level of satisfaction was higher. Further studies are needed to determine the role of pessary as an adjunct therapy in the treatment of cervical insufficiency.

Abbreviations

RR: Relative Risk; CI: Confidence Interval; NICU: Neonatal Intensive Care Unit; ANOVA: Analysis of variance; ECC: emergency cervical cerclage; WK: Weeks; SD: standard deviation; RCT: Randomized Clinical Trial.

Declarations

Ethics approval and consent to participate

All study procedures were performed in accordance with the ethical standards of Royan Institute ethics committees and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval was received (date: 2017-3-7, approval No. IR.ACECR.ROYAN.REC.1395.81. and date: 2018-2-5, approval No. IRCT20180302038914N1). Informed written consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors announce that they have no competing interests.

Funding

No financial support has been granted.

Authors' contributions

MMoshfeghi: designing the research. MMoshfeghi, MA and ME contributed in patient selection, data collection, interpretation of data and manuscript editing. MA wrote the manuscript. M Mohammadi helped in the analysis of the data. All authors read and approved the final manuscript.

Acknowledgments

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

References

1. Goldenberg R, Culhane J, Iams J, Romero R. Epidemiology and causes of preterm birth Lancet 371: 75–84. Find this article online. 2008.
2. SCPE EPPw, EUROCAT. European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010. Euro-Peristat Paris; 2013.
3. Hille ET, Weisglas-Kuperus N, Van Goudoever J, Jacobusse GW, Ens-Dokkum MH, de Groot L, et al. Functional outcomes and participation in young adulthood for very preterm and very low birth weight infants: the Dutch Project on Preterm and Small for Gestational Age Infants at 19 years of age. Pediatrics. 2007;120(3):e587-e95.
4. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. The Lancet. 2012;379(9814):445-52.
5. Harger JH. Comparison of success and morbidity in cervical cerclage procedures. Obstetrics and gynecology. 1980;56(5):543-8.
6. Debbs RH, Chen J. Contemporary use of cerclage in pregnancy. Clinical obstetrics and gynecology. 2009;52(4):597-610.
7. Park JC, Kim DJ, Kwak-kim J. Upregulated amniotic fluid cytokines and chemokines in emergency cerclage with protruding membranes. Am J Reprod Immunol. 2011;66(4):310-9.
8. Berghella V, Szychowski JM, Owen J, Hankins G, Iams JD, Sheffield JS, et al. Suture type and ultrasound-indicated cerclage efficacy. J Matern Fetal Neonatal Med. 2012;25(11):2287-90.

9. Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. Obstetrics & Gynecology. 2011;117(3):663-71.
10. Obstetricians ACo, Gynecologists. ACOG practice bulletin No. 142: cerclage for the management of cervical insufficiency. Obstetrics and gynecology. 2014;123(2 Pt 1):372.
11. Cross R. Treatment of habitual abortion due to cervical incompetence. The Lancet. 1959;274(7094):127.
12. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. Cochrane Database of Systematic Reviews. 2013(5).
13. Arabin B, Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. Ultrasound in obstetrics & gynecology. 2013;42(4):390-9.
14. Arabin B, Halbesma JR, Vork F, Hübener M, van Eyck J. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? Journal of perinatal medicine. 2003;31(2):122-33.
15. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. The Lancet. 2012;379(9828):1800-6.
16. Hui SYA, Chor CM, Lau TK, Lao TT, Leung TY. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. Am J Perinatol. 2013;30(04):283-8.
17. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. New England Journal of Medicine. 2003;348(24):2379-85.
18. Visintine J, Airoldi J, Berghella V. Indomethacin administration at the time of ultrasound-indicated cerclage: is there an association with a reduction in spontaneous preterm birth? American journal of obstetrics and gynecology. 2008;198(6):643. e1-. e3.
19. Berghella V, Prasertcharoensuk W, Cotter A, Rasanen J, Mittal S, Chaithongwongwatthana S, et al. Does indomethacin prevent preterm birth in women with cervical dilatation in the second trimester? Am J Perinatol. 2009;26(01):013-9.
20. Sieroszewski P, Jasiński A, Perenc M, Banach R, Oszukowski P. The Arabin pessary for the treatment of threatened mid-trimester miscarriage or premature labour and miscarriage: a case series. J Matern Fetal Neonatal Med. 2009;22(6):469-72.
21. Alfirevic Z, Owen J, Carreras Moratonas E, Sharp A, Szychowski J, Goya M. Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. Ultrasound in obstetrics & gynecology. 2013;41(2):146-51.
22. E B Fonseca EC, M Singh, KH Nicolaides. Progesterone and the risk of preterm birth in women with a short cervix. The New England Journal of Medicine. 2007;5:462-69.

23. Hassan S, Romero R, Vidyadhari D, Fusey S, Baxter J, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011;38(1):18-31.
24. King JF, Flenady V, Murray L. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Cochrane Database of Systematic Reviews. 2002(4).
25. Kovacevich GJ, Gaich SA, Lavin JP, Hopkins MP, Crane SS, Stewart J, et al. The prevalence of thromboembolic events among women with extended bed rest prescribed as part of the treatment for premature labor or preterm premature rupture of membranes. Am J Obstet Gynecol. 2000;182(5):1089-92.
26. Maloni JA. Antepartum bed rest for pregnancy complications: efficacy and safety for preventing preterm birth. Biol Res Nurs. 2010;12(2):106-24.
27. Kosinska-Kaczynska K, Bomba-Opon D, Zygula A, Kaczynski B, Wegrzyn P, Wielgos M. Adjunctive pessary therapy after emergency cervical cerclage for cervical insufficiency with protruding fetal membranes in the second trimester of pregnancy: a novel modification of treatment. Biomed Res Int. 2015;2015.
28. Altman DG, Bland JM. Treatment allocation in controlled trials: why randomise? Bmj. 1999;318(7192):1209-.
29. Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore T, Greene MF. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice E-Book: Expert Consult Premium Edition-Enhanced Online Features: Elsevier Health Sciences; 2013.
30. DeFranco EA, Valent AM, Newman T, Regan J, Smith J, Muglia LJ. Adjunctive therapies to cerclage for the prevention of preterm birth: a systematic review. Obstet Gynecol Int. 2013;2013.
31. Timofeev J. Use of Cervical Pessary in the Management of Cervical Insufficiency. Clinical obstetrics and gynecology. 2016;59(2):311-9.
32. A. Jorde KK, B.Hamann, H. Pockrandt. Detection of changes of the vaginal flora due to supporting pessary treatment during pregnancy. Zentralbl Gynakol. 1983;105:855-62.

Tables

Table 1.
Participant Characteristics

Characteristics	Pessary Group (n = 83)	Control Group (n = 81)	*P* value
Age, mean (SD), y	31.44(5.01)	32.08(4.86)	0.407
Education			
Under diploma/ Diploma	51(61.4)	44(54.3)	0.429
Academic	32(38.6)	37(45.7)	
Body mass index, mean (SD)[a]	26.51(3.66)	25.49(3.71)	0.07
Nulliparous, No. (%)	29(34.9)	36(44.4)	0.26
Parous, No. (%)	12(20)	13(22)	0.48
Prior cervical cerclage, No. (%)	7(8.4)	10(12.3)	0.41
Prior preterm delivery, No. (%)	18(21.7)	25(30.9)	0.30
Gestation age at randomization, mean (SD), w	17.09(2.23)	16.7(2.18)	0.45

[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2.

Primary and secondary outcomes in the pessary and control groups

Outcomes	Pessary Group (n = 83)	Control Group (n = 81)	Between-Group Difference in % or Mean (95% CI)	Relative Risk (95% CI)	*P* Value
Primary Outcome					
preterm birth <37 w, No. (%)	16(19.3)	17(21.0)	1.11(0.518-2.388)	1(0.161-6.202)	0.47
Secondary Outcomes					
Gestational age 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
preterm birth <34 w, No. (%)	5(6)	6(7.4)	6.9(6.07-7.80)	1(0.006-156.83)	0.76
Vaginal delivery, No. (%)	16(19.28)	7(8.65)	0.1(-0.01-0.21)	2.2306(0.9690-5.1349)	0.05
Maternal Adverse Effects					
Vaginal discharge, No. (%)	9(10.84)	5(6.17)	0.54(0.17-1.70)	0.76(0.30-1.90)	0.56
Pelvic Pain, No. (%)	6(7.22)	21(25.9)	4.5(1.70-11.82)	1.73(1.04-2.87)	0.03
Vaginal Bleeding, No. (%)	0(0%)	9(11.11)	1.12(1.04-1.21)	2.68(1.31-5.46)	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

Outcomes	Pessary Group (n = 83)	Control Group (n = 81)	Between-Group Difference in % or Mean (95% CI)	Relative Risk (95% CI)	*P* Value
Neonatal intensive care unit, No. (%)	13(15.66)	15(18.51)	1.22(0.54-2.76)	1(0.32-3.06)	0.68
Neonatal intensive care unit(Days), mean (95% CI)	2.91(0-12)	2.42(0-9)	0.49(-2.04-3.03)		0.7
Maternal Satisfaction					
mean (95% CI) (Min-Max)	5.73(0-6)	5.25(0-6)	0.47(0.10-0.84)		0.01

Figures

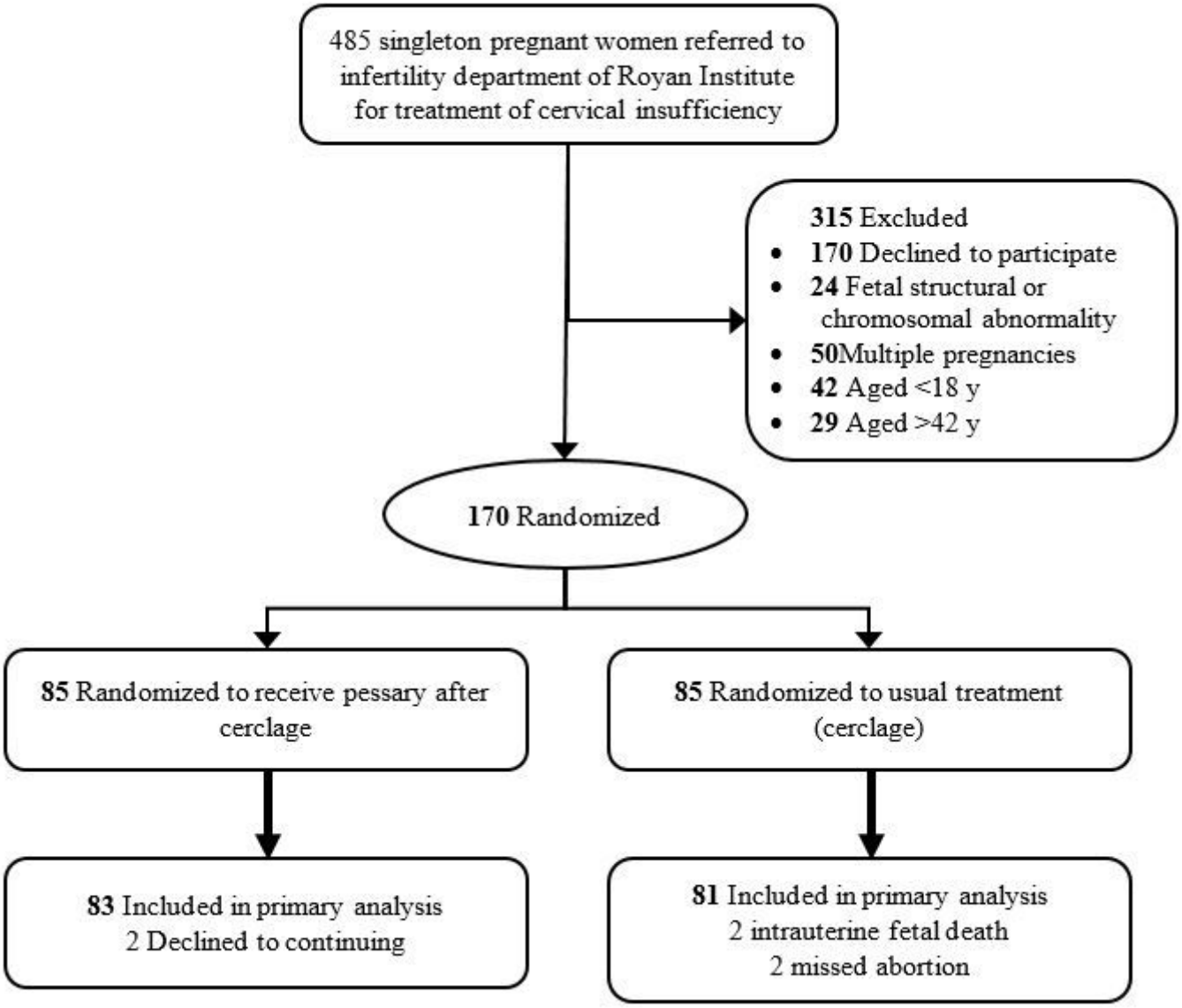

Figure 1

Flow chart of the study population

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc