Effect of cervical pessary on pregnancy outcome in patients with twin pregnancies: a systematic review and meta-analysis

Yue Wang[1], Jiaxing Wu[2], Di Ma[1], and mingli Huang[1]

[1]First Affiliated Hospital of Harbin Medical University
[2]Shanghai Jiaotong University School of Medicine Xinhua Hospital

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Abstract

Conclusion The cervical pessary can extend the gestational week of short-cervix twin pregnancy without clinical symptoms, reduce the premature birth rate before 34 weeks of gestation, improve pregnancy outcome, reduce neonatal mortality, reduce necrotizing enterocolitis incidence, neonatal sepsis incidence, and improve neonatal outcome. For patients with a cervical length less than 38mm, a cervical pessary can be performed to extend the gestational week. For patients with a cervical length less than 25mm, a cervical pessary can effectively prolong the gestational age and improve the maternal and fetal outcomes. The cervical pessary is safe for patients with twin pregnancies. Suggest that twin-preganct-patients with CL<38mm should consider take cervical pessary in advance. In terms of long-term efficacy, there is no evidence of cervical support placement on the long-term maternal prognosis. In terms of economic benefits, cervical support is better than vaginal progesterone, but this conclusion still needs more research to prov

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Wang yue[1],Wu jiaxing[2], Ma di[3] Huang mingli[*],[1]Department of Obstetrics and Gynecology, First Affiliated Hospital of Harbin Medical University Harbin, Heilongjiang, CN[2]Department of Obstetrics and Gynecology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Shanghai,[3]Department of Obstetrics and Gynecology, First Affiliated Hospital of Harbin Medical University Harbin, Heilongjiang, CN,China.Medical University,Harbin China.

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[Abstract]

Background Preterm birth is the main cause of child death under 5years of age. The incidence of twin pregnancies is less than 2%, but the incidence of preterm delivery is 50% and the risk of neonatal death is 5 times higher in twin pregnancies than in singleton pregnancies. However, there is still no consensus on the effect of cervical pessary on preventing preterm delivery, prolonging the pregnancy cycle, and improving maternal and infant outcomes in patients with twin pregnancies.

Objectives To explore the effect of cervical pessary on the pregnancy outcome of unselected twin pregnancy patients.

Search Strategy Up to Jan 2022, researchers searched PubMed, EMBASE, COCHRANE, Web of Science, Wanfang, Weipu, and CNKI databases for research.

Study eligibility criteria Randomized controlled trials that compared cervical pessary with standard care (no pessary) or alternative interventions (conventional and standard treatment (e.g., Atoxiban therapy) or vaginal progesterone) in patients with twin pregnancies.

Study appraisal and synthesis methods.

Data Collection and Analysis Two authors independently extracted information related to the study characteristics and test results from each of the included literature, and used Revman 5.3 to analyze the data. Pooled relative risks with 95% confidence intervals were calculated. Cohrane collaborative tools were used to assess the risk of bias in individual studies.The main results were premature delivery at <34 weeks, preterm delivery <37 weeks, and abortion <28 weeks. Secondary results included spontaneous preterm delivery <34 weeks, spontaneous preterm delivery <34 weeks, spontaneous abortion <28 weeks, and preterm prelabour rupture of membranes <34 and preterm prelabour rupture of membranes, vaginal bleeding, chorioamnionitis, delivery week, vaginal infection, vaginal discharge, cesarean section, intrauterine death or stillbirth, neonatal death, low weight birth, very low weight birth, neonatal respiratory distress syndrome, neonatal intraventricular hemorrhage, necrotizing enterocolitis, retinopathy, sepsis.

Results The researchers included a total of 7 documents with a total of 3120 patients. Among them, 4 studies included pregnancy outcomes and neonatal outcomes for patients with cervix length <25mm, and 7 studies included pregnancy outcomes and neonatal outcomes for patients with cervix length <38mm. The results showed that cervical pessary increase the incidence of delivery week, vaginal discharge, and vaginal bleeding, which was statistically significant. For neonates, cervical pessary decreases the incidence of low-weight children, necrotizing enterocolitis and neonatal septicemia, which were statistically significant. Subgroup analysis results based on cervical length <38mm showed that cervical pessary could reduce the preterm birth rate before 34 weeks, the spontaneous preterm birth rate before 34 weeks, prolong the gestational week of delivery, reduce neonatal mortality, occurrence of neonatal necrotizing enterocolitis and neonatal sepsis. However, the incidence of events such as increased vaginal discharge and vaginal bleeding in the experimental group was significantly higher than that in the control group, and the results were statistically significant. The results of subgroup analysis based on the cervical length < 25mm showed that cervical pessary was better than the control group in reducing the preterm birth rate before 34 weeks, the spontaneous preterm birth rate before <34 weeks, and the incidence of low-birth-weight infants, and the results were statistically significant. Otherwise, the subgroup analysis based on merely Arabin cervical pessary prove merely Arabin cervical pessary has similar results.

Conclusion The cervical pessary can extend the gestational week of short-cervix twin pregnancy without clinical symptoms, reduce the premature birth rate before 34 weeks of gestation, improve pregnancy outcome, reduce neonatal mortality, reduce necrotizing enterocolitis incidence, neonatal sepsis incidence, and improve neonatal outcome. For patients with a cervical length less than 38mm, a cervical pessary can be performed to extend the gestational week. For patients with a cervical length less than 25mm, a cervical pessary can effectively prolong the gestational age and improve the maternal and fetal outcomes. The cervical pessary is safe for patients with twin pregnancies. Suggest that twin-preganct-patients with CL<38mm should consider take cervical pessary in advance. In terms of long-term efficacy, there is no evidence of cervical support placement on the long-term maternal prognosis. In terms of economic benefits, cervical support is better than vaginal progesterone, but this conclusion still needs more research to prove.

Keywords: cervical pessary; pregnancy outcome; fetal outcome; preterm birth;preterm delivery;

Introduction

Studies have shown that the mortality rate for children under 5 years of age in China is 37%, with the main cause of death being complications from premature birth, accounting for about 17% of all deaths[1].Surviving preterm infants are at greater risk for short-term complications, with higher rates of respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, intraventricular hemorrhage, paraventricular leukodystrophy, and retinopathy than in term-born neonates[2,3].The incidence of twin pregnancies is less than 2%, but the incidence of preterm delivery is 50% and the risk of neonatal death is 5 times

higher in twin pregnancies than in singleton pregnancies[4,5].Cervical insufficiency as a cause of spontaneous preterm delivery in patients with twin pregnancies[6].

Currently, the main therapeutic measures regarding the prevention of preterm delivery in patients with twin pregnancies are the vaginal progesterone, cervical cerclage and cervical pessary. In the Clinical Guidelines for the Management of Twin Pregnancies published in China in 2020, it is clearly stated that in asymptomatic patients with twin pregnancies with a short cervix, the use of progestins can effectively reduce the risk of preterm delivery before 35 weeks of gestation[7].As for cervical cerclage, for singleton patients, this treatment is currently considered effective in preventing preterm birth[8],but for patients with twin pregnancies, the efficacy of the treatment remains controversial[7,9].

Originally used to treat pelvic organ prolapse, cervical pessary placement has been used to prevent preterm birth since 1990. Currently, the Arabin uterine support is widely used in the treatment of spontaneous preterm labor. It is designed with the intention not only to support and compress, but also to tilt the cervix and possibly rotate it towards the sacrum, mainly by supporting the inner cervical opening and preventing it from being overburdened with gravity[10].Currently studies show that cervical pessary placement is effective in reducing the rate of preterm birth in patients with singleton pregnancies[11,12],while cervical pessary placement remains controversial in patients with twin pregnancies. A retrospective analysis in 2016 showed that cervical pessary placement reduced the rate of preterm delivery before 37 and 34 weeks of gestation in patients with twin pregnancies[13].In 2019, an RCT trial suggested that cervical pessary placement reduces preterm birth rates and improves pregnancy outcomes in patients with twin pregnancies[14],but There were RCT experiments and meta-analyses that came to the opposite conclusion[15-17].

No specific and effective treatment exists to prevent preterm birth in the 2014 ACOG guidelines for twin women[18]. In 2019, the Canadian Association of Obstetricians and Gynecologists (SOGC) still believed that, even in twin patients with a short cervix, there was still no evidence that cervical pessary could effectively prevent premature birth[9]. China updated its guidelines in 2020 and did not give clear recommendations on the use of cervical pessary to prevent premature birth in twin patients. However, Chinese guidelines clearly support that vaginal progesterone can reduce the preterm birth and neonatal prevalence before 35 weeks in pregnant women with asymptomatic ultrasound showing a short cervix[7]. As for cervical cerclage, as an invasive treatment, its efficacy varies due to its different timing and indications. In 2014, ACOG noted that existing data demonstrated that ring ligation actually significantly increased preterm birth rates in asymptomatic twin pregnancies with CL <25mm[18]. The SOGC guidelines also indicate that cerclage increases asymptomatic preterm rates in twin pregnancies with CL <25mm, arguing that without physical evidence of physical examination, taking cerclage merely indicated by ultrasound hints of cervical shortening or previous second trimester abortion history increases the risk of preterm pregnancy.

In conclusion, there is still no consensus on the effect of cervical pessary on preventing preterm delivery, prolonging the pregnancy cycle, and improving maternal and infant outcomes in patients with twin pregnancies. In this article, we present a meta-analysis of the effects of cervical pessary placement on pregnancy outcomes in patients with twin pregnancies and discuss the effectiveness of cervical pessary placement in improving adverse pregnancy outcomes and neonatal outcomes.

Materials and Methods

1.1 Literature Search

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[19],and was registered with PROSPERO, number CRD42021275530.Two authors independently extracted all study data into a canonical form. When there is a difference of opinion, the two authors reach a consensus through negotiation.

Up to Jan 2022, researchers searched PubMed, EMBASE, COCHRANE, Web of Science, Wan fang, Wi Pu and CNKI databases, for example, in the PubMed database, they searched for (((((((cervical) OR pessary) OR cervical pessary)) OR pessary[MeSH Terms])) AND ((((((prematurity) OR prematurity[MeSH Terms])

OR premature birth) OR premature birth[MeSH Terms]) OR Preterm delivery) OR Preterm delivery[MeSH Terms])) AND (((((Twin) OR pregnancy) OR Twin pregnancy[MeSH Terms]) OR Multiple pregnancy) OR Multiple pregnancy[MeSH Terms])) AND ((cervical length) OR short cervix). Investigators selected studies for inclusion that met the inclusion standards. Relevant publications were searched. Researchers also systematically reviewed the references of the literature included in the study. Clinical pregnancy outcomes and neonatal outcomes were collected in the cervical pessary group (experimental group) and the non-cervical pessary group (control group). Cervical cerclage was excluded at an early stage of the study for the following reasons: 1. Meta-analysis has been conducted in relevant studies[20] ; Cervical cerclage is more irritating to patients than cervical pessary, cervical pessary as a non-invasive means, combined with non-invasive conventional fetal preservation methods such as bed rest, atosiban, vaginal progesterone, etc., compared with conventional fetal care methods, lower heterogeneity, more reliable results.

Two reviewers reviewed each potential eligibility article separately, analyzed the quality of the studies according to the Corhrane scale, and extracted data. Two authors (W-Y and M-D)independently performed the original screening of all study titles and abstracts, excluding literature that was deemed irrelevant by both observers. The PRISMA flowchart provides more detailed information about the article selection process (picture 1: flowchart). The researchers recorded in detail the year of publication of the records, country, study type, number of participants, week of gestation and range of cervical length (CL) at the time of placement of the cervical pessary, and mode of treatment for both groups of patients (table 1: characteristics of the included studies).

1.2 Eligibility criteria

The purpose of the included study was to investigate the effect of cervical pessary placement on pregnancy outcomes in patients with twin pregnancies. The inclusion criteria were1. Patients with twin pregnancies who underwent gynecological trans-vaginal ultrasound after 16 weeks of gestation and underwent cervical pessary because of the short cervix. There were no special requirements for the mode of pregnancy (ART and non-ART), and medical history of patients with twin pregnancy), 2.Must be done for RCT studies, 3.The experimental group must be patients undergoing cervical pessary, which can be performed in combination with conventional and standard treatment (e.g.Atoxiban therapy) or vaginal progesterone, 4.The control group must be routine noninvasive treatment such as conventional therapy (such as atoxeban) or vaginal progesterone. The exclusion criteria were: 1. The patient underwent cervical cerclage at this pregnancy, 2. patients who needed to receive fetoscopy, 3. Exclusion abnormal fetal development, pregnancies of three and more fetuses, medically indicated preterm birth of medical origin (Twin-twin transfusion syndrome, severe preeclampsia, placenta abruption, placenta previa, prenatal bleeding); 4. non-RCT experiments.

1.3 Outcome measures and data item extraction

Two researchers extracted information related to the study characteristics and test results from each of the included literature. The main outcome was preterm delivery (ptd) before 34 weeks gestation, preterm delivery before 37 weeks, miscarriage a before 28 weeks(China officially defines miscarriage as occurring before 28 weeks' gestation). Secondary outcomes included spontaneous preterm delivery(sptd) before 34 weeks, spontaneous preterm delivery before 37 weeks, spontaneous miscarriage before 28 weeks(SM), preterm prelabor rupture of membranes(PPROM),preterm prelabor rupture of membranes before 34 week, deliver week(DW),vaginal bleeding(VB),chorioamnionitis(C),vaginal infection(VI),vaginal discharge(VD),C-section, intrauterine death or stillbirth, neonatal death , low-birth weight (<2500g), very low birth weight (<1500g), Respiratory distress syndrome (RDS),Intraventricular hemorrhage(IVH),Necrotizing Enterocolitis (NE),Retinopathy (RE),Sepsis (S).

1.4 Risk assessment of bias

Cochrane collaborative tools were used to assess the risk of bias in individual studies,including: 1.selection bias; 2. implement bias; 3. detection bias; 4. attribution bias; 5. reporting bias; 6. Other bias (including measuring bias; sampling bias and follow-up bias) (See details in the table2:bias of included literature assessment table).The quality of evidence for primary and

secondary outcomes was assessed by using the GRADE approach, which takes into account 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.The GRADE

approach categorizes the certainty of the evidence into 4 levels: (1) high: we are very confident that the true effect lies close to that of the estimate of the effect,and further research is unlikely to change our confidence in the estimate other effect; (2) moderate: we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is apossibility that it is substantially different; (3) low: our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect; and (4) very low: we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

1.5 Data processing and analysis

Researchers used Revman 5.3 to analyze the data. It belonged to two categorical outcome variables and relative rate (RR) was used as the effect indicator. For the outcome index belonging to the continuous variables, the standards mean difference (SMD) was used as the effect indicator.95% confidence interval was calculated to evaluate the strength of the association between cervical pessary and the risk of adverse pregnancy-related outcomes. The RR values were calculated by the Z test. The P-value of <0.05 was defined as meaningful. Random-effects and fixed-effects models were applied in this meta-analysis. To assess inter-study heterogeneity, the Q test was applied to calculate I^2. The I^2values were defined as 25%, 50%, and 75%, representing low, moderate, and high heterogeneity, respectively. When high heterogeneity was observed, random-effects models were used to pool results, and a fixed-effect model. When the heterogeneity is too high, there should be further excluded clinical and methodological heterogeneity, and a random effect model is used for analysis. If there was evidence of statistical heterogeneity (I^2>50%), it is necessary to explore the possible sources by using sensitivity and subgroup analyses to search for evidence of bias or methodological differences among trials. Researchers used the exclusion method article by piece exclusion literature method for sensitivity analysis. Differences in the elimination results and the original merger results were also assessed. Publication bias was visually judged by drawing funnel plots.

Results

2.1 Results of literature search

A total of 7 literature studies have included 3120 patients, and 4 studies containing <25mm for CL.For patient pregnancy and neonatal outcomes, seven studies included pregnancy and neonatal outcomes for patients with CL <38mm.

2.2 Primary and secondary outcome summary

2.2.1.A meta analysis was performed for all of the literature

First, we performed meta analyses on all included literature to compare the efficacy of cervical support in improving pregnancy outcomes with neonatal outcomes (see table3: Summary Results 1),It was found that the patients in the experimental group (cervical pessary group) had a longer deliver week (RR 6.82, P<0.00001), higher incidence of vaginal discharge (RR12.96 , P<0.00001) and vaginal bleeding (RR 5.34, P<0.0001) than in the control group, which was statistically significant. As neonates, in experimental groups, the incidence of low birth weight (RR 4.14, P<0.00001), NE (RR2.45, P=0.01) and neonatal septicemia (RR2.21, P=0.03) were significantly lower than control group, which were statistically significant. Compared DW, vaginal discharge, vaginal bleeding, low birth weight, S, remarkable heterogeneity could be seen. The sensitivity analysis was performed article by article, and the exclusion literature name and the p values after analysis are shown in the figure below. The funnel map suggests publication bias in part of the study.

2.2.2 Subgroup analysis was performed based on the CL

During the process of literature inclusion, the researchers found differences in the CL of the included patients, and to avoid the outcome bias caused by different CL, the subgroup analysis was performed.

Results of the subgroup analysis based on CL <38mm rows are shown in table 4. It can be seen that cervical pessary was better than the control group of preventing spontaneous premature delivery before 34 weeks(RR2.18, P=0.03) and premature delivery before 34 weeks (RR2.9, P=0.004), prolonged delivery week (RR6.31, P<0.00001), reducing neonatal mortality(RR2.47, P0.01), neonatal necrotic enterocolitis (RR3.52, P=0.0004) and neonatal sepsis(RR2.21, P=0.03).All the results were statistically significant. However, the incidence of increased vaginal discharge and vaginal bleeding in the cervical pessary group was significantly higher than in the control group. Some studies funnel plots suggest publication bias.

Results of the subgroup analysis based on the <25mm line of CL are shown in table 5.Due to insufficient data, comparisons were made only between premature delivery before 34 weeks (RR3.82, P=0.0001) , spontaneous premature delivery before 34 weeks (RR2.7, P=0.04), low weight birth (RR6.32 ,P<0.00001) and vary low weight birth (RR0.16, P0.87). Results showed that cervical pessary was better in reducing spontaneous preterm birth <34 weeks and preterm birth <34, decreased the born of lower weight infants, and the results were statistically significant. Some study funnel plots suggested publication bias.

2.2.3 Subgroup analysis was performed based on the type of cervical pessary.

Because of Bioteque cervical pessary in Berghella2017, which could cause performance bias, the result of subgroup analysis after excluding Berghella2017 show in table 6 that the patients in the experimental group (merely Arabin cervical pessary group) had a longer deliver week (RR6.82 P<0.00001), higher incidence of vaginal discharge (RR12.23, P<0.00001) , C-section (RR2.05, P=0.04), vaginal bleeding(RR 5.43, P<0.04),which was statistically significant. For neonates, In experimental groups, the incidences of low birth weight(RR 4.14, P<0.0001), NE(RR2.59, P=0.01) and S (RR2.61, P=0.009) were lower ,which was statistically significant. Remarkable heterogeneity could be seen. The sensitivity analysis was performed article by article, and the exclusion literature name and the p values after analysis are shown in the figure below. After sensitivity analysis, the ptd <34 weeks, DW, VD, PPROM, DE, low birth weight were statistically significant, and the P value of sptd <34 weeks and S changed, but were not statistically significant. The funnel map suggests publication bias in part of the study.

Results of the subgroup analysis based on CL <38mm rows are shown in table 7. It can be seen that Arabin cervical pessary was better than the control group of preventing ptd<34 (RR3.05, P=0.002) and sptd<34 (RR2.24, P=0.03),prolonged delivery week(RR2.24, P<0.03), increased VD (RR9, P<0.00001)and VB(RR5.34, P<0.00001), decreased incidence of PPROM (RR2.31, P<0.02),reducing neonatal mortality(RR6.02, P<0.006),the incidences of low birth weight(RR 4.14, P<0.00001), NE (RR3.68, P=0.0002), S(RR 2.61, P<0.009),which was statistically significant. Remarkable heterogeneity could be seen. The sensitivity analysis was performed article by article.Funnel plots show the publication bias in part of the studies.

Results of the subgroup analysis based on the CL<25mm are shown in table 8. Due to insufficient data, comparisons were made only between premature delivery before 34 weeks(RR3.82 ,P=0.001) , spontaneous premature delivery before 34 weeks(RR2.07, P=0.04), low weight birth (RR6.32, P<0.00001) and vary low weight birth (RR 0.16, P=0.87). Results showed that merely Arabin cervical pessary was better in reducing spontaneous preterm birth <34 weeks and preterm birth <34, decreased the born of lower weight infants, and the results were statistically significant. Some study funnel plots suggested publication bias. Remarkable heterogeneity could be seen. The sensitivity analysis was performed article by article, and the exclusion literature name and the p values after analysis are shown in the figure below. After sensitivity analysis, sptd<34 keep his statistically significant, but low birth weight was not.

2.3 Quality evaluation and bias evaluation

These literatures were assessed for the risk of bias (as table 2 and picture2). Considering the particularity of the study, that the patients in the experiment knew all about their intervention after participating in the experiment, the researchers default that patient's blindness are low-risk, and only evaluate the blind method of the researchers and the results assessors. The high uncertain risk of Merced 2019,Norman 2021and Berghella 2017 are exposed as missing visits and bias burned when selected patients.Dang's high uncertain

risk is from missing visits,and it has uncertain selection bias and reporting bias. Berghella 2017 has high preform bias.The results of GRADE approach categorizing the certainty of the evidence are in table 3-8.During analysis,we found that the quality of evidences could be influenced by Berghella 2017 because of his bias from patients selection.besides,the bias from Merced 2019,Norman 2021 and Dang 2019 could influence the certificate evidence quality.All in all,the quality of evidences in table 3-5 is low.But after subgroup analysis, it is obvious that the quality of evidences has improved.

Discussion

3.1Main findings and interpretation

The results found that the efficacy of cervical pessary in twin patients suggested that cervical support prolonged the gestational week of twin patients and reduced the incidence of low weight birth, NE and the incidence of neonatal sepsis. In 2012, the CL <25 mm can be considered as short cervix by singleton guidelines published by American Obstetricians and Gynecologists (ACOG)[21].However, there were also studies using a CL of less than the 25th percentile (<38mm)[22,23].Therefore, the researchers used these two sets of digital row subgroup analysis, respectively. The results suggested that in twin patients with <38mm of CL, cervical pessary reduced preterm birth <34 weeks, decreased rate of spontaneous premature delivery <34 weeks, prolonged delivery week, reduced neonatal mortality, neonatal necrotizing enterocolitis, and neonatal sepsis; For patients with CL <25mm, although the data are insufficient, limited data still suggest that cervical pessary is better than conventional treatment in reducing preterm birth rate <34 weeks, spontaneous preterm birth <34 weeks, and reducing the incidence of low-weight infants. Although, increased vaginal secretions and higher vaginal bleeding rate were higher in the experimental group when <38mm of the CL was observed, there was no significant difference in the incidence of vaginitis and chorioamnionitis compared with the control groups. This shows that cervical pessary can effectively reduce the rate of preterm birth before 34 weeks in twin patients with CL less than 38mm, effectively prolong pregnancy week, reduce neonatal mortality, neonatal necrotizing enterocolitis and neonatal sepsis, and effectively improve adverse maternal pregnancy outcome.

Considering type of cervical pessary, merely Arabin cervical pessary prolonged the gestational week of twin patients and reduced the incidence of low weight birth, necrotizing enterocolitis and neonatal sepsis, but it also increased the incidences of vaginal discharge, C-section and vaginal bleeding without any changed of vaginal infection and chorioamnionitis. The results suggested that in twin patients with <38mm of CL, cervical pessary reduced preterm birth <34 weeks, spontaneous preterm delivery before 34 weeks and incidence of PPROM, prolonged delivery week, decreased neonatal mortality, neonatal necrotizing enterocolitis, and neonatal sepsis, but increased the incidences of VD and VB; For patients with CL <25mm, although the data are insufficient, limited data still suggest that cervical pessary is better than conventional treatment in reducing preterm birth rate <34 weeks, spontaneous preterm birth <34 weeks, and reducing the incidence of low-weight infants. Although, increased vaginal secretions and higher vaginal bleeding rate were higher in the experimental group. Importantly, while Arabin cervical pessary do increase vaginal discharge and vaginal bleeding rate, but there is no difference of vaginal infection and chorioamnionitis, which means cervical pessary is safe to twin-pregnancy women. Comparing our data, different CL seems to do not influence the effect of cervical pessary, especially on sptb<34 weeks, ptb<34weeks and low birth weight, but patients with CL <38mm have great effect and less side effect. The effect of cervical pessary in CL<25 mm is still need more research.The results of the subgroup analysis were significantly improved after excluding Berghella 2017, and the level of evidence was also significantly increased, which proved that the subgroup analysis was effective.

3.2 Sensitivity analysis

During the course of the sensitivity analysis, the researchers found the phenomena of altered P values after the sensitivity analysis. After analyzing the sources of heterogeneity one by one, the researchers thought that the reasons for the heterogeneity were: 1. The data gap is too large; 2. There is a publication bias. 3.Existing bias in 7 research, particularly Berghella 2017.4. There are other potential unmeasured confounders. Researchers

found several factors could cause confounders such as cervical surgery history, miscarriage history, difference race, the time of pregnancy or delivery, ART history, time of placing or removing cervical pessary, vaginal progesterone. Particularly, vaginal progesterone has been proven to prevent preterm birth. It is possible to cover the effect of cervical pessary. Otherwise, combined treatment of cervical pessary plus vaginal progesterone is uncertain. One retrospective cohort study of twin pregnancies draws a conclusion that cervical pessary combined with vaginal progesterone could prolonged pregnancy and reduce risk of adverse neonatal outcomes[24]. In 2020, a retrospective study of 57 patients with (dichorionic diamniotic twin (DCDA) showed that a cervical pessary combined with vaginal progesterone reduced the rate of preterm birth in patients [25]. There is one study showed that cervical pessary combined with vaginal progesterone could prolonged pregnancy, reduce prematurity rate and a low rate of perinatal complications[26]. However, a meta-analysis[27] and a RCT [28]in 2016 showed that combined treatment did not decrease the risk of preterm birth compared with cervical pessary in singletons with short CL. Therefore, it is not sure if vaginal progesterone could enhance or weaken the influence of cervical pessary to twin pregnancy. More clinical trials are needed to prove the efficiency of combined treatment. As for Berghella 2017, it was published as a small RCT research[29]. In stand of Arabin cervical pessary, Berghella choosed Bioteque cup cervical pessary included 46 women. After subgroup based on type of cervical pessary, comparing data, all the difference seems to indicate that the different type of cervical pessary had similar effects .However, Kyvernitakis believes that there are differences in the appearance of Bioteque and Arabin, and these may have different effects[30].

3.3 Current research

Twin gestations are different from singleton patients, because of their excessive uterine enlargement, intrauterine pressure increases too much, beyond the limit that the cervix can bear, easy to lead to cervical insufficiency, and then cause premature birth.

For twin patients, cervical pessary is still controversial. Leim2013 was the first to study the treatment effect of cervical support in twin pregnancy patients through RCT experiments, and proposed that cervical uterine care could not effectively prevent adverse perinatal outcome or premature birth in multiple pregnant women, but its subgroup analysis proved that cervical pessary of the cervix in twin patients can reduce adverse perinatal outcome of <38mmm[31].This provided later researchers with ideas to study the relationship between different cervical length and the efficiency of cervical pessary. In 2016, a retrospective analysis revealed that cervical pessary placement reduced the rate of preterm delivery that occurred before 36 and 34 weeks[13]. A network meta-analysis published in 2021 suggested that cervical pessary, progesterone and cerclage do not show a significant effect in reducing the rate of PTB or perinatal morbidity in twins[20].

Contradictory findings also exist in the RCT study. A RCT experiment published by Goya in 2015 for the first time that cervical pessary reduced the rate of preterm delivery by 34 weeks in twin patients with a CL <25mm[16].However, In 2016, Kypros believes that cervical pessary does not reduce the preterm rate in twin patients with cervical insufficiency[15]. In 2017, by comparing treated patients with cervical pessary, cervical cerclage and vaginal progesterone, a meta analysis proposed that only vaginal progesterone extended the gestational week, but not statistical significance[32]. In 2019, an RCT experiment proposed that cervical pessary reduced the rate of preterm birth and improved pregnancy outcomes in patients with twin gestation [14]. The latest meta analysis in 2020 does not support the use of cervical pessary to prevent premature birth or improve perinatal outcomes in twin short cervix and unselected twin pregnancies[17]. It can not deny that it[17] is inspired to singletons. However, this paper studied high-risk pregnant women, not twin pregnant women alone, and it included only two studies about twin pregnancy, the data are so grossly insufficient that leads to a bias in their findings. About Xiong YQ [33], I have read this document when I collected the literature, and it has some guiding significance for this research. However, the differences between this article and this paper are as follows 1.The control group differs,our study excluded patients with cervical cerclage, and Yi-Quan Xiong did not. 2. We contain 7 studies and 4 in Xiong . 3. In Xiong's study, no subgroup analysis was performed based on cervical length, which may lead to biased results.

3.4 Long-term effects of cervical pessary

In terms of the long-term effects of cervical pessary, only Noor E [34]followed up participants for up to four years based on the Leim study. The results showed that the intervention group (CL<38mm), but no difference in abnormal growth and development outcomes between the two groups. Van published his RCT research which evaluated the effect of a cervical pessary on the outcome of subsequent pregnancies and maternal quality of life four years after twin pregnancy among 408 women [35].The results showed that no long term effects of pessary use on the outcome of subsequent pregnancies and maternal quality of life. However, there were a large number of missed visits in the study, so at present, there is still insufficient data to prove that cervical care can lead to long-term adverse outcomes in mothers.

3.5 Efficacy and economic benefits of cervical pessary

In 2014, Leim concluded that the cost of treatment in the cervical pessary group was comparable to that of the control group when comparing costs alone. However, when the cervical length was less than 38 mm, the placement of a cervical pessary not only prolonged the gestational cycle and reduced adverse neonatal outcomes, but also, was less costly than in the control group [36] ◦ In 2020, one study[37] has proposed that after comparing the efficacy and economic benefits of cervical pessary with vaginal progesterone, cervical care improved adverse pregnancy outcomes and reduced costs.The connection between pessary and his economic effect still requires sufficient data support.

3.6 Strengths and limitations

7 RCT studies were included with a total of 3120 patients who performed a subgroup analysis based on different CL and type of cervical pessary. The results proved that cervical pessary could prolong the delivery weeks. Particularly, it effectively reduces the preterm birth rate of twins before 34 weeks for patients with CL less than 38mm, effectively prolong gestational week, reduce neonatal mortality, neonatal necrotic enterocolitis, and neonatal sepsis, and effectively improve the adverse pregnancy outcome.

There are shortcomings in this research. First, even if more than 3,000 patients were included, the results were still affected by insufficient sample size and uneven sample distribution, resulting in altered results after sensitivity analysis. Second, only one of the seven studies included was about the efficacy comparison of cervical pessary placement and vaginal progesterone, which brought some bias to our study. At the same time, the researchers regretted that the inability to compare the treatment effect of cervical pessary with vaginal progesterone to prevent premature birth in twin patients had failed. Furthermore, only one study included was from Asia, and researchers similarly regret the inability to perform a race-based subgroup analysis. Otherwise, The subjects were unselected twin pregnancies and had no clear requirements for the mode of pregnancy (ART or non-ART) , choriogenin, medical history (with a history of miscarriage, delivery and cervical surgery), which may bias the results. For this part of the patients, additional attention is needed. Alternatively, timing differences in the inclusion literature exist to the current lack of uniform guidelines. It is seen that most of the pessary were placed between $16 - 24$ weeks, but Merced was at $24 - 34$ weeks. Norman choose patients with CL < 35mm. Those reasons for this difference is selection bias due to the different subjects selected each study.

3.7 Implications for practice and research

Despite the multiple regrets, our approach is scientific, and the results are valid. This paper reverses the conclusion proposed in the previous meta-analysis and guidelines that "cervical pessary cannot effectively prolong gestational weeks and prevent preterm birth in twin pregnancies" and proves the effectiveness of cervical trust placement in patients with twin pregnancies.

Conclusion

1. Cervical pessary can extend the gestational week of short-cervix twin pregnancy without clinical symptoms, reduce the premature birth rate before 34 weeks of gestation, improve pregnancy outcome, reduce neonatal mortality, reduce neonatal enterocolitis incidence, neonatal sepsis incidence, and improve neonatal outcome.

2. For patients with a cervical length less than 38mm, cervical pessary can be performed to extend the gestational week.
3. For patients with cervical length less than 25mm, cervical pessary can effectively prolong the gestational age and improve the maternal and fetal outcome.
4. Cervical pessary is safe for patients with twin pregnancies.
5. Although, different CL seems to do not affect the effect of cervical pessary, especially on sptb<34 weeks, ptb<34 weeks and low birth weight, but patients with CL <38mm have great effect and less side effect, so we suggest that twin-pregant-patients with CL<38mm should consider take cervical pessary in advance. Patients with CL<25mm could take cervical pessary in order to prevent preterm birth before 34 weeks, but side effect of cervical pessary to patients with CL<25 mm is still need more research.
6. In terms of long-term efficacy, there is no evidence of cervical support placement on the long-term maternal prognosis.
7. In terms of economic benefits, cervical support is better than vaginal progesterone, but the conclusion still needs more research to prove.
8. The influence from different type of cervical pessary needs more attention.

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Picture 1:flowchart

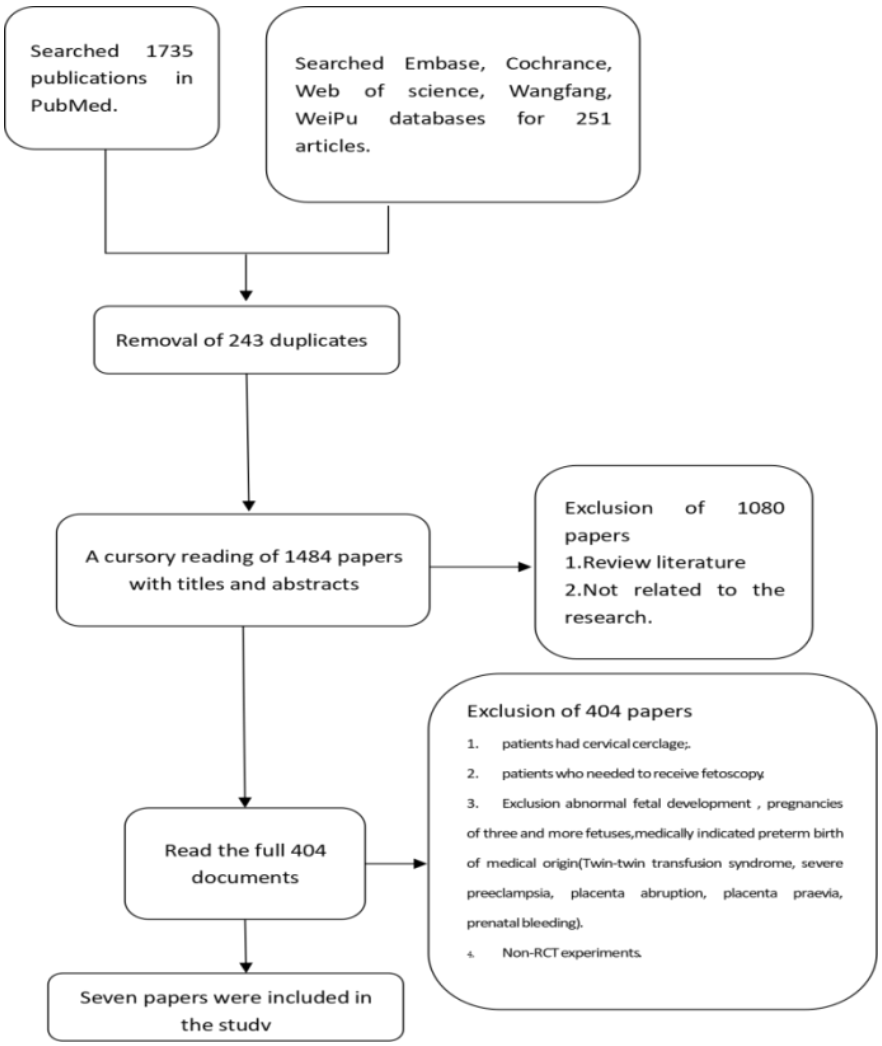

Table 1: **Characteristics of the included studies**

Name	Country	Type	Number	**Characteristics**	Treatment
Goya 2015[16]	Spain	RCT	154	18-22week CL<25mm	Arabin Pessary Conventional treatment
Nicolaided 2015[38]	Multiple center	RCT	1180	18-25weel CL unlimitated	Arabin Pessary Conventional treatment
Liem 2013[31]	Netherlands	RCT	808	16-22week CL unlimitated	Arabin Pessary Conventional treatment
Merced 2019[39]	Spain	RCT	132	24-34week CL<20mm	Arabin Pessary Conventional treatment
Norman 2021[40]	UK	RCT	503	18-21week CL<35mm	Arabin Pessary Conventional treatment

Dang 2019[22]	Vietnam	RCT	297	16-22week CL<38mm	Arabin Pessary Vaginal progesterone400mg
Berghella 2017[41]	Multiple center	RCT	46	18-24week CL<30mm	Arabin Pessary Conventional treatment

Table 2: the Bias of included Literature assessment table

Name	selection bias	implement bias	detection bias	attribution bias	reporting bias	Other bias
Berghella2017	-	-	+	-	-	?
Goya2015	?	-	-	-	?	+
Nicolaided 2015	-	-	-	-	-	-
Liem2013	-	-	-	-	-	-
Merced2019	+	-	-	-	-	+
Norman2021	+	-	-	-	-	-
Dang 2019	?	-	-	-	?	+

Table 3: **summary results 1**

Results	P	95%CI	95%CI	I^2	RR	Exclude the literature name	The p value
ptb<34	0.07	0.85	0.72,1.01	57%	1.83	Nicolaided 2015	0.004*
ptb<37	0.18	0.95	0.88,1.02	0%	1.35	-	-
miscarriage	0.76	0.95	0.69,1.31	0%	0.31	-	-
sptb<34	0.06	0.83	0.68,1.01	60%	1.86	Nicolaided 2015	0.003*
sptb<37	0.34	0.93	0.8,1.08	0%	0.96	-	-
SM	0.18	0.72	0.44,1.17	0%	1.34	-	-
DW	<0.00001*	0.25	0.18,0.32	82%	6.82	Dang 2019	<0.00001*
C	0.87	1.04	0.64,1.71	0%	0.17	-	-
VI	0.13	1.45	0.9,2.34	23%	1.52	-	-
VD	<0.00001*	5.41	4.17,7.02	97%	12.69	Merced2019	<0.0001*
<34PPROM	0.56	1.25	0.59,2.64	66%	0.58	Goya2015	0.08
PPROM	0.14	1.33	0.91,1.94	63%	1.49	Norman2021	0.62
C-section	0.07	1.09	0.99,1.19	8%	1.84	-	-
VB	<0.0001*	1.56	1.32,1.83	93%	5.34	Merced2019	<0.00001*
intrauterine death or stillbirth	0.48	0.86	1.57,1.30	0%	0.71	-	-
neonatal death	0.95	0.99	0.68,1.45	0%	0.06	-	-
<2500	<0.00001*	0.90	0.86,0.95	93%	4.14	Merced2019	0.03*
<1500	0.98	1.00	0.85,1.19	0%	0.03	-	-
NE	0.01*	0.57	0.36,0.89	40%	2.45	-	-
IVH	0.55	1.14	0.73,1.79	0%	0.59	-	-
RDS	0.93	0.99	0.83,1.19	28%	0.08	-	-
RE	0.08	2.32	0.9,6.00	40%	1.73	-	-
S	0.03*	0.64	0.43,0.95	55%	2.21	Norman2021	0.003*

(*It indicates that the statistical results were statistically significant)

CL<38mm	P	95%CI	95%CI	I^2	RR	Exclude the literature name	The p values
ptb<34	0.004*	0.72	0.57,0.90	43%	2.9	-	-

ptb<37	0.06	0.92	0.84,1.01	11%	1.85	-	-
miscarriage	0.21	0.77	0.5,1.16	30%	1.26	-	-
sptb<34	0.03*	0.77	0.61,0.97	61%	2.18	Nicolaided 2015	0.003*
sptb<37	0.34	0.93	0.80,1.08	0%	0.96	-	-
SM	0.18	0.72	0.44,1.17	0%	1.34	-	-
DW	<0.00001*	0.37	0.26,0.48	83%	6.31	Norman2021	<0.00001*
C	0.71	1.14	0.58,2.21	0%	0.37	-	-
VI	0.26	1.36	0.8,2.33	38%	1.14	-	-
VD	<0.00001*	3.22	2.52,4.11	94%	9.37	Merced2019	<0.00001*
<34PPROM	0.56	1.25	0.59,2.64	66%	0.58	Goya2015	0.08
PPROM	0.07	1.67	0.96,2.9	62%	1.82	Norman2021	0.69
C-section	0.93	1.01	0.9,1.12	0%	0.09	-	-
VB	<0.00001*	1.56	1.32,1.83	93%	5.34	Norman2021	<0.00001
intrauterine death or stillbirth	0.18	1.41	0.86,2.33	0%	1.36	-	-
neonatal death	0.01*	0.50	0.29,0.87	73%	2.47	Leim2013	0.99
<2500	0.00001	0.74	0.67,0.81	90%	6.02	Merced2019	0.003
<1500	0.9	1.02	0.77,1.34	0%	0.13	-	-
NE	0.0004*	0.33	0.18,0.61	0%	3.52	-	-
IVH	0.5	0.79	0.41,1.55	41%	0.68	-	-
RDS	0.18	0.81	0.6,1.1	11%	1.34	-	-
S	0.03*	0.64	0.43,0.95	55%	2.21	Dang 2019	0.42

Table 4: **summary results 2**

(*It indicates that the statistical results were statistically significant)

Table 5: **summary results 3**

CL<25mm	P	95%CI	95%CI	I^2	RR	Exclude the literature name	The p values were after the sens
sptb<34	0.04*	0.73	0.54,0.98	80%	2.07	Nicolaided 2015	0.0005*
ptb<34	0.0001*	0.53	0.38,0.73	0%	3.82	-	-
<2500	<0.00001*	0.62	0.54,0.72	95%	6.32	Merced2019	0.05
<1500	0.87	0.97	0.68,1.38	0%	0.16	-	-

(*It indicates that the statistical results were statistically significant)

Table 6: **summary results 4**

Results	P	95%CI	95%CI	I2	RR	Exclude the literature name	The p valu
ptd<34	0.06	0.84	0.71,1.00	64%	1.91	Nicolaided 2015	0.002*
ptd<37	0.17	0.95	0.88,1.02	0%	1.36	-	-
miscarriage	0.40	0.94	0.69,1.30	0%	0.69	-	-
sptd<34	0.06	0.82	0.67,1.01	69%	1.9	Goya2015	0.32
sptd<37	0.32	0.93	0.79,1.08	0%	1	-	-
SM	0.16	0.68	0.4,1.16	0%	1.42	-	-
DW	<0.00001*	0.25	0.18,1.32	82%	6.82	Dang 2019	<0.00001*
C	0.82	0.94	0.56,1.57	0%	0.23	-	-
VI	0.49	1.2	0.72,1.99	0%	0.69	-	-
VD	<0.00001	6.35	4.72,8.54	98%	12.23	Goya2015	<0.00001*!
<34PPROM	0.56	1.25	0.59,2.64	66%	0.58	Goya2015	0.08
PPROM	0.08	1.44	0.96,2.15	70%	1.77	Leim2013	0.004!

C-section	0.04*	1.1	1,1.21	2%	2.05	-	-
VB	<0.00001*	1.56	1.32,1.82	93%	5.43	Dang 2019	0.32!
intrauterine death or stillbirth	0.48	0.86	0.57,1.3	0%	0.71	-	-
neonatal death	0.87	0.97	0.65,1.44	8%	0.16	-	-
<2500	<0.0001*	0.9	0.86,0.95	93%	4.14	Merced 2019	0.03*
<1500	0.98	1	0.85,1.19	0%	0.03	-	-
NE	0.01*	0.54	0.34,0.86	45%	2.59		
IVH	0.63	1.12	0.71,1.77	0%	0.49		
RDS	0.81	0.98	0.81,1.18	37%	0.24		
RE	0.11	2.26	0.83,6.12	70%	1.6		
S	0.009*	0.57	0.38,0.87	52%	2.61	Merced 2019	0.07

(*It indicates that the statistical results were statistically significant)

CL<38mm	P		95%CI	I^2	RR	Exclude the literature name	The p values w
ptd<34	0.002*	0.69	0.55,0.88	46%	3.05	-	-
ptd<37	0.06	0.92	0.84,1.00	28%	1.97	-	-
miscarriage	0.16	0.74	0.48,1.13	41%	1.4	-	-
sptd<34	0.03*	0.76	0.6,0.97	70%	2.24	Nicolaided 2015	0.002*
sptd<37	0.32	0.93	0.79,1.08	0%	1	-	-
SM	0.16	0.68	0.40,1.15	0%	1.42	-	-
DW	<0.00001*	0.37	0.26,0.48	83%	6.31	Norman 2021	<0.00001*
C	0.86	0.94	0.46,1.91	0%	0.17	-	-
VI	0.88	1.05	0.58,1.88	0%	0.16	-	-
VD	<0.00001*	3.57	2.71,4.72	97%	9	-	-
<34PPROM	0.56	1.25	0.59,2.64	66%	0.58	Goya2015	0.08!
PPROM	0.02*	2.17	1.12,4.17	64%	2.31	Leim2013	0.004!
C-section	0.7	1.02	0.92,1.14	0%	0.39	-	-
VB	<0.00001*	1.56	1.32,1.83	93%	5.34	Norman 2021	<0.00001*
intrauterine death or stillbirth	0.18	1.41	0.86,2.33	0%	1.36	-	-
neonatal death	0.006*	0.42	0.23,0.78	78%	2.78	Leim2013	0.84
<2500	<0.00001	0.74	0.57,0.81	90%	6.02	Merced 2019	0.003*
<1500	0.9	1.02	0.77,1.34	0%	0.13	-	-
NE	0.0002*	0.29	0.15,0.56	0%	3.68	-	-
IVH	0.37	0.73	0.36,1.47	54%	0.86	Norman 2021	0.05
RDS	0.09	0.76	0.55,1.04	0%	1.7		
S	0.009*	0.57	0.38,0.87	52%	2.61	Merced 2019	0.07

Table 7: **summary results 5**

(*It indicates that the statistical results were statistically significant)

Table 8: **summary results 6**

CL<25mm	P		95%CI	I2	RR	Exclude the literature name	The p values were after the sensitivi
sptd<34	0.04*	0.73	0.54,0.98	80%	2.07	Nicolaided 2015	0.005*
ptd<34	0.0001*	0.53	0.38,0.73	0%	3.82	-	-
<2500	0.00001*	0.62	0.54,0.72	95%	6.32	Merced 2019	0.05
<1500	0.87	0.97	0.68,1.38	0	0.16	-	-

(*It indicates that the statistical results were statistically significant)

Picture 2: **Risk bias assessment**

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`image2.emf` available at https://authorea.com/users/442762/articles/563195-effect-of-cervical-pessary-on-pregnancy-outcome-in-patients-with-twin-pregnancies-a-systematic-review-and-meta-analysis