Cervical cerclage for preventing preterm birth in twin pregnancies

A systematic review and meta-analysis

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ABSTRACT

الأهداف: تقيم تاثير الطوق العنقي في منع ولادة الخدج في حمل التوائم.

الطريقة: قمنا بإجراء بحث للدراسات العشوائية، ومكتبة كوكرين، والتجارب المحكمة، ووقاعدة بيانات الصين للمعلومات الوطنية، ووقاعدة بيانات الصين للمجلات خلال الفترة من أبريل حتى أغسطس 2012م. كما أدرجنا كذلك جميع التجارب العشوائية لمقارنة آثار الطوق العنقي لمنع ولادة الخدج عند حمل التوائم للذين خضعوا للطوق العنقي والذين لم يخضعوا.

النتائج: اشتملت الدراسة على 5 دراسات صالحة ومكونة من 310 شخص. لم يظهر أي اختلاف إحصائي بين المرضى الذين استخدموا الطوق العنقي والذين لم ستخدموه من ناحية الخديج (RR0.93,95%CI0.87 - 0.91,95%CI0.78-1.18)، حياةالجنين، نوع الولادة (RR 1.34, 95% CI 0.61-2.98)، لكل إمرأة بشكل عشوائي. ولم تتغير هذه المتغيرات قبل أو بعد اختبار الحساسية.

خاتمة: لم يكن هنالك اختلاف إحصائي بين مجموعة الطوق العنقي والمجموعة التي لم تستخدم طوق عنقي في حمل التوائم والتجارب العشوائية. ونحن بحاجة إلى المزيد من الدراسات المخبرية لزيادة الاستخدام الكلينكي للطوق العنقي.

Objectives: To evaluate the effect of cervical cerclage on preventing preterm birth in twin pregnancies.

Methods: We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Current Controlled Trials, China Biology Medicine (CBM), Chinese National Knowlegde Infrastructure (CNKI) and VIP Chinese Journal database (VIP) from April to August 2012. All available randomized trials comparing the effects of cervical cerclage for preventing preterm birth in twin pregnancies with no cerclage were included. The study took place in the First Affiliated Hospital of ChongQing Medical University, Chongqing, People's Republic of China.

Results: Five eligible studies with a total of 310 participants were finally included. No statistically significant differences were found between patients who received cervical cerclage and those who did not receive cervical cerclage, in terms of preterm birth (RR 0.91, 95% CI 0.78-1.18), live births (RR 0.93, 95% CI 0.87-1.01) and mode of delivery (RR 1.34, 95% CI 0.61-2.98) per randomized woman. These results of preterm birth, premature rupture of menbrane, model of delivery did not change before and after sensitivity analysis.

Conclusion: No significant difference was observed between cervical cerclage group and no cerclage group in twin pregnancies and large scale randomized controlled trials are needed to strengthen clinical usage of cervical cerclage.

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Preterm birth is defined as the birth of an infant prior to 37 completed weeks' gestation.[1] Among 4 million of neonatal deaths every year, preterm birth accounts for an estimated 27%, which constitutes the most common cause of neonatal mortality.[2] Preterm birth rate in the published literatures ranges from 5% in high-income countries to 25% in low- and middle-income countries.[2] Cervical incompetence defined as painless dilatation and shortening of the cervix in the second-trimester resulting in a pregnancy loss, was considered to be one of the causes of preterm birth. The placement of cervical suture is the only treatment for patients with this diagnosis to prevent preterm birth by now. Cervical cerclage, involving in positioning of a suture (stitch) around the neck of the womb (cervix), has been introduced to obstetrics since 1955 by Shirodkar.[3] In 1957, McDonald reported his experience of using suture of the cervix for inevitable miscarriage in 70 patients.[4] Since then, cervical cerclage has become a procedure used in the management of women considered to be at high risk for a preterm birth, such as women with one or more abortions in the first-trimester or second-trimester, multiple pregnancies, uterine and cervical anomalies, a history of cervical trauma through destructive procedures or forced dilatation, and cervical shortening seen by transvaginal ultrasound examination, and so on.[5] It may have effect on prolonging the gestation and increasing the chance of viable pregnancy outcomes.[6-8] A huge number of clinical trials have been performed to compare the efficacy of cervical cerclage in singleton pregnancy, and multiple pregnancies, separately or combined. But the results are variable, and some studies have even yielded conflicting results on the efficacy of cerclage. In the Cochrane system review conducted by Alfirevic et al,[9] they concluded that cervical cerclage reduced the incidence of preterm birth in singleton pregnancy women at risk of recurrent preterm birth, without statistically significant reduction in perinatal mortality or neonatal morbidity. There is no systematic review on twin pregnancies at high risk of preterm birth. With the use of assisted reproductive techniques (ARTs) and some other multiple causes since 1980, the twinning rates had increased in many countries, and the incidence of preterm birth also increased with the high rate of twin pregnancies undeniably.[10] Therefore, there is an urgent need to resolve the evidential uncertainty. The objective of this study was to conduct a systematic review of randomized controlled trials to assess the efficacy of cervical cerclage in preventing preterm birth in twin pregnancies at high risk of preterm birth.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to August 2012), EMBASE (1980 to August 2012), Current Controlled Trials, China Biology Medicine (CBM) (1978 to August 2012), Chinese National Knowledge Infrastructure (CNKI) (1994 to August 2012), and VIP Chinese Journal database (VIP) (1989 to August 2012). The following Medical Subject Headings (MeSH) and words were combined using "OR": "cervical suture", "cervical stitch", "cervical cerclage", "twin pregnancies", "preterm birth", et al. The reference lists of all known primary and review articles were examined to further identify cited articles not captured by electronic searches. No language restrictions were placed on any of the searches.

Inclusion criteria. All randomized trials comparing the effects of cervical cerclage with no cerclage in twin pregnancies women were included. Twin pregnancies women who had a history of one or more second-trimester loss or preterm delivery, or finding of a short cervix on transvaginal ultrasound scanning, or physical exam-detected cervical changes or cervical surgery were included.

Exclusion criteria. Abstracts, letters, case reports, comments and conference proceedings were excluded in this review. Singleton pregnant women, triplet pregnant women or more pregnant women were excluded. The women who have complications of pregnancy such as preeclampsia and other internal or surgical diseases, were excluded, too.

Data selection. Two reviewers independently extracted the following from each studies: first author, publication data, study design, inclusion criteria, exclusion criteria. Both published and unpublished data were considered in this study.

We assessed risk of bias in included studies according to the guidelines recommended in the Cochrane Handbook for Systematic Review of Intervention,[11] which including the adequacy of sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Disagreements were discussed and resolved by consensus with a third reviewer.

We used forest plots graphically and chi-squared test statistically to aid in decisions on how to proceed

with quantitative synthesis in assessing heterogeneity of relative risk (RR). A p value of ≤0.10 was considered heterogeneous and heterogeneity can be accepted when I^2 is ≤50%. For the groups that were found to be homogenous, fixed-effects model was used for summary analysis and for the groups that were found to be heterogeneous, random-effects model was employed. We planned to use variation in features of the population (inclusion and exclusion criteria), intervention (methods of cerclage), outcome (clinical heterogeneity), and study quality (methodological heterogeneity) to explore the causes of heterogeneity. No pooling would be undertaken in the presence of a significant source of heterogeneity. Statistical analyses were carried out using Review Manager (Version 5.1.0).

Results. *Literature search results.* The total number of citations from electronic searches and from examination of reference lists of primary and review articles were 1,128. One thousand and one hundred six were excluded by screening titles and/or abstracts. The selected studies were assessed for methodological quality using Cochrane handbook and 9 studies were excluded as they were not randomized trials. Eight were excluded by reading the full-text articles because 4 reported only singleton pregnancy,[12-15] 2 reported twin pregnancies but the data on twins were not separately analyzed,[16,17] one reported multiple pregnancies[18] and one only have English abstract but the full text cannot be found.[19] There were 5 articles identified as relevant to our review, including 310 participants.[20-24] Detailed search procedures are summarized in the flow chart (**Figure 1**).

The methodological quality of included studies. Only one study provided an adequate randomization model[23] and 2 studies had adequate model for allocation concealment[22,23] using telephone or sealed and opaque envelopes. As a result of the procedure needed anesthesia, all of the studies did not blind their personnel, participants and results analysts or did not mention blinding in the trials. The number of the included studies is so small that it was impossible to conduct a meaningful assessment of publication bias using a funnel plot.

The characteristics of included studies. The study reported by Medical Research Council/Royal College of Obstetricians and Gynaecologists Multicentre Randomised Trial of Cervical Cerclage (MRC/RCOG)[22] is a multi-center study which performed in the United Kingdom and 11 other countries, but the number of twin pregnancies in this trial is not very large and the other selected studies[20-24] were performed in Philadelphia, Saudi Arabia, and Israel, involving 310 participants, originally studied between 1977 and 2006. Four of the studies were compared from McDonald's cerclage or cervical suture with no cerclage,[20,22-24] one comparing cervical cerclage and prophylactic tocolysis with no cerclage.[21] The time of cerclage is variable in different studies, 2 of which in the first trimester[20,24] and 3 in the second trimester.[21-23] The characteristics of selected studies are present in **Table 1**.

Preterm birth. In the subgroup of preterm birth before 34 weeks' gestation, 10 in 66 participants had preterm birth in cerclage group compared to 16 in 68 participants in the control group. There was no significant difference between cerclage group (15.2%, 10/66) and no cerclage group (23.5%, 16/68) (p=0.12, RR 0.58, 95% CI 0.30-1.15) in preterm birth. No statistical heterogeneity in this comparison was observed

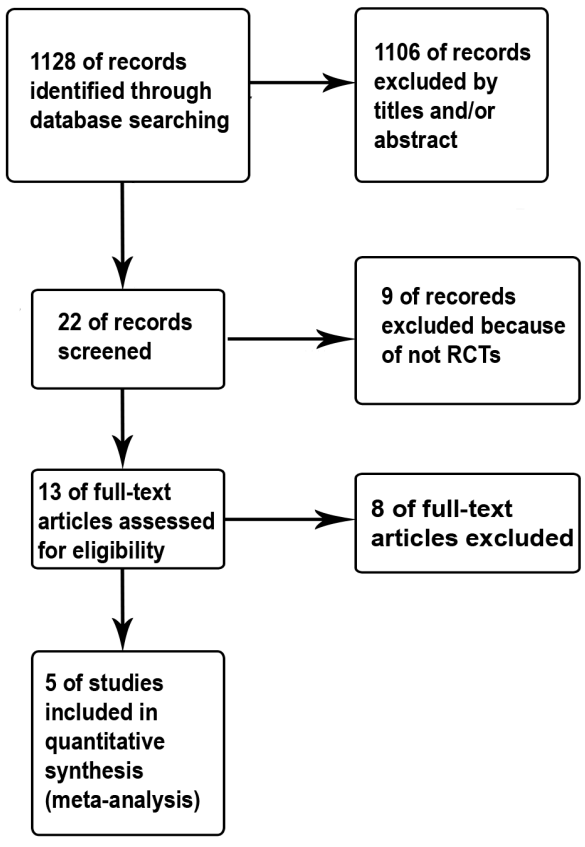

Figure 1 - Study selection process for the systematic review of cerclage for preventing preterm birth in twin pregnancies.

Table 1 - Characteristics of included studies in the systematic review of cervical cerclage for preventing preterm birth in twin pregnancies.

Study	Year	Gestation age (weeks)	Pregnancy	Inclusion criteria	Exclusion criteria	Intervention	Control
Dor et al[20]	1982	13	Twin	Women after induction of ovulation with clomiphene or gonadotropin	Unclear	Cervical cerclage	No cerclage
Kunsch et al[21]	1984	<27	Twin	Unclear	Unclear	Cervical cerclage +tocolysis	No cerclage
MRC/RCOG[22]	1993	Average 15.9	Mixed	Women' obstetrician was uncertain whether to advise her to have cervical cerclage	Not specified	Cervical cerclage	No cerclage
Berghella et al[23]	2004	14 - 23^{+6}	Mixed	High risk for preterm birth or cervical dilatation or membrane bulging	Last pregnancy delivered at term, major fetal, current drug abuse, regular contractions	Cervical cerclage	No cerclage
Eskandar et al[24]	2007	12 - 14	Twin	Twin pregnancies women	Patients with cervical incompetence, major fetal, uterine bleeding, chorioamnionitis	Cervical cerclage	No cerclage

MRC/RCOG - Medical Research Council/Royal College of Obstetricians and Gynaecologists Multicentre Randomised Trial of Cervical Cerclage

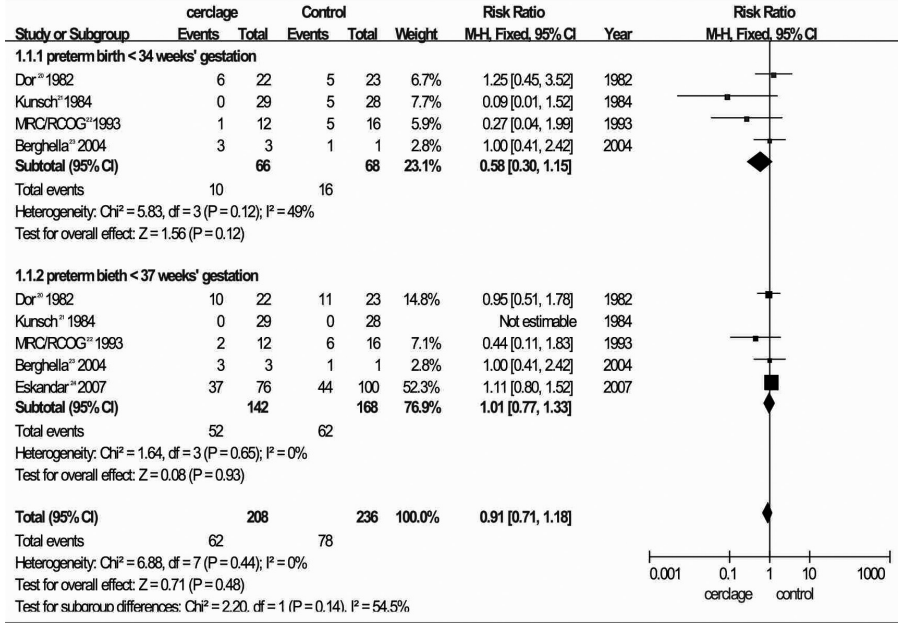

Figure 2 - Estimates of effectiveness of cerclage to prevent preterm birth before 34 weeks' gestation and before 37 weeks' in cerclage and control group of twin pregnancies. MRC/RCOG - Medical Research Council/ Royal College of Obstetricians and Gynaecologists Multicentre Randomised Trial of Cervical Cerclage

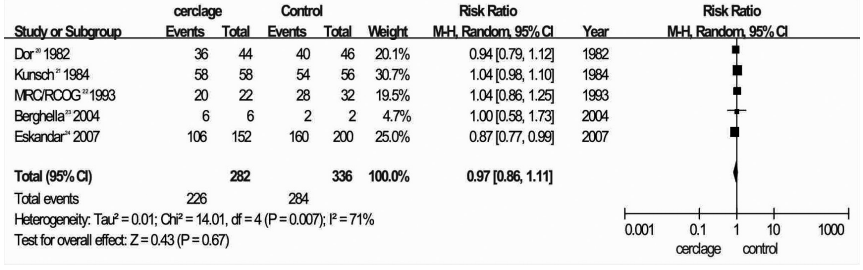

Figure 3 - Estimates of effectiveness of cerclage to prevent preterm birth in live births rate in cerclage and control group of twin pregnancies. MRC/RCOG - Medical Research Council/Royal College of Obstetricians and Gynaecologists Multicentre Randomised Trial of Cervical Cerclage

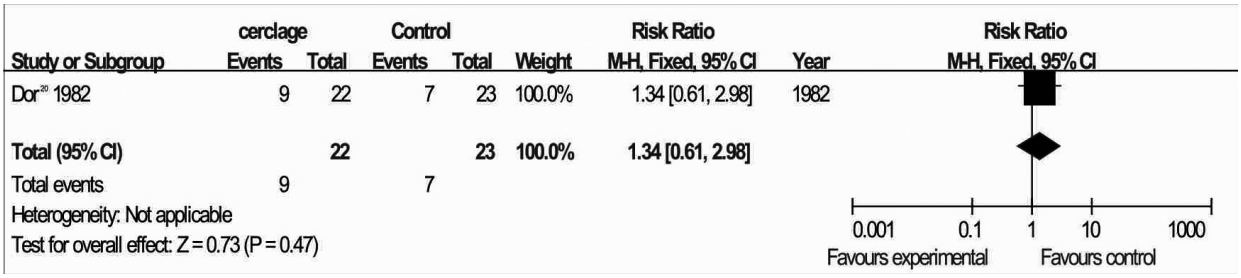

Figure 3 - Estimates of effectiveness of cerclage to prevent preterm birth in cesarean rate in cerclage and control group of twin pregnancies.

(Chi-square = 5.83, df = 3, p=0.12, I^2 = 49%) (**Figure 2**). In the subgroup of preterm birth before 37 weeks' gestation, there were 52/113 participants had preterm birth in cerclage group compared to 62/140 participants in control. There was no significant difference for preterm birth between cerclage group (46.0%, 52/113) and the control group (44.3%, 62/140) (p=0.93, RR 1.01, 95% CI 0.77-1.33). No statistical heterogeneity in this comparison was observed (Chi^2 = 1.64, df = 3, p=0.65, I^2 = 0%) (**Figure 2**).

Live births. All the selected studies talked about the live births. There were 226 live births in 282 babies in cerclage group comparing 284 live births in 336 in control group. The I^2 statistic was 71% and indicated heterogeneity. Accordingly, random effects model was used for pooling and no difference was found in the RR of live births between cerclage and control group (p=0.67, 95% CI 0.86-1.11, p=0.007, I^2 71%) (**Figure 3**). Two studies caused the heterogeneity[21,24] and when these studies were excluded the obtained RR was 0.98 (95% CI 0.86-1.11) using fixed effects model.

Mode of delivery. The study performed by Dor et al[20] reported the cesarean rate. In the cerclage group, 9 participants had cesarean deliveries in 22 patients. While in the control group, 7 participants had cesarean deliveries in 23 patients. No significant difference was observed between the 2 groups (p=0.47, RR 1.34, 95% CI 0.61-2.98) (**Figure 4**).

Discussion. Cervical cerclage is one of the well-known surgical procedures in obstetrics. But there is a debate on the effectiveness of cervical cerclage for preventing preterm birth in twin pregnancies. The evidence from the 5 trials included in our review suggests that, compared with expectant management, cervical cerclage in twin pregnancies does not show a significant difference in preventing preterm birth, or mode of delivery. The result is different from that conducted by Alfirevic et al, which shows cerclage can reduce the incidence of preterm birth in singleton pregnancy.[9] Three of the 5 included trials also revealed no significant difference by using cervical cerclage versus no cerclage in twin pregnancies,[20,23,24] which is consistent with our review. As to the reason why cervical cerclage did not decrease the incidence of preterm birth, we think it has relationship with the intra-uterine infection caused by the procedure. Infection has been thought to be one of the causes of premature rupture of menbrane (PROM) and preterm birth.[25] Intra-uterine infection is not only one of the common complications of cerclage, but also one of the high risk factors in preterm birth. The appropriate use and the choice of antibiotics before or after the procedure are very important to evaluate the result of trials. In included trials, Dor et al[20] showed that suturing the cervix in mid-trimester can develop sepsis and the MRC/RCOG trial[22] concluded that puerperal pyrexia, both overall and ascribed to infection, was twice as common in the cerclage group. Only Berghella et al[23] mentioned using antibiotics to their participants by the obstetrician. So whether to use antibiotics plays an important role in evaluating the efficacy of the procedure. Moini et al[26] suggested that the risk of preterm birth in assisted reproduction technology group was higher than in the spontaneously conceived group in twin pregnancies. There are spontaneous twins, *in vitro* fertilization twins and ovulation-induced twins. All the participants in the trial conducted by Dor et al[20] were ovulation-induced twin pregnancies. Therefore, whether cervical cerclage has the same effects on preventing preterm birth in different types of twins deserves further research. Besides, comparing the influence of cervical cerclage on preventing preterm birth in singleton, twin and multiple (≥3) pregnancies deserves further research, too.

There are also some weaknesses. The inclusion criteria in the 5 included studies were questionable

as to their relationship to high risk of preterm birth. The variation in inclusion criteria was illustrated in **Table 1**. The Kunsch et al[21] and Eskandar et al,[24] which remain the 2 largest trials in our literatures, used lenient inclusion criteria. While this pragmatic approach might cause a wider variety of cases included, the possibility of including cases, which may have a low risk for preterm birth. The 2 trials demonstrated significant heterogeneity constraining our ability to draw a definite conclusion. Besides, as to the quality of the included studies, the sequence generation and concealment of allocation, which were only described clearly in 2 of the 5 included studies, are very important to the system review. The quality of the RCTs, which has a direct relationship with the of system review and the number of RCTs, which aims to evaluate the efficacy of cerclage in twin pregnancies, was so small, these imply for us that conclusions regarding its usefulness could only be safety drawn through large and high quality RCTs in future. We considered cervical length measured by trans-vaginal sonographic as one of the inclusion criterias, however, there is no studies taking this valuable technique in the five included studies. This technique is an objective measurement in predicting cervical incompetence, which means its practical value is more bigger than history of preterm birth or physical exam-detected. We think trans-vaginal sonographic evaluation for measurement of cervical length should be used in further research.

In summary, cervical cerclage does not seem to decrease the incidence of the preterm birth in twin pregnancies who are at high risk of preterm birth. However, the sample size in the 5 articles is not big enough and the quality of trials is not well enough, the influence of cervical cerclage on preventing preterm birth in twin pregnancies deserves further research.

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