Citation for published version (APA):

Citing this paper
Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights
Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the Research Portal

Take down policy
If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Cervical cerclage for preterm birth prevention in twin gestations with short cervix: a retrospective cohort study

Authors: Christopher Houlihan¹, Liona C.Y. Poon², Michele Ciarlo¹, Eugene Kim¹, Edwin R. Guzman¹, Kypros H. Nicolaides²

¹. Department of Obstetrics and Gynecology, Saint Peter’s University Hospital (SPUH), New Brunswick, NJ, USA
². Harris Birthright Research Centre for Fetal Medicine, King’s College Hospital, London, UK

Key Words: Twins, Cervix, Cervical Ultrasound, Cerclage, Prematurity

Financial Support: No source of financial support for this research.

Corresponding author:
Dr Edwin R. Guzman, Saint Peter’s University Hospital, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, MOB 4th Floor, 254 Easton Avenue, New Brunswick, NJ 08901, USA
Telephone: 732-745-8600, ext 8182
Fax: 732-249-3475
Email: eguzman@saintpetersuh.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.15918

This article is protected by copyright. All rights reserved.
Abstract

Objective: To determine if cervical cerclage reduces the rate of spontaneous early preterm birth in cases of ultrasound detected short cervix in dichorionic/diamniotic (DC-DA) twins.

Methods: This was a retrospective cohort study on DC-DA twins. The cases were 40 consecutive DC-DA twins at Saint Peter's University Hospital from November 2006 through May 2012 where cervical cerclage was performed for ultrasound determined cervical length of 1-24 mm at 16-24 weeks’ gestation. The cases were matched with 40 controls with no cerclage for cervical length and gestational age at cervical assessment. The primary outcome measure was spontaneous birth at <32 weeks.

Results: There was no difference between the two groups in maternal age, body mass index, cigarette smoking, use of in-vitro fertilization, parity and prior spontaneous preterm birth. There were statistically more Caucasian women in the controls. In the cases, compared to controls, spontaneous delivery at <32 weeks was significantly less frequent (20.0% vs. 50.0%; relative risk, 0.40; 95% confidence interval [CI], 0.20 to 0.80). In the prediction for spontaneous delivery at <32 weeks, logistic regression analysis demonstrated that the risk was reduced with the insertion of cervical cerclage (odds ratio 0.22, 95% CI 0.058-0.835, P=0.026), corrected for maternal age, body mass index, racial origin, smoking, in-vitro fertilization, parity and previous preterm birth.

Conclusion: In DC-DA twins with a short cervix, treatment with cervical cerclage may reduce the rate of early preterm birth. The findings suggest the need for adequate RCTs on cerclage in twins with a short cervix.
Introduction

Twins, with a prevalence of less than 2% of pregnancies, account for more than 25% of spontaneous early preterm births.\textsuperscript{1,2} Strategies for prevention of preterm birth include the use of vaginal progesterone, cervical pessary and cervical cerclage. Individual patient data meta-analyses (IPDMA) from randomized controlled trials (RCTs) reported that vaginal progesterone in twins with sonographic short cervix did not significantly reduce preterm birth at <33 weeks, but it reduced the risk of composite neonatal morbidity and mortality.\textsuperscript{3,4} The Arabin pessary has been shown to be effective in reducing early preterm birth in singleton pregnancies with short cervix and generated interest in use in twins.\textsuperscript{5} A RCT in twins found that prophylactic use of the Arabin pessary reduced the rate of early preterm birth, but only in the subgroup with short cervix.\textsuperscript{6} However, a large multicenter RCT on the use of the Arabin pessary in unselected twin gestations either prophylactically or with cervical lengths ≤25 mm had no effect on spontaneous birth <34 weeks and neonatal outcome.\textsuperscript{7} An IPDMA of RCTs primarily on singletons which included 49 sets of twins, found that in twins with short cervix use of cervical cerclage may double the rate of spontaneous early preterm birth.\textsuperscript{8} This led to recommendations in the Choosing Wisely program to warn patients against physician recommendations to perform cerclage for the short cervix in twins.\textsuperscript{9} The IPDMA was subsequently repeated, controlling for confounders, and concluded that cerclage did not reduce the incidence of delivery at <34 weeks’ gestation, and its use was associated with an increase in respiratory distress syndrome and birth weights <1500 grams.\textsuperscript{8,10} However, a recent retrospective cohort study reported that cerclage in
twins with short cervix reduced the rate of early preterm birth (57 cerclage vs. 83 expectant).\textsuperscript{11}

Our group has routinely screened twin gestations and offered cerclage for short cervix since the 1990’s with encouraging results.\textsuperscript{12} As a result, we have continued to perform cervical ultrasound screening and offered cervical cerclage for a progressively shortening cervix. The purpose of this retrospective cohort study is to determine whether cerclage in dichorionic-diamniotic (DA-DC) twins gestations with short cervix reduces spontaneous preterm birth at <32 weeks.
Materials and Methods

This is a retrospective cohort study using DC-DA twin gestations followed by serial vaginal cervical sonography in women who were asymptomatic. Excluded were monoamniotic and monochorionic-diamniotic twin gestations, major fetal defects, and women who had a placenta previa or complained of contractions or vaginal bleeding, or were found to have signs or symptoms of intra-amniotic infection. Approval was obtained from the institutional review board committees of all involved institutions.

The cases were 49 consecutive asymptomatic DC-DA twin pregnancies routinely screened with vaginal sonographic cervical length assessments every two weeks from 16 to 24 weeks at Saint Peter’s University Hospital, New Brunswick, New Jersey between November 2006 and November 2014. Nine of these cases with cervical length of 0 mm, a dilated external cervical os, and membranes visible were excluded from subsequent case-control matching and statistical analysis. The 40 cases included in the analysis were treated with cervical cerclage at 16-24 weeks for short cervix. Cerclage placement was considered when the cervical length was <25 mm. Cervical lengths of 16-25 mm are considered as intermediately short and additional factors utilized to offer a cerclage included rate of cervical shortening, progressive shortening within this range, history of prior spontaneous preterm birth or mid-trimester loss, and gestational age at onset of cervical shortening. A cervical length of ≤15 mm was a definitive indicator for offering cerclage. The ultrasound cervical length is not used, by itself, to determine whether to place the cerclage. The technical difficulty is the same regardless of cervical length including zero length since these cervices are equally thick and long and simply dilate from within. The patient had to be asymptomatic. The pre-operative evaluation
assessed for vaginal bleeding, vaginal discharge, cervical lacerations, intra-amniotic infection and uterine contractions. Speculum examinations were performed with the use of Q-tips to evert the exocervix to look for vaginal-cervical discharge, cervical lacerations and appearance and location of the membranes, if visible. All patients had an evaluation of serum white blood cell count and differential. The patient was observed for a period of up to 48 hours before surgery if there was any concern of infection, presence of contractions and/or labor. An isolated finding of a vaginal discharge was evaluated for a definitive diagnosis and treated for at least two days.

Evaluation of vaginal discharge included a wet mount microscopic evaluation without cultures. Amniocentesis was considered if there was a clinical/laboratory suspicion of infection or the cervix was dilated with membranes at or past the external os. If amniocentesis was indicated it was the last step of the evaluation process and performed within several hours of the cerclage procedure so that the amniocentesis results were a true assessment of intra-amniotic infection at the time of cerclage placement. Evidence of intra-amniotic infection was defined as >50 WBC, glucose level <15 mgs/dl and gram stain positive for WBCs or bacteria. Cultures were taken but results were not used in decisions regarding cerclage placement. Evidence of intra-amniotic infection was a contraindication for cerclage. During this period of observation repeat vaginal sonography was sometimes performed to identify any unfavorable change in cervical status. If membranes were beyond the exocervix, membrane tension, ability to reduce membranes digitally, and cervical thickness/effacement was assessed by digital examination to determine technical feasibility of cerclage placement. An effaced cervix was considered evidence of labor and a contraindication to cerclage.
Those that did not satisfy our criteria for cerclage placement during our period of preoperative evaluation were not offered the procedure. Pre-operative prophylactic antibiotics, initially Clindamycin and then Rocephin, and perioperative indomethacin were administered. The modified McDonald cervical cerclage procedures were performed by one of two authors (C.H. and E.R.G.). In the operating room a sponge stick was placed in the endocervical canal to determine the location of the membranes and the anterior lip of the cervix was grasped with the sponge stick. A Foley catheter was passed within the endocervical canal and its balloon was inflated with 30 mL of fluid to displace the membranes from the operative site and avoid inadvertent membrane puncture during suture placement. Two pieces of 0 Prolene (Ethicon, Somerville, New Jersey, USA) on a CT needle with placement begun at the first to second cervical-vaginal rugal folds at 12 o’clock. We use Prolene because 1) it is non-reactive and monofilament, and therefore could be associated with less inflammation and microbial growth within the suture in comparison to other suture materials, 2) the needles attached to this suture material are of a size that allows the operator better access to the upper areas of the vagina and cervix leading to consistent high cerclage placement. If a cervical laceration is present the sutures had to be placed beyond the apex of the laceration with or without dissection of the cervical-vaginal mucosa. We place two sutures for added reinforcement and the second suture is placed above the first by 3 to 10 mm. Before tying the sutures it is important to perform a digital examination to identify whether the sutures had entered the endocervical canal. If this occurs the sutures will tear from within the cervix and lead to cerclage failure, and if identified the suture is removed and replaced. Second, the bladder should be catheterized and the
urine allowed to drip onto a clean gauze pad and observed for evidence of hematuria signifying suture entry into the bladder. When the sutures are tied we create approximately 12 alternating knots. This was to assist in its removal when appropriate. Post-operatively the suture knots will migrate into the cervical stroma. The multiple knots will help in guiding the scissors during cerclage removal. At the time of suture removal the scissors should be kept parallel to the knots in order to guarantee cutting the circular portion rather than the “suture tails”. The patients were discharged within 24 hours of surgery without medications. Through the years, approximately 1 week after surgery, we have performed post-operative sonography to identify the height of cerclage placement. This is done to give us feedback on cerclage placement. This feedback is used to train us on placing the suture material as high as feasible and reduce inter-operator variability. This information is not used to determine whether to reoperate. We are generally within 5 mm of the base of the bladder or approximately 2 cm from the external cervical os.

The controls were selected from a cohort of DC-DA twin pregnancies participating European multicenter studies of sonographic screening for preterm birth by cervical length at 19+0-24+6 weeks’ gestation in one observational and two randomized interventional studies for the prevention of preterm birth. All ultrasound scans were carried out by sonographers who had received the appropriate Certificate of Competence of The Fetal Medicine Foundation (www.fetalmedicine.com). Each transvaginal scan was performed over a period of about 3 minutes and the shortest of three measurements was recorded. The databases were searched for 40 asymptomatic controls with no cerclage and were expectantly managed, that would match to the cases
treated with cerclage for the following characteristics: cervical length and the gestational age at cervical assessment. In the first study, women underwent cervical length assessment as part of an observational study and women with cervical length <19 mm were referred to their obstetrician for expectant management but in some cases they had cervical cerclage or the administration of progesterone vaginal pessaries.\textsuperscript{13} In the second study, women with cervical length <15 mm were randomized to vaginal progesterone or expectant management.\textsuperscript{14} In the third study, women were randomized to the Arabin cervical pessary or expectant management.\textsuperscript{7}

The outcome measure was spontaneous preterm birth at <32 weeks’ gestation. Data on pregnancy outcome were collected from hospital maternity records or general practitioners. The obstetric records of all patients delivered at <32 weeks (<223 days) were examined to determine if the preterm birth was iatrogenic or spontaneous. The latter included those with spontaneous onset of labor and those with preterm pre-labor rupture of membranes.

Continuous variables were summarized by the median and interquartile range (IQR) and categorical variables were presented in numbers and percentages (%). Comparison between the outcome groups was by Chi-square or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. Logistic regression analysis was used to demonstrate whether the risk for spontaneous delivery at <32 weeks was reduced with the insertion of cervical cerclage, corrected for maternal age, body mass index, racial origin, smoking, in-vitro fertilization, parity and prior preterm delivery. The risk of spontaneous preterm birth from insertion of cervical cerclage or expectant management until 32 weeks was assessed using Kaplan-Meier
analysis\textsuperscript{15} where gestational age was the time scale, spontaneous delivery was the event and elective deliveries were treated as censored. Significance was set at a P value of <0.05, two-tailed. Using the primary outcome measure of spontaneous preterm birth at <32 weeks’ gestation, with the effect size of 60\% at the error level of \( \alpha=0.05 \), a sample size of 40 women in each of the cervical cerclage and expectant management groups (total of 80 women) achieved a power of 82\%. The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.
Results

Maternal characteristics in cases and controls are compared in Table 1. We matched for cervical length and gestational age at cervical assessment. In both the cerclage and control groups the distribution of the pre-operative cervical lengths was: 0 case <5mm, 9 cases 5-9 mm, 24 cases 10-14 mm, 5 cases 15-19 mm, and 2 cases 20-24 mm. One case had cerclage placement at a 23 mm cervical length because it was identified at 16 week and there was a history of a prior spontaneous preterm birth.

Perinatal outcomes in the cases and controls are described in Table 2. In both cases and controls all babies survived. In the cervical cerclage group, compared to controls, there was significantly lower rate of spontaneous birth at <32 weeks and higher gestational age at birth and birth weight of both twins. In addition there were significantly lower rate of spontaneous birth <34, <30 and <28 weeks’ gestation in the cerclage treated group. There were no differences between the groups in rates of spontaneous labor/preterm premature rupture of the membranes or no labor. The difference in birth at 32 weeks represented a 60% reduction in the cerclage group (relative risk, 0.40; 95% confidence interval 0.20 – 0.80).

In the prediction for spontaneous delivery at <32 weeks, logistic regression analysis demonstrated that the risk was reduced by the insertion of cervical cerclage (odds ratio 0.22, 95% CI 0.058-0.835, P=0.026), corrected for maternal age, body mass index, racial origin, smoking, in-vitro fertilization, parity and prior preterm delivery.

In the Kaplan–Meier analysis (Figure 1), the cumulative percentage of patients who did not give birth spontaneously before 32 weeks’ gestation was significantly higher
in the cervical cerclage group than in the control group (hazard ratio, 0.300; 95% CI 0.142 to 0.633; P=0.002).
Discussion

This retrospective cohort study in DC-DA twins with short cervix has shown that cervical cerclage was associated with a 60% reduction in the rate of spontaneous birth <32 weeks’ gestation. These results are consistent with those of a recent retrospective cohort study in twins with cervical length ≤15 mm at 16-24 weeks’ gestation which also showed benefit from cerclage placement with a reduction in the rate of spontaneous birth at <34 weeks by 49%. These findings are in marked contrast to the findings of the IPDMA on three RCTs on the use of cervical cerclage for short cervix in twins, which reported no impact on rate of spontaneous birth at <34 weeks.10

The strengths of the study include firstly, the relatively large cohort of DC-DA twins with short cervix consecutively treated with cerclage by two physicians at one center who used a standardized pre-operative protocol and cerclage procedure, good matching with a group of controls that were managed expectantly, and the methodology for cervical length measurement was standardized.

The main limitation of the study arises from its retrospective nature and that it was not a randomized trial. Cases were selected from several European RCTs and we attempted to reduce potential bias by ensuring similar demographic characteristics with controls. There may have been differences in the care of the cases and controls, other than the use of cerclage, which could have affected perinatal outcome. However, there were no known effective therapies to reduce spontaneous early preterm birth in twins during the study period. Despite the matching process there were dissimilarities in maternal characteristics between the cases and controls. We have addressed this
limitation by performing a logistic regression analysis to demonstrate whether the risk for spontaneous delivery at <32 weeks was reduced by the insertion of cervical cerclage, corrected for maternal age, body mass index, racial origin, smoking, in-vitro fertilization, parity and prior preterm delivery. Finally, we did not report on neonatal morbidities and therefore could not assess the impact of cerclage on these perinatal outcome measures.

We presented a clinical and surgical approach associated with a better perinatal outcome than controls. As a result twins with a short cervix were identified who responded favorably to cerclage placement. It is our hope that the approach described can help in the design of RCTs. We suggest that women randomized to the cerclage group should undergo the described clinical approach and if the results are not satisfactory they should not be offered the procedure. Deviation from this approach may actually conceal cerclage benefit. If the proportion of appropriately chosen cases are less than those that should not be surgically treated it could give the impression that cerclage is of no benefit or harmful. This may explain the difference in outcome from this study and the meta-analysis report on the RCTs on the use of cerclage in twins. 8

Our study findings along with of those of Roman et al 11 provide evidence that the use of cervical cerclage for twin pregnancies with short cervix can potentially reduce spontaneous early preterm birth. Ultimately, the results require confirmation from prospective RCTs. We have provided information on cervical length assessment, pre-operative assessment and decision-making, and cerclage technique to assist in the development of such a trial.
References


Table 1. Maternal characteristics in cases and controls.

<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>Cervical cerclage (n=40)</th>
<th>No cervical cerclage (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>31.0 (28.0-34.8)</td>
<td>34.9 (31.4-37.4)</td>
<td>0.940</td>
</tr>
<tr>
<td>Maternal BMI (Kg/m2)</td>
<td>27.0 (24.0-31.0)</td>
<td>25.1 (22.1-28.2)</td>
<td>0.467</td>
</tr>
<tr>
<td>Racial origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>17 (42.5)</td>
<td>28 (70.0)</td>
<td>0.024</td>
</tr>
<tr>
<td>Black</td>
<td>13 (32.5)</td>
<td>7 (17.5)</td>
<td>0.196</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (25.0)</td>
<td>5 (12.5)</td>
<td>0.252</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>2 (5.0)</td>
<td>1 (2.5)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>In-vitro fertilization</td>
<td>13 (32.5)</td>
<td>14 (35.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>24 (60.0)</td>
<td>30 (75.0)</td>
<td>0.232</td>
</tr>
<tr>
<td>Previous SPTB</td>
<td>9 (22.5)</td>
<td>9 (22.5)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>No previous SPTB</td>
<td>7 (17.5)</td>
<td>1 (2.5)</td>
<td>0.057</td>
</tr>
<tr>
<td>Cervical length (mm)</td>
<td>12 (5-23)</td>
<td>12 (5-24)</td>
<td>0.985</td>
</tr>
<tr>
<td>Gestational age at cervical assessment (w)</td>
<td>21.9 (16.1-24.9)</td>
<td>22.9 (16.6-24.9)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Results presented in n (%) or median (interquartile range).
SPTB – spontaneous preterm birth
<table>
<thead>
<tr>
<th>Perinatal outcome variable</th>
<th>Cervical cerclage (n=40)</th>
<th>No cervical cerclage (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth (w)</td>
<td>36.0 (32.9-37.4)</td>
<td>31.6 (27.1-36.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spontaneous birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At &lt;34 w</strong></td>
<td>12 (30.0)</td>
<td>25 (62.5)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>At &lt;32 w</td>
<td>8 (20.0)</td>
<td>20 (50.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>At &lt;30 w</td>
<td>3 (7.5)</td>
<td>14 (35.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>At &lt;28 w</td>
<td>3 (7.5)</td>
<td>12 (30.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Onset of labor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous/PPROM</td>
<td>31 (77.5)</td>
<td>32 (80.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>No labor</td>
<td>9 (22.5)</td>
<td>8 (20.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal for both twins</td>
<td>6 (15.0)</td>
<td>17 (42.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Vaginal/ cesarean section</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
<td>0.494</td>
</tr>
<tr>
<td>Cesarean section for both twins</td>
<td>32 (80.0)</td>
<td>23 (57.5)</td>
<td>0.053</td>
</tr>
<tr>
<td>Birth weight twin A (g)</td>
<td>2357 (1870-2643)</td>
<td>1600 (850-2435)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight twin B (g)</td>
<td>2338 (1960-2673)</td>
<td>1687 (923-2277)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Results presented in n (%) or median (interquartile range).
Figure 1. Kaplan–Meier plot of the probability of continued pregnancy without delivery among patients treated with cervical cerclage as compared with expectant management. Cervical cerclage reduces the risk of spontaneous birth at <32 weeks’ gestation by 70% (hazard ratio for cervical cerclage, 0.300; 95% CI 0.142 to 0.633; P=0.002). Solid line represents the cases with short cervix treated with cerclage. Dashed line represents the untreated controls.