Can prophylactic transvaginal cervical cerclage improve pregnancy outcome in patients receiving cervical conization? A meta-analysis

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ORIGINAL PAPER / OBSTETRICS

Can prophylactic transvaginal cervical cerclage improve pregnancy outcome in patients receiving cervical conization? A meta-analysis

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ABSTRACT

Objectives: Cervical conization could increase the risk of cervical insufficiency. This study systematically evaluated the value of prophylactic transvaginal cervical cerclage following cervical conization with regards to pregnancy outcome.

Material and methods: We performed a systematic review of the literature, using Web of Science, and Embase, the published time ranged from the date that database established to December 2019. Pregnant patients, who had a previous history of cervical conization for CIN or early cervical cancer, were enrolled. Two researchers searched these databases and estimated the included studies’ quality independently, depending on the same criteria.
**Results:** Our meta-analysis is incorporate 3560 cases eventually. Meta-analysis showed that when compared to the no-cerclage group, the risk ratio (RR) of preterm birth in the prophylactic transvaginal cervical cerclage group was 1.85 [95% confidence interval [CI]: 1.22–2.80; p = 0.004); the RR of premature rupture of membranes was 1.5 (95% CI: 1.17–1.93; p = 0.001).

**Conclusions:** The rates of preterm birth were significantly higher in women following cervical conization with transvaginal cerclage than those without cerclage.

**Key words:** cervical conization; prophylactic cervical cerclage; preterm birth; premature rupture of membranes

**INTRODUCTION**

The diagnosis rate of cervical intraepithelial neoplasia (CIN) and micro-invasive cervical carcinoma is much higher in recent years because of the wide usage of cervical sampling [1]. In addition, as delayed childbearing becomes a global trend, the proportion of women of reproductive age who are diagnosed with CIN, and early cervical cancer, is gradually increasing.

High grade CIN and micro-invasive cervical carcinoma can be treated with excisional procedures, also referred to as conization. These procedures include cold knife conization, the loop electrosurgical excision procedure (LEEP), and laser conization. The aim of these procedures is to remove a segment of the cervix for histological examination. The women of reproductive age who experienced these treatments may face negative fertility and pregnancy outcomes in the future.

It is currently considered that cervical conization may increase the risk of cervical insufficiency [2]. Some recent studies have revealed that previous cervical conization is associated with an increased risk of second-trimester pregnancy loss [3, 4], preterm premature rupture of membranes (PPROM), preterm delivery, and perinatal mortality.
A prospective series of research previously revealed that the detection of a short cervix ( < 25 mm) on second-trimester transvaginal ultrasound examination was predictive of an increased risk of preterm birth in women who had experienced conization previously [5, 6]. It is generally accepted that cervical conization may increase the risk of cervical insufficiency; the role of prophylactic cervical cerclage has not been fully studied in women who have undergone previous cervical conization. The effectiveness of prophylactic transvaginal cervical cerclage remains controversial, and its use is associated with perinatal risks. Therefore, this study used the meta-analysis method to systematically evaluate the value of prophylactic transvaginal cervical cerclage following cervical conization in pregnant outcome, in order to provide evidence-based medical evidence for clinical treatment.

MATERIALS AND METHODS

Information retrieval

We searched the database (Web of Science and Embase), setting the published time range from the date that database established to December 2019. The topic term words or free-searching term words used in the database included: cervical conization, cold knife conization, CKC, loop electrosurgical excision, LEEP, and cervical cerclage.

Inclusion and exclusion criteria

Inclusion criteria

There were three types of inclusion criteria — 1. study type: studies were included in our meta-analysis if they represented a prospective or retrospective and were written in English; 2. research target: patients giving birth after cervical conization, those who received transvaginal cervical cerclage represented the case group, while those who did not receive cerclage represented the control group; 3. outcome index: studies were included in our meta-analysis if they reported the risk of
preterm birth, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), perinatal mortality, or low birth weight.

Exclusion criteria

Studies were excluded if they were conference papers, reviews, lectures, or abstracts. Studies were also excluded if the full text was not available, or if they did not include the detailed information or enough data. Self-control clinical trials were also excluded, as were studies that included outcomes for twins, or higher-order multiple births; this was because of the association between plurality and preterm birth.

Quality evaluation

Cochrane risk of bias tool was used to evaluate the quality of incision articles. There were two researchers who searched these databases, estimated the included studies' quality independently, depending on the same criteria. In order to do this, the researchers used self-made data extraction forms, which targeted information relating to patient characteristics, the number of samples, obstetric outcomes, and neonatal outcomes. Subgroup analyses were only performed for cases involving preterm birth at < 34 weeks, and 34–36 + 6 weeks of gestation.

Statistical analysis

Meta-analysis was carried out using Review Manager 5.3 software. Our meta-analysis used both fixed-effects and random-effects depending on the heterogeneity. Statistical heterogeneity of results featured in the selected studies was assessed using the chi-squared test, expressed with the I2 index or p-value; when p > 0.10 or I2 ≤ 50%, we considered that there was no obvious heterogeneity in the included studies, and the fixed-effect model was used. When heterogeneity was detected, we made intensive efforts to identify a possible explanation. If a reasonable cause was found, then subgroup analysis was performed. Otherwise, a random-effects model was used. Variables are represented by relative risks (RRs); interval estimates are all based on
95% confidence intervals (95% CIs). Differences were considered to be statistically significant when p < 0.05.

RESULTS

Information retrieval

After first-circle database searching, 261 articles were detected. Following reading and screening, we accepted nine studies to be included in our final meta-analysis [7–15]. Figure 1 illustrated the literature screening process.

Basic characteristics and literature quality

Table 1 and Table 2 demonstrated the basic characteristics of studies included and Figure 2 showed the literature quality. Ultimately, nine studies were included in the final meta-analysis, featuring a total of 3560 patients; 605 women were treated by prophylactic transvaginal cervical cerclage following conization, while 2,955 women were not.

Systematic review

A risk ratio forest plot showed that the total risk ratio. The total risk ratio for preterm birth was 1.85 (p = 0.004), while I2 was 71%. The total risk ratio of PROM was 1.5 (p = 0.001), with an I2 value of 47%. The total risk ratio of PPROM was 1.18 (p = 0.52), with an I2 value of 52%.

The results of our meta-analysis are shown in Figures 3–7. The use of prophylactic transvaginal cervical cerclage in women with cervical conization was associated with a significantly higher risk of preterm birth < 37 weeks (RR, 1.85; 95% CI, 1.22–2.80), 34–36 + 6 weeks (RR, 2.75; 95% CI, 1.69–4.47) and < 34 weeks (RR, 3.03; 95% CI, 1.06–8.67), and PROM (RR,1.5; 95% CI, 1.17–1.93).

Prophylactic transvaginal cervical cerclage, either with and without cerclage, was not significantly associated with the risk of PPROM (RR, 1.18; 95% CI,0.71–
1.96), low birth weight (RR, 0.63; 95% CI, 0.24–1.67), or perinatal mortality (RR, m1.14; 95% CI, 0.23–5.63).

**Evaluation of publication evaluation**

Funnel plot test results showed that there was no publication bias for preterm birth, PROM, PPROM, low birth weight, and perinatal mortality (Fig. 8).

**DISCUSSION**

Cervical conization is a standard treatment for women with high-grade CIN and micro-invasive carcinoma (Stage 1a1) [16–18]. Women with cervical dysplasia are at an increased baseline risk of preterm birth, and surgical excision confers additional risk [19, 20]. Pregnant patients, with a history of surgical excision, should therefore be considered as having high risk pregnancies [20]. Currently, more studies have found that conization therapy may have adverse effect on the following pregnancy outcomes, including preterm delivery, perinatal death and lower birth weight [3]. There are several factors that may underlie these associations. First, the removal or destruction of a large portion of the collagen that makes up the cervical stromal may reduce tensile strength, thus reducing the mechanical competence of the cervix [21], and ultimately leading to premature dilation of the cervix during pregnancy. Second, excision of tissue and the absence of cervical glands may increase the risk of ascending infection. Third, cervical shortening causes bacteria to enter the uterine cavity from the vagina, thus promoting the migration of bacteria.

In order to prolong pregnancy, surgery remains the mainstay form of therapy. Cervical cerclage is a common method [22]; this method aims to provide mechanical support to the cervix and thereby reduce the risk of preterm birth, thus prolonging the period of gestation in pregnant women with cervical insufficiency [23, 24]. This procedure was initially described as a purse string suture around the cervix, performed using a vaginal approach. Some studies have indicated that cervical cerclage reduces
the risk of preterm birth in women at high risk of preterm birth, and probably reduces the risk of perinatal deaths; furthermore, existing data appear to suggest that this method is more or less effective than other preventative treatments, particularly vaginal progesterone [25]. However, this method can lead to some adverse outcomes [26], including membrane rupture, chorioamnionitis, cervical lacerations, and suture displacement [27]. The incidence of complications varies widely with regards to the timing and indications for cerclage [28]. Overall, there is a low risk of complications with prophylactic cervical cerclage. Some studies have reported that cervical cerclage may increase the risk of preterm birth in women with a cervical length < 25 mm on ultrasound [29]. There is no consensus on the effect of cervical cerclage on pregnancy outcome following cervical conization. Therefore, in the present study, a systematic review discovered the advantage of prophylactic transvaginal cervical cerclage on pregnant outcome following cervical conization.

A transabdominal cerclage is used as an alternative for women for whom a transvaginal cerclage fails, or for women who have had large portions of their cervix removed during the treatment of oncological conditions [30]. This meta-analysis did not include publications relating to transabdominal cervical cerclage. There were two reasons for this. Firstly, when searching the literature, we only retrieved some case reports relating to transabdominal cervical cerclage after cervical conization [31–34]. Secondly, the indication for prophylactic cerclage through the abdomen is slightly different from that of transvaginal cerclage. Patients with cervical weakness who have an extremely short, deformed, or scarred cervix, cannot be adequately managed by prophylactic transvaginal cerclage [35]. There is a difference in the probability of adverse pregnancy outcomes when compared between patients who received transabdominal cerclage, and patients who received cerclage [36]. We retrieved four case reports; the characteristics of these cases are shown in Table 3. We consider that prophylactic transabdominal cerclage is an important treatment modality to improve obstetric prognosis and prevent unexpected complications for those with a history of transvaginal cervical cerclage failure, or multiple cervical cerclage operations. It is
likely that the importance of transabdominal cerclage will increase with the development of conservative operations for invasive uterine cervical cancer. In addition, Ioannis Kyvernitakis previously reported that the results of transabdominal cerclage were comparable to those in singleton pregnancies, and that indications for transabdominal cerclage may be justifiable even in multiple gestations [33]. There is only a limited amount of data relating to prophylactic transabdominal cervical cerclage following cervical conization; further studies are now needed with larger sample sizes.

In order to avoid the significant levels of heterogeneity among different publications relating to pregnancy outcomes, we selected publications for our analysis, using strict criteria. The results were calculated by fixed models due to slight heterogeneity. The results of our meta-analysis showed that there was a large variation between the two groups with regards to the occurrence of preterm birth and PROM. The rates of preterm birth and PROM were significantly higher in women with prophylactic transvaginal cervical cerclage than those without cerclage. However, there was no significant difference in the risk of PPROM, low birth weight, and perinatal mortality, when compared between patients with prophylactic transvaginal cervical cerclage than those without cerclage. In most studies, the indication for cerclage operation was not stated in detail. Some of the heterogeneity between studies that we observed during our meta-analysis may have been associated with the different basic characteristic line, including pregnancy time, auxiliary exam level, medical history and whether there was a subjective judgment for cerclage.

This meta-analysis suggested that prophylactic transvaginal cerclage following conization increases the risk of preterm birth and PROM. In France, a history-indicated cerclage is not recommended for women with only a history of conization [37]. In another study, Kaye and Giraldo-Isaza considered that the increasing risk of PROM following cervical cerclage may related to the risk of ascending infection [38, 39].

Thus far, a variety of treatment methods has been used for cervical conization,
including electrocautery, cryotherapy, laser ablation, cold knife conization, hot knife conization, and LEEP [40, 41]. Some studies reported that different conization methods have different effects on pregnancy outcomes [42, 43]. A recent meta-analysis reported that the risk of preterm birth and adverse sequelae in a subsequent pregnancy was increased after any local cervical treatments [44]. Furthermore, the larger the scope of the operation, the more obvious the adverse effect on the following pregnancy outcomes [cold knife conization (CKC) > large loop excision of the transformation zone (LLETZ) > laser ablation (LA)], and was also higher for excision than ablation. The risk of preterm birth increased with the increasing conization depth [44].

The present meta-analysis includes the most recent literature. We used strict criteria, which could ensure the quality of the including published studies. We also calculated Newcastle-Ottawa-Scale (NOS) in order to determine the quality of the studies included. We also determined publication bias in order to ensure that our results were robust. For strengthening our conclusions, we also adopt meta-regression and in influence analyses.

There are some limitations in this meta-analysis that should be considered. First, the publications included were retrospective studies, and the overall quality of these studies was not high. Secondly, although we applied strict inclusion and exclusion criteria, it was possible that we did not include other biological factors that could have affected pregnancy outcome. Third, our analyses only considered publications that were written in English. Finally, we were not able to sub-divide the conization according to the height of the cervical conization column.

CONCLUSIONS

In conclusion, our meta-analysis suggested that prophylactic transvaginal cervical cerclage following conization increases the risk of preterm birth and PROM. Further studies, with a larger sample size, should now be performed in order to confirm our findings.
REFERENCES


Table 1. Basic characteristics of the studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Nation</th>
<th>Study design</th>
<th>Transvaginal prophylactic cerclage specific method</th>
<th>Maternal age (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geum Joon Cho</td>
<td>2018</td>
<td>Korea</td>
<td>Retrospective</td>
<td>not clear</td>
<td>30.70</td>
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<tr>
<td>Harald Zeisler</td>
<td>1997</td>
<td>Austria</td>
<td>Retrospective</td>
<td>not clear</td>
<td>30.5 (22–41)</td>
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<tr>
<td>Ka Hyun Nam</td>
<td>2010</td>
<td>Korea</td>
<td>Retrospective</td>
<td>not clear</td>
<td>31 ± 3.7</td>
</tr>
<tr>
<td>Kei Miyakoshi</td>
<td>2019</td>
<td>Japan</td>
<td>Retrospective</td>
<td>not clear</td>
<td>33.80</td>
</tr>
<tr>
<td>Lindsay M. Kindinger</td>
<td>2016</td>
<td>Mexico</td>
<td>Retrospective</td>
<td>Monofilament/Braided cerclages</td>
<td>33.22</td>
</tr>
<tr>
<td>Minling Wei</td>
<td>2018</td>
<td>China</td>
<td>Retrospective</td>
<td>Transvaginal cervicoisthmic cerclage</td>
<td>29.9 ± 3.6</td>
</tr>
<tr>
<td>Mi-Young Shin</td>
<td>2010</td>
<td>Korea</td>
<td>Retrospective</td>
<td>not clear</td>
<td>32 (28–40)</td>
</tr>
<tr>
<td>Sharon Armarni</td>
<td>2011</td>
<td>Israel</td>
<td>Retrospective</td>
<td>not clear</td>
<td>32.22 ± 4.58</td>
</tr>
<tr>
<td>Tal Rafaeli-Yehudai</td>
<td>2014</td>
<td>Israel</td>
<td>Retrospective</td>
<td>Mcdonald and Shirodkar cerclage</td>
<td>32.80</td>
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</table>

Table 2. Outcomes of the studies included in this meta-analysis
<table>
<thead>
<tr>
<th>Cesarean delivery</th>
<th>&lt; 28</th>
<th>&lt; 34</th>
<th>&lt; 37</th>
<th>Preterm premature rupture of membranes (weeks)</th>
<th>&lt; 3 4</th>
<th>34 – 36 + 6</th>
<th>Preterm labor (weeks)</th>
<th>Outcome/number</th>
<th>Study</th>
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<tbody>
<tr>
<td>63</td>
<td>/</td>
<td>/</td>
<td>10</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>17</td>
<td>Geum Joon Cho</td>
</tr>
<tr>
<td>185</td>
<td>/</td>
<td>/</td>
<td>22</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>39</td>
<td>Harald Zeisler</td>
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<td>/</td>
<td>4</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>7</td>
<td>Ka Hyun Nam</td>
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<td>6</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>8</td>
<td>Kei Miyakoshi</td>
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<tr>
<td></td>
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<td>22</td>
<td>15</td>
<td>/</td>
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<td>49</td>
<td>Minling Wei</td>
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<td>155</td>
<td>82</td>
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<td>/</td>
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<td>281</td>
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<td>/</td>
<td>/</td>
<td>/</td>
<td>6</td>
<td>18</td>
<td>24</td>
<td>Minyoung Shin</td>
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<td>8</td>
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<td>/</td>
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<tr>
<td>Birth weight (g)</td>
<td>Low birth weight</td>
<td>Perinatal mortality</td>
<td>Apgar score &lt; 7 at 1 min</td>
<td></td>
<td></td>
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<td>2300–3090</td>
<td>3044 (1150–4500)</td>
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<td>3327–3600</td>
<td>3000 (680–4200)</td>
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<tr>
<td>3600+</td>
<td>3000 (680–4200)</td>
<td>3</td>
<td>0</td>
<td></td>
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</tr>
</tbody>
</table>

Birth weight (g): mean ± STD.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Nation</th>
<th>Case number</th>
<th>Conization method</th>
<th>Pregnancy outcome</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ioannis Kyvernitakis [33]</td>
<td>2014</td>
<td>Germany</td>
<td>15 (twins)</td>
<td>Radical Surgical Conization (15)</td>
<td>Vaginal bleeding (1); Preterm labor (1); PPROM (1)</td>
<td>Alive (26); perinatal deaths (3); stillborn(1)</td>
</tr>
<tr>
<td>M. Besio [31]</td>
<td>2004</td>
<td>Chile</td>
<td>7 (singleton)</td>
<td>Wide conization (5); unknown (2)</td>
<td>Miscarriage (4); Second trimester of pregnancy (2); not conceive (1)</td>
<td>Not clear</td>
</tr>
<tr>
<td>Shinichi Ishioka [34]</td>
<td>2018</td>
<td>Japan</td>
<td>10 (singleton)</td>
<td>Conization twice (3), conization (2); radical Surgical Conization (5)</td>
<td>Chorioamnionitis (2), conization method unknown</td>
<td>Stillborn(1)</td>
</tr>
<tr>
<td>Mads Riiskjaer [32]</td>
<td>2012</td>
<td>Denmark</td>
<td>11 (singleton)</td>
<td>two or three previous conizations or a cervical amputation</td>
<td>Miscarriage (4); Second trimester of pregnancy (2); not conceive (1)</td>
<td>Not clear</td>
</tr>
</tbody>
</table>
Figure 1. Document screening process and results

Obtain relevant literature through database search(n=261): Web of Science(n=115), Embase(n=146)

Delete the duplicate(n=71)

Read the abstract(n=190)

Delete(n=177)
  Article type do not match (n=48)
  Not suitable for research purposes(n=125)
  Unable to get full text(n=4)

Read the full text(n=13)

Delete(n=4)
  Cannot get four-table(n=2)
  Incomplete data(n=2)

Inclusion article(n=9)
Figure 2. The risk of bias about the inclusion studies.
Figure 3. Meta-analysis of preterm birth.

Figure 4. Meta-analysis of premature rupture of membranes (PROM)
Figure 5. Meta-analysis of preterm premature rupture of membranes (PPROM)

Figure 6. Meta-analysis of low birth weight

Figure 7. Meta-analysis of perinatal mortality.
Figure 8. Funnel plot. A — preterm birth; B — PROM; C — PPROM; D — low birth weight; E — perinatal mortality