Depth of Cervical Cone Removed by Loop Electrosurgical Excision Procedure and Subsequent Risk of Spontaneous Preterm Delivery

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OBJECTIVE: To investigate the association between cone depth of the loop electrosurgical excision procedure (LEEP) of the cervix and subsequent risk of spontaneous preterm delivery.

METHODS: The study included all deliveries in Denmark over a 9-year period, 1997–2005, with information obtained from various public health registries. Of the 552,678 singleton deliveries included in the study, 19,049 were preterm and 8,180 were subsequent to LEEP. Of the 8,180 deliveries with prior LEEP, 273 were subsequent to two or more LEEPs. Of the deliveries subsequent to only one LEEP, we extracted information about cone depth on 3,605 deliveries, of which 223 were preterm (6.2%). Logistic regression analyses were used to evaluate association between cone characteristics and the subsequent risk of preterm delivery, with simultaneous adjustment for potential confounders.

RESULTS: Increasing cone depth was associated with a significant increase in the risk of preterm delivery, with an estimated 6% increase in risk per each additional millimeter of tissue excised (odds ratio 1.06, 95% confidence interval 1.03–1.09). Severity of the cone histology and time since LEEP were not associated with the risk of preterm delivery. Having had two or more LEEPs increased the risk almost fourfold for subsequent preterm delivery when compared with no LEEP before delivery, and almost doubled the risk when compared with one LEEP before delivery.

CONCLUSION: Increasing cone depth of LEEP is directly associated with an increasing risk of preterm delivery, even after adjustment for several confounding factors.

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LEVEL OF EVIDENCE: II

Cervical intraepithelial neoplasia (CIN) is a potential precancerous lesion in the cervical epithelium. Although CIN can occur at any age, the peak incidence is in women aged 25–35 years.1 Appropriate intervention after a diagnosis of high-grade lesions is important in the prevention of cervical cancer.2 Several studies have shown an association between surgical treatment for CIN and subsequent risk of preterm delivery,3-9 but CIN itself has also been suggested to increase the risk.10 In a recent study of singleton deliveries, we found an increased risk of preterm delivery subsequent to the loop electrosurgical excision procedure [LEEP].11 In LEEP, abnormal tissue including the transformation zone of the cervix is removed, thereby providing an adequate specimen for histologic evaluation.12-14 Confirmation of complete removal of the lesion by observation of specimen margins diminishes the potential risk of missing microinvasive cancers. A possible adverse effect of the procedure is unnecessary removal of normal healthy tissue, thereby affecting cervical function. In theory, one would logically expect that the adverse effect on cervical function is associated with the amount of tissue removed; however, the association between cone depth of LEEP and subsequent risk of...
preterm delivery has only been assessed in three small studies with conflicting results.\textsuperscript{3,15,16} Archarya et al\textsuperscript{15} (2002) found an inverse relationship between cone depth and risk of preterm delivery based, however, on a small sample size (79 deliveries, of which nine were preterm). In a study of LEEP and laser conization, Sadler et al\textsuperscript{16} (2004) found an increasing risk of preterm delivery with increasing cone depth (331 women, of whom 57 had a preterm delivery), but they found no association between conization and overall preterm delivery (relative risk 1.2, 95% confidence interval [CI] 0.8–1.8). In contrast, Samson et al\textsuperscript{4} (2005) found a significant association between conization and overall preterm delivery (558 deliveries, of which 44 were preterm; odds ratio [OR] 3.50, 95% CI 1.90–6.95) but detected no difference between preterm and term deliveries in cone depth ($P=.65$). The mean cone depth in this study was, however, small (7 mm).

The objective of the present study was to assess the association between cone depth of LEEP and the subsequent risk of spontaneous preterm delivery in a large population-based study of singleton deliveries. Furthermore, we assessed the association between the histologic diagnosis made from the cone and time since LEEP, and the subsequent risk of spontaneous preterm delivery.

**MATERIALS AND METHODS**

This study included all deliveries in Denmark over a 9-year period, 1997–2005, from the population-based Medical Birth Registry and National Patient Registry. Details of the study have been described elsewhere.\textsuperscript{11} Briefly, we obtained data on 566,428 singleton deliveries at 21–45 completed weeks of gestation from the two registries for the period January 1, 1997, through December 31, 2005. Linkage between the registries was made with the unique, personal identification number allocated to all Danish inhabitants, which contains the date of birth and sex and is used throughout Danish society, including various public health registries. The deliveries were then linked to the Danish Registry of Pathology, from which we obtained information about all excisional cervical procedures performed (cold knife conizations, laser conizations, and LEEPs). Information about destructive procedures (ablutions) was obtained from the National Patient Registry, and information about in vitro fertilization was obtained from the In Vitro Fertilization Registry. Preterm delivery was defined as a delivery occurring between 21 and 36 weeks of gestation inclusive. The study was approved by the Danish Data Protection Board. In Denmark, approval from an ethical review board is not required for register studies.

All deliveries to women who had undergone conization before 1996 (n=3,692) were excluded because we could not separate cold knife conizations from LEEPs for that period. In addition, deliveries subsequent to cold knife conization in the investigated period were excluded (n=256). Although we were unable to differentiate laser conization from LEEP, laser conization has become rare in Denmark since the introduction of LEEP. To rule out preterm deliveries of another origin than spontaneous, we excluded 2,835 deliveries in which medical induction had been performed before 37 completed weeks, 6,911 deliveries in which cesarean deliveries before initiation of birth had been performed before 37 completed weeks, and 56 deliveries subsequent to a colum amputation. The proportion of deliveries preceded by LEEP in these groups was not different from that in the group of deliveries in the main analysis (3.5%, $P=.27$). Thus, the risk of introducing a competing risk bias was considered to be minimal.

Thus, 552,678 spontaneous deliveries were eligible for further analysis, of which 19,049 were preterm (3.5%). To obtain information about obstetric history before 1997, we linked back to the Medical Birth Registry and the National Patient Registry a second time.

There are no uniform guidelines for the pathologic description of a cone specimen in Denmark. Therefore, before extracting information from the pathology reports, a pathologist was consulted to draw up standardized guidelines for registration. The depth of tissue removed was recorded in millimeters. Most of the cone depths included in the present study were specified as cone height or cone depth in the description (distance between the ectocervical and the endocervical margin); the remainder were obtained from a surface measurement (length, height/depth) but were included only if it was clear that the cone specimen had been cut open before measurements were made. If the cone specimen was not described in the aforementioned way or was cut into more than one piece, cone depth was registered as unknown. All descriptions were reviewed by one of the authors (B.N.).

Logistic regression analyses were used to evaluate the association between cone characteristics and the subsequent risk of preterm delivery, with simultaneous adjustment for potential confounders. The confounders were selected from the literature and applied if the information was available in the registries.\textsuperscript{17,18} We conducted analyses by cone depth specified in categories (12 mm or less, 13–15 mm, 16–19 mm,
20 mm or greater [quartiles]; as a linear spline (a piecewise connected linear function) with three knots placed at the quartiles\textsuperscript{16}; or as linear, histologic findings in cone specimen (normal, CIN 1, CIN 2, CIN 3 or worse, diagnosis not specified, no procedure), number of LEEPs (one, two or more, none), and time since last LEEP (less than 1, 1–2, 2–4, more than 4 years). In the cone depth analysis, LEEPs with unknown depth and two or more LEEPs were not included. The confounders included calendar time (year of delivery), maternal age at delivery, smoking during pregnancy (yes: stopped during first trimester; stopped after first trimester; less than 5, 6–10, 11–20, or more than 20 cigarettes per day; amount unknown; no; missing data), and marital status during pregnancy (no partner, no registered partner, married, unknown). The continuous variables calendar time and maternal age at delivery were modeled as linear splines with knots placed at the quartiles among preterm deliveries (ie, 1999, 2001, 2003, and 26 years, 29 years, 33 years, respectively). Smoking and marital status during pregnancy were grouped according to the categories in the Medical Birth Registry.

Because the number of patients (381,239 women) was large relative to the number of observations per patient (maximum seven, average 1.4 deliveries per woman) the influence of correlation on point estimates was expected to be small, and the correlation was expected only to influence the estimated variances. However, the estimated CIs did not change markedly when using robust variance estimates (data not shown). Secondary analyses were performed to investigate the association between deliveries with two or more prior LEEPs and risk of preterm delivery, compared with deliveries after one LEEP and deliveries after no LEEP. The linearity of the association between cone depth and risk of preterm delivery was evaluated using a linear spline model with three knots placed at the quartiles (ie, 13, 16, and 20 mm) and the estimated ORs (on a logarithmic scale) were plotted as a function of cone depth using deliveries not preceded by LEEP as the reference level. The deviations from a straight line were not significant ($P=.55$, likelihood ratio test).

In addition, we conducted an estimation with additional adjustment for obstetric history, specified as previous spontaneous abortion (yes, no), number of previous spontaneous abortions (linear), previous induced abortion (yes, no), number of previous induced abortions (linear), previous delivery (yes: only term, term and preterm, only preterm; no), number of previous term deliveries (linear), and number of previous preterm deliveries (linear). Associations were expressed as ORs with 95% CIs. Analyses were conducted with SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The 552,678 singleton deliveries in the study were to 381,239 women, of whom 18,007 (4.7%) had at least one spontaneous preterm delivery during the study period and 6,531 (1.7%) had at least one delivery subsequent to LEEP. In the distribution of risk factors for both exposure and outcome, smoking and having no spouse during pregnancy were more frequent in the LEEP group, and smoking and cohabiting rather than being married were more frequent in the preterm delivery group.

Selected demographic characteristics are shown in Table 1. In deliveries subsequent to LEEP, maternal age was slightly higher, and having no spouse in pregnancy and smoking during pregnancy were more frequent. The distributions of characteristics among LEEP exposed with known and unknown cone depth were similar.

A total of 8,180 deliveries with prior LEEP were found, of which 273 were subsequent to two or more LEEPs. We were able to extract information about cone depth on 3,605 deliveries after one LEEP, of which 223 were preterm (6.2%). In the remaining group of 4,302 deliveries after one LEEP of unknown depth, 276 were preterm (6.4%). Table 2 shows the delivery groups of known and unknown cone depth in deliveries after one LEEP by severity of prior CIN in cone diagnosis. Comparing the groups of known and unknown cone depths, there was a tendency of a higher proportion of CIN 3 or worse and a lower proportion of no dysplasia in the group of known depths, and the inverse was seen in the group of unknown depths. Furthermore, within the group of known cone depths, a slightly higher proportion of CIN 3 or worse than CIN 1 and 2 was seen in the deeper cone samples, and the inverse was seen in the smaller cones.

The distributions of known cone depth in the groups of preterm and term delivery after one LEEP were 44.7% and 45.7%, respectively. In the preterm group, the cone depth varied from 5 to 33 mm, with a mean depth of 16.5 (standard deviation 4.9) mm; in the term group, the cone depth varied from 3 to 43 mm, with a mean depth of 15.3 (standard deviation 4.7) mm.

Table 3 shows the associations between LEEP characteristics and preterm delivery. After mutual adjustment and adjustment for year of delivery, maternal age, smoking during pregnancy, and marital status, we found a significant increase in the risk of
preterm delivery with increasing cone depth, with an estimated 6% increase in risk per each additional millimeter of tissue excised (OR 1.06, 95% CI 1.03–1.09). When cone depth was divided into categories according to quartiles, the risk of preterm delivery showed an increasing trend with increments in cone depth. We found no significantly increased risk of preterm delivery with increasing severity of histologic findings in the cone (P<.50). Furthermore, we found no association between time since LEEP and risk of preterm delivery (OR 1.00, 95% CI 0.93–1.08, per year since LEEP).

The association between cone depth and risk of preterm delivery, with deliveries with no prior LEEP as reference, is shown in Figure 1. Thus, the estimated OR for preterm delivery after a cone depth of 10 mm was 1.46 (95% CI 1.11–1.92), and that after a cone depth of 20 mm was 2.85 (95% CI 2.15–3.77).

Among the 273 deliveries after two or more LEEPs (of which 11.4% were preterm), we found an almost fourfold increased risk of subsequent preterm delivery with an OR of 3.78 (95% CI 2.58–5.53) when compared with no LEEP before delivery, and the risk of preterm delivery almost doubled with an OR of 1.88 (95% CI 1.27–2.78) when compared with one LEEP before delivery (data not shown). Adjustment for obstetric history variables did not markedly change any of the estimates for the different cone depths.

DISCUSSION
This study shows that increasing cone depth is directly associated with an increasing risk of pre-

Table 2. Deliveries With Prior Loop Electrosurgical Excision Procedure: Cone Depth by Severity of Histologic Loop Electrosurgical Excision Procedure Diagnosis

<table>
<thead>
<tr>
<th>Severity of CIN</th>
<th>No Dysplasia</th>
<th>CIN 1</th>
<th>CIN 2</th>
<th>CIN 3 or Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone depth (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 or less</td>
<td>68</td>
<td>14.2</td>
<td>130</td>
<td>17.6</td>
</tr>
<tr>
<td>13–15</td>
<td>61</td>
<td>12.7</td>
<td>91</td>
<td>12.4</td>
</tr>
<tr>
<td>16–19</td>
<td>26</td>
<td>5.5</td>
<td>52</td>
<td>7.1</td>
</tr>
<tr>
<td>20 or more</td>
<td>48</td>
<td>10.0</td>
<td>58</td>
<td>7.9</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>42.4</td>
<td>331</td>
<td>45.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>276</td>
<td>57.6</td>
<td>405</td>
<td>55.0</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia. Deliveries with unknown severity of CIN (n=30) are not included in the table.
term delivery, even after adjustment for several confounding factors. In addition, we found an increased risk of preterm delivery with number of prior LEEPs, but no significant association between severity of CIN or time since last LEEP and subsequent risk of preterm delivery among pregnancies with prior LEEP.

The present study has several strengths. First, the study cohort is considerably larger than those in previous studies, which were all limited by small numbers of cases. Thus, our risk estimates are relatively precise. Second, the Danish health information system has almost complete coverage of all deliveries and surgical procedures with data from every hospital and outpatient clinic in the country. Third, standardized guidelines for registration of cone depth were applied to all pathology reports, and only unambiguous measurements were obtained. Last, we adjusted for several potential confounding factors, including calendar time, maternal age, smoking during pregnancy, and marital status. Obstetric history variables were not included in the main analysis, but the estimates were virtually unchanged when they were included.

A potential limitation of the study is the lack of information on socioeconomic status, although smoking and having no partner during pregnancy reflect lower socioeconomic status in Denmark to some extent. In Denmark, laser conization has become rare since the early 1990s; because we included only

Table 3. Deliveries With Prior Loop Electrosurgical Excision Procedure: Association Between Loop Electrosurgical Excision Procedure Characteristics and Subsequent Risk of Preterm Delivery

<table>
<thead>
<tr>
<th>Cone depth (mm)</th>
<th>n</th>
<th>% Preterm Deliveries</th>
<th>OR*</th>
<th>95% CI</th>
<th>OR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 or less</td>
<td>1,022</td>
<td>5.3</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>13–15</td>
<td>1,118</td>
<td>4.4</td>
<td>0.82</td>
<td>0.55–1.23</td>
<td>0.82</td>
<td>0.55–1.23</td>
</tr>
<tr>
<td>16–19</td>
<td>650</td>
<td>7.2</td>
<td>1.44</td>
<td>0.96–2.16</td>
<td>1.45</td>
<td>0.97–2.19</td>
</tr>
<tr>
<td>20 or more</td>
<td>801</td>
<td>9.0</td>
<td>1.76</td>
<td>1.21–2.55</td>
<td>1.79</td>
<td>1.23–2.60</td>
</tr>
<tr>
<td>Linear (per mm)</td>
<td>3,591</td>
<td>6.2</td>
<td>1.05</td>
<td>1.03–1.08</td>
<td>1.06</td>
<td>1.03–1.09</td>
</tr>
</tbody>
</table>

Histologic findings in cone

| Normal          | 203 | 5.9 | 0.68 | 0.33–1.41 | 0.70 | 0.34–1.45 |
| CIN 1           | 331 | 6.3 | 1.17 | 0.74–1.85 | 1.24 | 0.78–1.96 |
| CIN 2           | 657 | 6.0 | 1.09 | 0.77–1.56 | 1.16 | 0.81–1.66 |
| CIN 3           | 2,400 | 6.5 | 1.00 | — | 1.00 | — |

Time since last LEEP (y)

| Less than 1     | 1,111 | 6.6 | 0.96 | 0.63–1.45 | 0.94 | 0.62–1.42 |
| 1–2             | 799 | 7.1 | 1.20 | 0.78–1.83 | 1.20 | 0.78–1.85 |
| 2–4             | 1,005 | 5.7 | 1.04 | 0.69–1.58 | 1.03 | 0.68–1.57 |
| More than 4     | 676 | 5.9 | 1.00 | — | 1.00 | — |
| Linear (per y)  | 3,591 | 6.3 | 1.00 | 0.93–1.08 | 1.00 | 0.93–1.08 |

OR, odds ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure.

* Adjusted for maternal age, year of delivery, smoking during pregnancy, and marital status.
† Mutually adjusted and further adjusted for maternal age, year of delivery, smoking during pregnancy, and marital status.

Deliveries after LEEP with no information on cone depth (n=4,302), deliveries after two or more LEEPs (n=273), and LEEPs with missing diagnosis (n=14) are not included in the model.
conizations from 1996 onward, we consider that the number of laser treatments in our cohort was minimal. A minor limitation to the adjustment in the analysis was missing information about smoking and marital status for the 596 deliveries at less than 28 weeks coming from the National Patient Register. The estimates did not, however, change when we excluded these 596 deliveries from the analyses. Although we were able to extract information about cone depth for only 44.7% (223 of 499) of the preterm deliveries with one prior LEEP, the distribution of preterm deliveries was similar in the group of deliveries after LEEP with known cone depths (6.2%) and those after unknown cone depths (6.4%).

Only a few studies have assessed cone depth of LEEP and subsequent risk of preterm delivery, with conflicting results. In a meta-analysis of three studies including LEEP and laser conization, Kyrgiou et al (2006) found a significantly increased risk of preterm delivery when the cone depth exceeded 10 mm (OR 2.61, 95% CI 1.28–5.34), compared with cone depths less than 10 mm. In another Danish cohort, we also previously found an increased risk of preterm delivery subsequent to conization (all modalities) with an estimated 20% increase in risk per each additional mm tissue excised (0.12, 95% CI 1.0–1.4).7

Bruinsma et al10 showed that women with treated (all modalities) and untreated CIN had significantly higher risks for preterm delivery than women in the general population (age-standardized prevalence ratios: 2.0, 95% CI 1.8–2.3 and 1.5, 95% CI 1.4–1.7, respectively). Although the untreated women had a significantly increased risk of preterm delivery, the risk of the treated women was significantly higher, indicating an additional effect of treatment or maybe an additional effect associated with the severity of CIN. In our assessment of cone height, we included severity of CIN and time since LEEP as covariates in a multivariate analysis. We found no significant association between either severity of CIN or time since LEEP and subsequent risk of preterm delivery, indicating that the increase in risk can be attributed to the procedure itself, the degree of risk depending on the depth of tissue removed.

The potential clinical implication of this study is that it should raise awareness of the association between depth of LEEP cone excised and the risk of preterm delivery. To obtain a suitable tissue specimen for histologic evaluation and to minimize the risk of recurrent disease, a certain depth is undoubtedly needed; however, in most cases of CIN, excessive LEEP cone depth probably adds unnecessarily to the risk of adverse effects in future pregnancies. In a recent meta-analysis by Arbyn et al22 investigating the association between treatment of CIN and severe pregnancy outcome, the authors suggested that most excisions in young women with fully visible transformation zone should not exceed 1 cm in depth.

In conclusion, we showed that increasing cone depth of LEEP was associated with an increasing risk of preterm delivery in subsequent pregnancies, with a 6% increase in risk per each additional millimeter of tissue excised. In addition, we found an increased risk of preterm delivery subsequent to two or more LEEPs as compared with deliveries after only one prior LEEP. The severity of the histologic diagnosis made from the cone and time since LEEP were not associated with the risk of preterm delivery in the present study.

REFERENCES


