# Treatment for Cervical Intraepithelial Neoplasia and Risk of Preterm Delivery

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**Context** It is unclear whether treatments for cervical intraepithelial neoplasia (CIN) increase the subsequent risk of preterm delivery. Most studies have lacked sufficient sample size, mixed heterogeneous subtypes of preterm delivery, and failed to control for confounding factors.

**Objective** To determine whether cervical laser and loop electrosurgical excision procedure (LEEP) treatments increase risk of preterm delivery and its subtypes.

**Design, Setting, and Participants** Retrospective cohort study conducted among women evaluated at a colposcopy clinic serving Auckland, New Zealand (1988-2000), comparing delivery outcomes of untreated women (n=426) and those treated (n=652) with laser conization, laser ablation, or LEEP. Record linkage using unique health identifiers identified women who had subsequent deliveries.

**Main Outcome Measures** Total preterm delivery and its subtypes, spontaneous labor and premature rupture of membranes before 37 weeks' gestation (pPROM).

**Results** The overall rate of preterm delivery was 13.8%. The rate of pPROM was 6.2% and the rate of spontaneous preterm delivery was 3.8%. Analyses showed no significant increase in risk of total preterm delivery (adjusted relative risk [aRR], 1.1; 95% confidence interval [CI], 0.8-1.5) or spontaneous preterm delivery (aRR, 1.3; 95% CI, 0.7-2.6) for any treatment. Risk of pPROM was significantly increased following treatment with laser conization (aRR, 2.7; 95% CI, 1.3-5.6) or LEEP (aRR, 1.9; 95% CI, 1.0-3.8), but not laser ablation (aRR, 1.1; 95% CI, 0.5-2.4). Moreover, risk of pPROM and total preterm delivery increased significantly with increasing height of tissue removed from the cervix in conization. Women in the highest tertile of cone height (≥1.7 cm) had a greater than 3-fold increase in risk of pPROM compared with untreated women (aRR, 3.6; 95% CI, 1.8-7.5).

**Conclusions** LEEP and laser cone treatments were associated with significantly increased risk of pPROM. Careful consideration should be given to treatment of CIN in women of reproductive age, especially when treatment might reasonably be delayed or targeted to high-risk cases.

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CERVICAL INTRAEPITHELIAL neoplasia (CIN) is a precancerous condition that can be effectively treated to prevent invasive cervical cancer. In the 1980s, the standard of treatment for CIN shifted from cold-knife conization toward less radical therapies, primarily excision diathermy and carbon dioxide laser conization or vaporization procedures. Loop electrosurgical excision procedure (LEEP) is widely used worldwide, removes less tissue, requires less operating time, is associated with lower rates of hemorrhage, pain, and infection, and is as effective as conventional surgical therapies.[1] Laser treatment is rarely performed now because it is more expensive and more technically difficult, and vaporization does not yield tissue for histological examination.

Recent screening data from New Zealand indicate that rates of high-grade squamous intraepithelial abnormalities peak among women aged in their 20s and decline markedly thereafter.[2] For this reason, accurate assessment of the effect of cervical procedures on risk of preterm delivery and other adverse pregnancy outcomes is of significant public health concern.

Although large registry-based studies of treatment with mixed modes of conization provide some evidence that cervical treatment is associated with preterm birth,[3,4] studies of cold-knife conization,[5-10] laser conization,[11-15] or LEEP[16-21] alone have been limited and inconclusive. Most studies were small and lacked the statistical power necessary to detect a doubling of risk.[6-8,12-17,19,21] Only a handful of studies controlled for potentially important confounding by smoking and socioeconomic status,[3,14] analyzed treatment by depth of tissue excised,[11,12,14,22,23] or evaluated risk of preterm delivery by its specific subtypes (ie, medical induction, premature rupture of membranes before 37 weeks' gestation [pPROM], and spontaneous preterm labor),[5,19,24,25] which are likely to be etiologically distinct.[26] It is plausible that cervical excisional or ablative treatments might affect the risk of preterm delivery by reducing the mechanical support provided by a short-

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ened cervix, by impairing local immunological defense mechanisms by destruction of glandular epithelia, or by altering cervicovaginal bacterial flora.[24]

To estimate the risk of preterm delivery and its subtypes following laser or LEEP treatment for CIN, we conducted a retrospective record linkage cohort study of treated and untreated women seen at a large hospital-based colposcopy clinic in Auckland, New Zealand, during a 12-year period. The study was designed to determine the influence of treatment type, height of cervical tissue excised, and number of treatments on subsequent risk of preterm delivery or its subtypes.

## METHODS

A retrospective cohort was constructed by linking the colposcopy service database at National Women's Hospital (NWH), Auckland, for the years 1988 through 1999 with the obstetric database at the same hospital for deliveries from 1989 through 2000. The hospital was the principal provider of public colposcopy services and inpatient obstetric care to women in the central Auckland area. Women were included in the cohort if they were seen and/or treated at the colposcopy clinic, subsequently carried a singleton pregnancy to at least 20 completed weeks' gestation, and delivered or had postpartum care at the study hospital. A pregnancy was included only if the visit to the colposcopy clinic or treatment occurred before the first menstrual period was missed (ie, last menstrual period + 30 days). The treated group consisted of women whose qualifying pregnancy occurred after treatment with laser ablation, laser conization, or LEEP. The untreated group had a qualifying pregnancy following a visit to the colposcopy service but before any cervical treatments that may have been administered. Women treated by modes other than laser ablation, laser conization, and LEEP were excluded from the treated group, as were women who had cervical treatments before 1988 and those whose prior treatment status was unknown. Only the first qualifying pregnancy per woman was included in the study.

Ethical approval for the study was obtained from the Auckland Ethics Committee.

Exact database linkage was possible using the unique identifier assigned to each individual using the public health system in New Zealand. The colposcopy and obstetric records and pathology reports were obtained and manually abstracted for women identified by the database linkage. Five percent of the included records were reabstracted by 1 of the investigators (L.S.) for quality control. If clinical notes could not be obtained (4%), data were taken directly from the original colposcopy and obstetric databases. Data collected included demographic characteristics, gynecological, obstetric, and medical history, colposcopic findings, cervical cytologic and histological findings, cervical treatment details, and pregnancy complications and outcomes. All data were abstracted onto data sheets before entry into a statistical database for analysis.

Gestational age was defined hierarchically as follows: (1) by date of the last menstrual period if within 7 days' agreement with an ultrasound scan performed by 14 completed weeks or within 14 days' agreement of a scan performed between 14 and 26 weeks; (2) by scan if the date of the last menstrual period was outside the aforementioned limits of agreement and the scan was performed by 26 weeks; or (3) by recorded clinical estimate during pregnancy if the first scan was performed after 26 weeks or if there was no scan. Preterm delivery (delivery before 37 weeks) was categorized into its subtypes: spontaneous labor leading to delivery before 37 weeks, pPROM leading to delivery before 37 weeks, and iatrogenic delivery before 37 weeks. The category of pPROM included any case in which spontaneous rupture of the membranes preceded onset of contractions. Iatrogenic delivery included induction for reasons other than ruptured membranes and cesarean delivery before onset of contractions, excluding cases of pPROM.

To estimate the risk of preterm delivery and its subtypes associated with treatment of CIN, we conducted analyses by treatment mode (LEEP, laser conization, or laser ablation), number of treatments (1 or >1), and vertical height of tissue removed among women treated by laser conization or LEEP. Untreated women served as the referent groups in the aforementioned analyses. Vertical height of tissue obtained at cervical biopsy was calculated from the histology reports of women having only 1 treatment. The length calculated was the vertical height of the specimen after fixation if only 1 pass of tissue was taken or the sum of the vertical heights if more than 1 pass was taken and orientation of the specimens was clear. If it was not possible to determine the height from the report, height was recorded as unknown. Height of tissue removed was divided into tertiles for multivariate analysis, and a category was assigned for women for whom this information was unavailable.

Several risk factors for preterm delivery were also examined to identify and adjust analyses for potential confounding effects on the relationship of treatment of CIN and preterm delivery risk. Socioeconomic status was measured by deprivation index, which is an area-based score from 1 to 10 incorporating 8 dimensions measuring deprivation from the New Zealand 1996 Census.[27] It was assigned according to the census "meshblock" where the mother lived at the time of first antenatal visit. A score of 10 describes individuals living in the most deprived areas. The deprivation indexes were then categorized into 3 groups for the analyses. Smoking describes smoking during pregnancy, as noted on the record of the first antenatal visit. A category was assigned for missing smoking data. Data on ethnicity were collected from forms completed by patients at the time of admission. Women of mixed ethnicity were classified by priority, in the order shown, as Maori, Pacific Islander, Asian, European, or other (including Middle Eastern, Latin American, and

African). Analyses could also adjust for the effects of transfers to NWH; transfers are women who planned to deliver at a hospital other than NWH and then transferred to NWH at some time during pregnancy, labor, or the immediate postnatal period. Data were not included on sexually transmitted diseases and bacterial vaginosis because swabs were not routinely taken during pregnancy.

**Table 1.** Preterm Delivery Subtypes and Demographic, Obstetric, and Pathological Characteristics by Treatment Status

| | Treated, No. (%) (n = 652) | Untreated, No. (%) (n = 426) | *P* Value |
|---|---|---|---|
| Delivery | | | |
| All preterm | 97 (14.9) | 52 (12.2) | .21 |
| <32 wk | 24 (3.7) | 13 (3.1) | .53 |
| pPROM | 52 (8.0) | 15 (3.5) | .004 |
| Spontaneous | 26 (4.0) | 15 (3.5) | .64 |
| Iatrogenic | 19 (2.9) | 22 (5.2) | .09 |
| Term | 555 (85.1) | 374 (87.8) | |
| Demographic characteristics | | | |
| Age, y | | | |
| <25 | 134 (20.6) | 102 (23.9) | .50 |
| 25-29 | 218 (33.4) | 145 (34.0) | |
| 30-34 | 203 (31.1) | 119 (27.9) | |
| ≥35 | 97 (14.9) | 60 (14.1) | |
| Ethnicity | | | |
| European/other | 445 (68.5) | 232 (54.7) | <.001 |
| Asian | 14 (2.2) | 32 (7.6) | |
| Maori | 110 (16.9) | 77 (18.2) | |
| Pacific Islander | 81 (12.5) | 83 (19.6) | |
| Socioeconomic status* | | | |
| 1-3 (High) | 136 (21.3) | 87 (20.7) | .58 |
| 4-6 (Intermediate) | 193 (30.2) | 116 (27.6) | |
| 7-10 (Low) | 311 (48.6) | 217 (51.7) | |
| Obstetric characteristics | | | |
| Smoked during pregnancy | | | |
| Yes | 271 (41.6) | 132 (31.0) | <.001 |
| No | 328 (50.3) | 265 (62.2) | |
| Unknown | 53 (8.1) | 29 (6.8) | |
| Nulligravid | 188 (28.8) | 111 (26.1) | .32 |
| Nulliparous | 324 (49.7) | 203 (47.7) | .51 |
| History of preterm delivery (parous only) | 30 (9.2) | 28 (12.6) | .20 |
| Interhospital transfer | 103 (15.8) | 36 (8.4) | <.001 |
| Antepartum hemorrhage | 69 (10.6) | 43 (10.1) | .78 |
| Pathological characteristics | | | |
| Referral cytology | | | |
| Normal | 24 (3.7) | 73 (17.1) | <.001 |
| LSIL† | 322 (49.4) | 256 (60.0) | |
| HSIL‡ | 268 (41.1) | 43 (10.1) | |
| Malignant | 3 (0.5) | 1 (0.2) | |
| Other diagnosis | 14 (2.1) | 33 (7.7) | |
| No smear | 21 (3.2) | 20 (4.7) | |
| Histological findings | | | |
| CIN 1/WVI | 209 (32.1) | 199 (46.6) | <.001 |
| CIN 2/CIN 3/AIS | 402 (61.7) | 22 (5.2) | |
| Microinvasive | 6 (0.9) | 0 | |
| No dysplasia/other diagnosis | 13 (2.0) | 90 (21.1) | |
| None | 22 (3.4) | 115 (27.0) | |

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; pPROM, premature rupture of membranes before 37 weeks' gestation; WVI, wart virus infection.
*Based on deprivation index; see "Methods" section of text for details.
†Includes WVI, CIN1, and unspecified atypical cells.
‡Includes CIN2, CIN3, and AIS.

Univariate and multivariate analyses were conducted using SAS software, version 8.1 (SAS Institute Inc, Cary, NC). Categorical variables were compared using $\chi^2$ or Fisher exact tests and continuous data using *t* tests. Logistic regression was performed to identify variables for potential confounding or effect modification of the association of treatment with risk of preterm delivery. Age, ethnicity, socioeconomic status, smoking in pregnancy, previous obstetric history, transfer, and antepartum hemorrhage were included as covariables in the models for a priori reasons and then removed manually if they were not important confounders. Interaction was explored between treatment variables and parity, smoking during pregnancy, and age, and between treatment mode and cone height. Significance testing of interactions was performed using the log likelihood ratio test. Risk factors were retained in the final models if they altered the parameter estimate of the exposure variable(s) by at least 10%. After the best model was determined using logistic regression, multivariate relative risk analysis was performed to obtain adjusted relative risk (aRR) estimates using the Genmod procedure in SAS. The relationship between height of tissue excised and risk of pPROM was explored by including cone height as a continuous variable in logistic regression models overall, within tertiles of height with untreated women as the referent group, and within treated women only.

## RESULTS

From the colposcopy database of 9226 women, 1208 women were found to have had a singleton live birth of at least 20 weeks' gestation, by linkage with the obstetric records. Of these, 27 were excluded for invalid treatments (13 cryotherapy, 8 Cartier biopsies, and 6 cold-knife conizations), 10 for unknown previous treatment status, and 93 be-

cause of previous treatment, leaving a cohort of 1078 women who had given birth following treatment or their first encounter at the colposcopy clinic. The clinical records of 1020 women (95%) were abstracted in full. Data were obtained from the database for women whose colposcopy or obstetric records could not be located (4%). Twenty-eight percent of women had had an ultrasound scan by 14 weeks' gestation and 70% by 26 weeks' gestation.

The overall rate of preterm delivery was 13.8% (n=149); 41 (27.5%) were iatrogenic, 41 (27.5%) resulted from spontaneous preterm labor, and 67 (45%) were due to pPROM. As shown in TABLE 1, the rates among treated women exceeded the rates for untreated women for total preterm delivery (14.9% vs 12.2%; $P=.21$), pPROM (8.0% vs 3.5%; $P=.004$), and spontaneous preterm labor (4.0% vs 3.5%; $P=.64$). Iatrogenic preterm delivery occurred in 2.9% of the treated group and in 5.2% of the untreated group ($P=.09$).

TABLE 2 shows significant univariate associations between preterm delivery and smoking during pregnancy, history of preterm delivery, interhospital transfer, and antepartum hemorrhage. Women with preterm deliveries are overrepresented by high-grade histological findings (51.0%) compared with women with term deliveries (37.5%).

Six hundred six women had 1 treatment, 44 had 2 treatments, 2 had 3 treatments, and 426 were untreated. Among those who had only 1 treatment, 105 (17%) were treated by laser conization, 278 (46%) by LEEP, and 223 (37%) by laser ablation. Among women who had 2 treatments, 9 had 2 ablations, 2 had 2 laser conizations, 10 had 2 LEEPs, 10 had a laser conization and a LEEP, 4 had a laser conization and an ablation, and 9 had a LEEP and an ablation. Among women who had 3 treatments, 1 had 2 laser conizations and an ablation, and 1 had 3 LEEPs.

The distributions of histological diagnoses across treatment modes for single treatments with laser conization or LEEP were similar. Data on height of cervical tissue excised were available for 331 women (86%) who had 1 laser conization or LEEP treatment. Mean height was 1.37 cm (SD, 0.57 cm) among all single treatments, 1.40 cm (SD, 0.46 cm) for laser conization, and 1.36 cm (SD, 0.61 cm) for LEEP. As shown in TABLE 3, women in the highest tertile of cone height more often had high-grade histological findings. Treatment mode was not associated with height tertile.

Adjusted RR analyses indicate that treatment for CIN was not associated with increased risk of total preterm delivery or spontaneous preterm delivery (TABLE 4). In contrast, increased risk of pPROM leading to preterm de-

**Table 2.** Demographic, Obstetric, and Pathological Characteristics by Delivery Type*

| | Spontaneous Labor (n = 41) | pPROM (n = 67) | Iatrogenic (n = 41) | All Preterm (n = 149) | Term (n = 149) | *P* Value† |
|---|---|---|---|---|---|---|
| Demographic characteristics | | | | | | |
| Age, y | | | | | | |
| <25 | 26.8 | 26.9 | 19.5 | 24.8 | 21.4 | .74 |
| 25-29 | 22.0 | 35.8 | 31.7 | 30.9 | 34.1 | |
| 30-34 | 41.5 | 17.9 | 34.2 | 28.9 | 30.0 | |
| ≥35 | 9.8 | 19.4 | 14.6 | 15.4 | 14.4 | |
| Ethnicity | | | | | | |
| European/other | 53.7 | 74.2 | 70.7 | 67.6 | 62.3 | .17 |
| Asian | 7.3 | 1.5 | 0 | 2.7 | 4.5 | |
| Maori | 24.4 | 19.7 | 14.6 | 19.6 | 17.1 | |
| Pacific Islander | 14.6 | 4.6 | 14.6 | 10.1 | 16.1 | |
| Socioeconomic status‡ | | | | | | |
| 1-3 (High) | 7.9 | 28.1 | 23.1 | 21.3 | 21.0 | .45 |
| 4-6 (Intermediate) | 26.3 | 26.6 | 20.5 | 24.8 | 29.8 | |
| 7-10 (Low) | 65.8 | 45.3 | 56.4 | 53.9 | 49.2 | |
| Obstetric characteristics | | | | | | |
| Smoked during pregnancy | | | | | | |
| Yes | 41.5 | 53.7 | 43.9 | 47.7 | 35.7 | <.001 |
| No | 39.0 | 38.8 | 46.3 | 40.9 | 57.3 | |
| Unknown | 19.5 | 7.5 | 9.8 | 11.4 | 7.0 | |
| History of preterm delivery (parous only) | 22.0 | 7.5 | 12.2 | 12.8 | 4.2 | <.001 |
| Gravidity | | | | | | |
| 1 | 29.3 | 25.4 | 22.0 | 25.5 | 28.1 | .51 |
| ≥2 | 70.7 | 74.6 | 78.1 | 74.5 | 71.9 | |
| Parity | | | | | | |
| 0 | 41.5 | 49.3 | 48.8 | 47.0 | 49.2 | .62 |
| ≥1 | 58.5 | 50.8 | 51.2 | 53.0 | 50.8 | |
| Interhospital transfer | 26.8 | 32.8 | 24.4 | 28.9 | 10.2 | <.001 |
| Antepartum hemorrhage | 31.7 | 20.9 | 17.1 | 22.8 | 8.4 | <.001 |
| Pathological characteristics | | | | | | |
| Referral cytology | | | | | | |
| Normal | 9.8 | 7.5 | 7.3 | 8.1 | 9.2 | .77 |
| LSIL | 46.3 | 44.8 | 63.4 | 50.3 | 54.1 | |
| HSIL | 34.2 | 41.8 | 17.1 | 32.9 | 28.2 | |
| Malignant | 0 | 0 | 0 | 0 | 0.4 | |
| Histological findings | | | | | | |
| CIN1/WVI | 26.8 | 25.4 | 39.0 | 29.5 | 39.2 | .04 |
| CIN2/CIN3/AIS | 46.3 | 64.2 | 34.2 | 51.0 | 37.5 | |
| Microinvasive | 0 | 1.5 | 0 | 0.7 | 0.5 | |

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; pPROM, premature rupture of membranes before 37 weeks' gestation; WVI, wart virus infection.
*All data are expressed as percentages.
†For comparison between term and preterm data.
‡Based on deprivation index; see "Methods" section of text for details.

livery was associated with a single treatment by laser conization (aRR, 2.7; 95% confidence interval [CI], 1.3-5.6) or LEEP (aRR, 1.9; 95% CI, 1.0-3.8) (Table 4). Moreover, risk of pPROM increased with increasing tertile corresponding to height of cervical tissue excised (Cochran-Armitage trend test, $P<.001$). Women who had a vertical cone height of at least 1.7 cm of tissue removed had more than a 3-fold greater risk than untreated women (aRR, 3.6; 95% CI, 1.8-7.5) and an 18% rate of pPROM. Analysis of cone height as a continuous variable showed that the strength of dose-response relationship with risk of pPROM was constant within each of the 3 tertiles. The β coefficients from these unadjusted logistic regression analyses for tertiles 1 through 3 are 0.7, 0.7, and 0.8, respectively, suggesting that pPROM risk increases linearly with increments in cone height and that there is no cone height threshold for risk of pPROM.

There was also a significant increasing trend of risk of all preterm delivery with increasing cone height. No significant interaction was found between treatment variables and parity, smoking during pregnancy, or age, or between treatment mode and cone height.

**Table 3.** Histological and Treatment Characteristics by Tertile of Cone Height Among Women Treated by Laser Conization or LEEP

| | Vertical Cone Height, No. (%) | | | |
|---|---|---|---|---|
| | Tertile 1 (0.1-1.0 cm) (n = 116) | Tertile 2 (1.1-1.6 cm) (n = 114) | Tertile 3 (≥1.7 cm) (n = 101) | *P* Value |
| Histological findings | | | | |
| CIN1/WVI | 36 (31.0) | 30 (26.3) | 18 (17.8) | .08 |
| CIN2/CIN3/AIS | 77 (66.4) | 81 (71.1) | 82 (81.2) | .047 |
| Microinvasive | 1 (0.9) | 1 (0.9) | 1 (1.0) | |
| Treatment mode | | | | |
| Laser conization | 30 (25.9) | 41 (36.0) | 32 (31.7) | .25 |
| LEEP | 86 (74.1) | 73 (64.0) | 69 (68.3) | |

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; WVI, wart virus infection.

## COMMENT

The findings in this study suggest that cervical treatment by laser conization or LEEP is associated with pPROM resulting in preterm delivery. Increasing cone height was directly associated with increasing risk of preterm delivery and pPROM. There was no association between laser ablation and risk of pPROM. Moreover, there was no association of any treatment or individual mode of treatment with risk of spontaneous preterm or overall preterm delivery outcomes.

It might be expected that if there is a real increase in risk of pPROM, then an increase in the risk of overall preterm delivery should also have been observed. However, the entities that make up total preterm deliveries are heterogeneous. In this study, there was a nonsignificantly higher rate of iatrogenic preterm delivery in untreated women, which may have contributed to the lack of effect on combined preterm delivery outcomes. We were able

**Table 4.** Relative Risk of Preterm Delivery and Subtypes Associated With CIN Treatment Characteristics

| | Treatment Mode | | | | | No. of Treatments | | Cone Height, cm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No Treatment* | Any Treatment | Laser Conization | LEEP | Laser Ablation | 1 | >1 | 0.1-1.0 | 1.1-1.6 | ≥1.7 | Missing |
| **All Preterm Delivery** | | | | | | | | | | | |
| No. of Patients | 426 | 652 | 105 | 278 | 223 | 606 | 46 | 116 | 114 | 101 | 52 |
| Rate, No. (%) | 52 (12.2) | 97 (14.9) | 20 (19.1) | 44 (15.8) | 23 (10.3) | 87 (14.4) | 10 (21.7) | 14 (12.1) | 18 (15.8) | 25 (24.8) | 7 (13.5) |
| cRR (95% CI) | 1.0 | 1.2 (0.9-1.7) | 1.6 (1.0-2.5) | 1.3 (0.9-1.9) | 0.8 (0.5-1.3) | 1.2 (0.9-1.6) | 1.8 (1.0-3.3) | 1.0 (0.6-1.7) | 1.3 (0.8-2.1) | 2.0 (1.3-3.1) | 1.1 (0.5-2.3) |
| aRR (95% CI) | 1.0 | 1.1 (0.8-1.5) | 1.3 (0.8-2.2) | 1.2 (0.8-1.8) | 0.8 (0.5-1.2) | 1.0 (0.7-1.5) | 1.3 (0.6-2.6) | 0.9 (0.5-1.6)† | 1.1 (0.6-1.9) | 1.7 (1.0-2.7) | 1.2 (0.5-2.6) |
| **pPROM and Preterm Delivery** | | | | | | | | | | | |
| No. of Patients | 389 | 607 | 100 | 256 | 210 | 566 | 41 | 109 | 105 | 93 | 49 |
| Rate, No. (%) | 15 (3.9) | 52 (8.6) | 15 (15.0) | 22 (8.6) | 10 (4.8) | 47 (8.3) | 5 (12.2) | 7 (6.4) | 9 (8.6) | 17 (18.3) | 4 (8.2) |
| cRR (95% CI) | 1.0 | 2.2 (1.3-3.9) | 3.9 (2.0-7.7) | 2.2 (1.2-4.2) | 1.2 (0.6-2.7) | 2.2 (1.2-3.8) | 3.2 (1.2-8.3) | 1.7 (0.7-4.0) | 2.2 (1.0-4.9) | 4.7 (2.5-9.1) | 2.1 (0.7-6.1) |
| aRR (95% CI)‡ | 1.0 | 1.8 (1.0-3.2) | 2.7 (1.3-5.6) | 1.9 (1.0-3.8) | 1.1 (0.5-2.4) | 1.8 (1.0-3.2) | 1.8 (0.6-5.1) | 1.1 (0.4-3.0)§ | 1.7 (0.7-4.0) | 3.6 (1.8-7.5) | 2.2 (0.7-6.9) |
| **Spontaneous Labor and Preterm Delivery** | | | | | | | | | | | |
| No. of Patients | 389 | 581 | 88 | 247 | 208 | 543 | 38 | 106 | 100 | 82 | 47 |
| Rate, No. (%) | 15 (3.9) | 26 (4.5) | 3 (3.4) | 13 (5.3) | 8 (3.9) | 24 (4.4) | 2 (5.3) | 4 (3.8) | 4 (4.0) | 6 (7.3) | 2 (4.3) |
| cRR (95% CI) | 1.0 | 1.2 (0.6-2.2) | 0.9 (0.3-3.0) | 1.4 (0.7-2.8) | 1.0 (0.4-2.3) | 1.2 (0.6-2.2) | 1.4 (0.3-5.8) | 1.0 (0.3-2.9) | 1.0 (0.4-3.1) | 1.9 (0.8-4.7) | 1.1 (0.3-4.7) |
| aRR (95% CI)‖ | 1.0 | 1.3 (0.7-2.6) | 0.9 (0.3-3.2) | 1.5 (0.7-3.2) | 1.4 (0.6-3.2) | 1.3 (0.7-2.6) | 1.5 (0.3-7.0) | 1.1 (0.4-3.6) | 1.0 (0.3-3.0) | 1.9 (0.7-5.1) | 1.4 (0.3-6.2) |

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; cRR, crude relative risk; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; pPROM, premature rupture of membranes before 37 weeks' gestation.
*The "no treatment" group served as the referent for all analyses in this table.
†Cochran-Armitage trend test, $P = .002$.
‡Adjusted for age (<25, 25-29, 30-34, or ≥35 years), smoking during pregnancy (no smoking, smoking, or unknown status), ethnicity (Maori, Pacific Islander, Asian, or other), history of preterm delivery, and transfer to National Women's Hospital.
§Cochran-Armitage trend test, $P<.001$.
‖Adjusted for age (<25, 25-29, 30-34, or ≥35 years), smoking during pregnancy (no smoking, smoking, or unknown status), ethnicity (Maori, Pacific Islander, Asian, or other), history of preterm delivery, transfer to National Women's Hospital, and antepartum hemorrhage.

to categorize and analyze preterm deliveries by their subtypes with sufficient sample size and power.

Most previous studies have concluded that there is no association between preterm delivery and laser or LEEP therapies, despite 2- to 6-fold increases in RR.[11,12,14-16,19,21,25] It is likely that these studies lacked sufficient power to detect an increase in risk of this magnitude. The present study reports the experience of a considerably larger cohort of women than any of the previously reported studies. A further strength is our use of a comparison group from the same colposcopy clinic from which the treated population was taken, instead of women from the general obstetric population. Thus, the same selection factors that led to evaluation and treatment at the colposcopy clinic are present in both the treated and untreated women comprising our study population. It is well known that women undergoing evaluation for cervical treatment for CIN have demographic, behavioral, and sexual histories that also put them at increased risk of preterm delivery outcomes. This is reflected in the rate of overall preterm delivery (12.2%) in the untreated group, suggesting that these women are a high-risk group because of factors other than cervical treatment. Nonetheless, the retrospective design of our study places potential limitations on accuracy and completeness of data on variables such as socioeconomic status, smoking, and infection.

A significant association between conization and pPROM was previously reported in a case-control study.[24] The authors found a history of conization (type unspecified) in 1 (3%) of 38 women in preterm labor, 9 (26%) of 35 women with pPROM, and 1 (1%) of 75 normal pregnancies. A further analysis of 78 pregnancies following LEEP compared with 78 controls matched for age, parity, and smoking found an RR of pPROM of 3.0 (95% CI, 0.6-14.4). Most previous studies, however, have looked at overall preterm delivery as the primary outcome, even though preterm delivery constitutes a heterogeneous group of outcomes with multifactorial etiologies.[26]

The literature examining the association between amount of tissue removed and preterm delivery risk is also limited and inconsistent. A study by Leiman et al[22] reported the outcomes of 88 pregnancies in 77 women following cold-knife conization. The rate of preterm delivery among women delivering after the second trimester who had had more than 2 cm removed (n=16) was 44% compared with 12% among women with removal of less than 2 cm (n=51) ($P<.01$). In the laser conization literature, 2 articles reported no association between cone height and total preterm delivery[11,12] and a third reported an adjusted odds ratio for preterm delivery with cone height of more than 1 cm of 11.1 (95% CI, 1.2-102.1).[14] A study reporting a mix of laser ablation and conization found a substantially higher rate of preterm delivery among 12 women who had had at least 10 mm of tissue removed (25%) compared with the rate among 42 women with less than 10 mm of tissue removed (7%; $P=.12$).[23] There are no data on the effect of cone height in the LEEP literature. In our study, a quarter of women who had a cone height of greater than 1.6 cm had a preterm delivery, and 18% had pPROM.

It could be argued that the effect on pPROM observed in this study is due to the disease itself. Women with pPROM more often had high-grade histological findings than other women. However, we would refute this hypothesis based on the following: (1) there is no effect of laser ablation on pPROM risk, even though 46% of women who had ablation had high-grade histological findings (Table 3) and (2) it is implausible because in the vast majority of cases, the diseased tissue was completely excised before pregnancy began. It could, however, be argued that unexplained confounding from factors associated with severity of CIN may explain at least some of the association found.

Ricciotti et al[28] measured the cervix by transvaginal ultrasound before and after LEEP and showed that there was a strong correlation between height of excised tissue and reduction in cervical length measured by ultrasound ($r=0.9$). The RR of spontaneous preterm delivery increases as cervical length shortens in mid pregnancy. It is not known whether cervical length prior to pregnancy is predictive of risk of spontaneous preterm delivery.

Premature rupture of membranes before 37 weeks' gestation is probably a final common pathway for pathologic initiators that result in increased breakdown of membrane collagen. The uncertainty regarding the pathophysiology of this process makes it difficult to hypothesize about the mechanism by which cervical excisional therapies might increase risk. The findings of this study suggest that the amount of cervical tissue removed is important. Mechanisms proposed include lack of mechanical support due to shortened length of the cervix, impairment of antimicrobial defense mechanisms after removal of cervical glands, and alteration of cervicovaginal bacterial flora.[24]

One of the limitations of this study is the unknown loss to follow-up of women who delivered at units other than the host institution. However, referral bias is unlikely to have occurred because of inclusion of women transferred after planning to deliver at other nearby institutions. This is because loss to follow-up resulting from delivery elsewhere, while associated with risk of pPROM, is unlikely to have been associated with treatment status among women either with or without pPROM. We believe that obstetric caregivers would always refer women with pPROM to a tertiary hospital for safe delivery, irrespective of their treatment status. In fact, the risk of preterm delivery overall was not significantly different between treatment groups, suggesting that obstetric caregivers were not biased in their referral of women with signs of preterm labor to the tertiary center. In addition, we included a dichotomous variable for transfer in all final statistical models.

The clinical implications of our findings relate to treatment of CIN and management of any subsequent preg-

nancies. Guidelines on the management of cytologic and histological abnormalities of the cervix were issued following a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology in 2001.[29,30] This study makes the case for careful adherence to and consideration of these guidelines, which reflect the importance of targeting treatment to women at high risk of progression. The guidelines for managing low-grade squamous intraepithelial lesions state that treatment as initial management of this condition is unacceptable in the absence of biopsy-confirmed CIN. In other words, single-visit diagnosis and treatment protocols, which invariably overtreat a percentage of women, should be abandoned. In the presence of biopsy-proven CIN stage 1, the guidelines recommend follow-up without treatment, including use of human papillomavirus testing as an option. Moreover, if any CIN is to be treated, excisional and ablative techniques are both acceptable unless the lesion is recurrent or colposcopy inadequate. Less radical treatment for younger women could reduce volume of tissue excised but might be balanced by an increase in persistent disease, need for retreatment, and cervical cancer risk. An implication for management of pregnancy is educating women about their risk so they present early with pPROM for antibiotic and steroid therapy. There is a possible role for cervical cerclage in women in whom ultrasound shows progressive cervical shortening during pregnancy.[31,32]

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*Study concept and design:* Sadler, Saftlas, Whittaker, McCowan.
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*Analysis and interpretation of data:* Sadler, Saftlas, Wang, McCowan.
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## REFERENCES

**1.** Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. *Gynecol Oncol.* 1994;54:175-179.
**2.** Coppell K, Paul C, Cox B. An evaluation of the National Cervical Screening Programme Otago site. *N Z Med J.* 2000;113:48-51.
**3.** El-Bastawissi AY, Becker TM, Daling JR. Effect of cervical carcinoma in situ and its management on pregnancy outcome. *Obstet Gynecol.* 1999;93:207-212.
**4.** Kristensen J, Langhoff-Roos J, Kristensen FB. Increased risk of preterm birth in women with cervical conization. *Obstet Gynecol.* 1993;81:1005-1008.
**5.** Jones JM, Sweetnam P, Hibbard BM. The outcome of pregnancy after cone biopsy of the cervix: a case-control study. *Br J Obstet Gynaecol.* 1979;86:913-916.
**6.** Weber T, Obel EB. Pregnancy complications following conization of the uterine cervix. *Acta Obstet Gynecol Scand.* 1979;58:347-351.
**7.** Moinian M, Andersch B. Does cervix conization increase the risk of complications in subsequent pregnancies? *Eur J Obstet Gynecol Reprod Biol.* 1982;14:135-142.
**8.** Buller RE, Jones HW. Pregnancy following cervical conization. *Am J Obstet Gynecol.* 1982;142:506-512.
**9.** Ludviksson K, Sandstrom B. Outcome of pregnancy after cone biopsy—a case-control study. *Eur J Obstet Gynecol Reprod Biol.* 1982;14:135-142.
**10.** Larsson G, Grundsell H, Gullberg B, Svennerud S. Outcome of pregnancy after conization. *Acta Obstet Gynecol Scand.* 1982;61:461-466.
**11.** Hagen B, Skjeldestad FE. The outcome of pregnancy after CO2 laser conisation of the cervix. *Br J Obstet Gynaecol.* 1993;100:717-720.
**12.** Sagot P, Caroit Y, Winer N, Lopes P, Boog G. Obstetrical prognosis for carbon dioxide laser conisation of the uterine cervix. *Eur J Obstet Gynecol Reprod Biol.* 1995;58:53-58.
**13.** Spitzer M, Herman J, Krumholz B, Lesser M. The fertility of women after cervical laser surgery. *Obstet Gynecol.* 1995;86:504-508.
**14.** Raoi L, Ghezzi F, Di Naro E, Gomez R, Luscher KP. Duration of pregnancy after carbon dioxide laser conization of the cervix: influence of cone height. *Obstet Gynecol.* 1997;90:978-982.
**15.** Forsmo S, Hansen M, Jacobsen B, Oian P. Pregnancy outcome after laser surgery for cervical intraepithelial neoplasia. *Acta Obstet Gynecol Scand.* 1996;75:139-143.
**16.** Gunasekera PC, Lewis BV, Phipps JH. Obstetric outcome after cervical surgery for intra-epithelial dysplasia. *J Obstet Gynaecol.* 1992;12:291-293.
**17.** Blomfield PI, Buxton JD, Luesley DM. Pregnancy outcome after large loop excision of the cervical transformation zone. *Am J Obstet Gynecol.* 1993;169:620-625.
**18.** Haffenden DK, Bigrigg A, Codling BW, Read MD. Pregnancy following large loop excision of the transformation zone. *Br J Obstet Gynaecol.* 1993;100:1059-1060.
**19.** Braet PG, Peel JM, Fenton DW. A case controlled study of the outcome of pregnancy following loop diathermy excision of the transformation zone. *J Obstet Gynaecol.* 1994;14:79-82.
**20.** Cruikshank ME, Flannelly G, Campbell DM, Kitchener HC. Fertility and pregnancy outcome following large loop excision of the cervical transformation zone. *Br J Obstet Gynaecol.* 1995;102:467-470.
**21.** Paraskevaidis E, Koliopoulos G, Lolis E, Papanikou E, Malamou-Mitsi V, Agnantis N. Delivery outcomes following loop electrosurgical excision procedure for microinvasive (FIGO stage IA1) cervical cancer. *Gynecol Oncol.* 2002;86:10-13.
**22.** Leiman G, Harrison NA, Rubin A. Pregnancy following conization of the cervix: complications related to cone size. *Am J Obstet Gynecol.* 1980;136:14-18.
**23.** Soutter WP, Abernethy FM, Brown VA, Hill AS. Success, complications, and subsequent pregnancy outcome relative to the depth of laser treatment of cervical intraepithelial dysplasia. *Colp Gynecol Laser Surg.* 1986;2:35-42.
**24.** Svare JA, Anderson LF, Langhoff-Roos J, et al. The relationship between prior cervical conization, cervical microbial colonization and preterm premature rupture of the membranes. *Eur J Obstet Gynecol Reprod Biol.* 1992;47:41-45.
**25.** Saunders N, Fenton DW, Soutter WP, Brown VA, Sharp F, Abernethy F. A case controlled study of the outcome of pregnancy following laser vapourisation cone of the cervix. *Reprod Perinat Med.* 1986;6:121-125.
**26.** Savitz DA, Blackmore CA, Thorp JM. Epidemiologic characteristics of preterm delivery: etiologic heterogeneity. *Am J Obstet Gynecol.* 1991;164:467-471.
**27.** Crampton P, Davis P. Measuring deprivation and socioeconomic status: why and how? *N Z Public Health Rep.* 1998;5:81-84.
**28.** Ricciotti HA, Burke L, Kobelin M, Slomovic B, Ludmir J. Ultrasound evaluation of cervical shortening after loop excision of the transformation zone (LETZ). *Int J Gynaecol Obstet.* 1995;50:175-178.
**29.** Wright T, Cox J, Massad L, Carlson J, Twiggs L, Wilkinson E. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol.* 2003;189:295-304.
**30.** Wright T, Cox J, Massad L, Twiggs L, Wilkinson E. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA.* 2002;287:2120-2129.
**31.** Althuisius S, Dekker G, Hummel P, Bekedam D, van Geijn H. Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol.* 2001;185:1106-1112.
**32.** Drakeley A, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. *Cochrane Database Syst Rev*. 2003(1):CD003253.