Published in final edited form as:
*Obstet Gynecol*. 2013 December ; 122(6): 1154–1159. doi:10.1097/01.AOG.0000435454.31850.79.

# Interval From Loop Electrosurgical Excision Procedure to Pregnancy and Pregnancy Outcomes

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## Abstract

**Objective—**Prior studies have shown mixed results for pregnancy outcomes after loop electrosurgical excision procedure (LEEP); however, evidence is lacking regarding the pregnancy outcome of spontaneous abortion with respect to time elapsed from LEEP to pregnancy. We investigated risk of spontaneous abortion and preterm birth as they relate to time elapsed from a LEEP to pregnancy.

**Methods—**A 10-year, multicenter cohort study of women who underwent LEEP was performed between 1996–2006. Trained research nurses conducted phone interviews with all patients to complete data extraction unavailable in charts. Median time from LEEP to pregnancy for spontaneous abortion compared with no spontaneous abortion and preterm birth before 34 and before 37 weeks compared with term birth were estimated. Patients with time intervals shorter than 12 months compared with 12 months or longer from LEEP to pregnancy were then compared to identify adjusted odds ratios for spontaneous abortion and preterm birth.

**Results—**Five hundred ninety-six patients met inclusion criteria. Median time from LEEP to pregnancy was significantly shorter for women with an spontaneous abortion (20 months, interquartile range 11.2–40.9 vs. 31 months, interquartile range 18.7–51.2, p-value 0.01), but did not differ for women with a term birth compared to preterm birth. Women with a time interval shorter than 12 months compared to 12 months or more had a significantly increased risk for spontaneous abortion (17.9% vs. 4.6%, aOR 5.6, 95%CI 2.5–12.7). No increased risk was identified for preterm birth before 34 or before 37 weeks.

**Conclusion—**Women with a shorter time interval from LEEP to pregnancy have an increased risk for spontaneous abortion, but not preterm birth.

## Introduction

Cervical excision procedures for diagnosis and treatment of cervical dysplasia are becoming increasingly common among women of reproductive age due to the prevalence of the HPV virus. (1) Loop electrosurgical excision procedure (LEEP) is the most common cervical excision procedure currently used. (2–4) The depth and breadth of the portion of cervix removed varies based on individual characteristics of the lesion, however in most cases part of the cervical body, the complete transformation zone, and a portion of the endocervical

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**Financial Disclosure:** The authors did not report any potential conflicts of interest.

Presented as a poster at the annual meeting of the Society of Maternal Fetal Medicine, February 11–16, 2013, San Francisco, California.

canal are removed. (2–4) Removing a portion of the cervix theoretically leaves future pregnancies at higher risk for complications related to cervical integrity. (5–6) In addition, given that healing and remodeling from a LEEP occurs over time, it is biologically plausible that the time interval from LEEP to pregnancy is an important factor in determining risk for complications.

Previous studies have investigated the link between time interval from LEEP to pregnancy and pregnancy complications, most relating to preterm delivery, with conflicting results. (7–12) However, evidence that investigates an association between time interval from LEEP to pregnancy and the effect on risk of spontaneous abortion (SAB) is lacking.

In this study, we aimed to estimate the effect of length of time between LEEP and subsequent pregnancy on risk for preterm delivery and spontaneous abortion. This could potentially provide health practitioners with an evidenced-based guide to counseling women on the optimal timing of pregnancy after LEEP to optimize subsequent pregnancy outcomes.

## Materials and Methods

This study was a secondary analysis of a 10-year multicenter retrospective cohort study. Patients included in the primary study were women who underwent a LEEP, a Pap test, or a cervical biopsy in one of nine centers (both tertiary and community) from 1996–2006. The parent study compared women with a prior LEEP to two groups of age-matched controls, women without a history of cervical dysplasia, and women with a history of cervical biopsy without LEEP for the primary outcome of preterm birth before 34 weeks. After approval by the institutional review boards at each center, patients were identified through review of pathology records through a search of clinical databases of surgical pathology. All pathology records and medical records were obtained and reviewed in detail. Trained obstetric research nurses conducted structured closed-ended phone interviews with each patient to complete demographic, historical, and obstetric data unavailable in the medical record. Data obtained included information on patient medical and surgical history, obstetric and gynecology history, prenatal history, antepartum records, and delivery records.

In this study, all women who had undergone a LEEP and had a subsequent pregnancy during the study period were included. The pregnancy evaluated in this analysis was the first pregnancy after LEEP. Women were excluded from analysis if the index pregnancy was a multiple gestation, medical records were missing, or if the date of LEEP or delivery were unknown. Pregnancies were dated by a woman's last menstrual period if that date was within 7 days of a first trimester ultrasound examination or within 10 days of a second-trimester ultrasound examination. Pregnancies were dated by ultrasonography if the last menstrual period was unknown or if the ultrasound dating was outside the aforementioned parameters. Spontaneous abortion was defined as a spontaneous pregnancy loss at less than 20 weeks post-menstrual age. All diagnoses of SAB were confirmed by review of medical record including positive HCG or ultrasound documentation. If a discrepancy was found between patient report of SAB and the medical records, the medical record was used. Induced abortions were excluded. Two study groups were defined by time interval from LEEP to pregnancy, women with an interval shorter than 12 months compared to an interval of 12 months or longer. The 12-month time interval was chosen based on results from a prior study. (7) Outcomes compared between groups were SAB before 20 weeks, and preterm delivery before 37 weeks and before 34 weeks. We performed secondary analyses for time interval strata of less than 6 months, 6–11 months, 12–23 months, and ≥ 24 months.

Median time elapsed from LEEP to pregnancy was calculated and compared for women with a SAB and no SAB, and women with preterm birth before 37 and before 34 weeks compared to term birth. Women with SAB were further stratified by gestational age at time of SAB, those prior to 12 weeks, and those who were 12–19 weeks compared to women without a SAB. Baseline characteristics were compared between groups using chi-square or Fisher exact test for categorical variables, and Student's t-test or Mann-Whitney U test for continuous variables as appropriate. Normality was tested with the Kolmogorov-Smirnov test. Stratified analyses were performed to identify potentially confounding variables. Incidence, crude relative risk, and 95% confidence interval for each of the primary outcomes were calculated. Multivariable logistic regression was used to adjust for confounding factors identified through the results of the univariable and stratified analyses. Backwards stepwise selection was used to reduce the number of variables. Fit of the final models were tested with the Hosmer and Lemeshow goodness of fit test. Tests with $p < 0.05$ were considered statistically significant. All statistical analyses were completed using STATA software package 10.0 (StataCorp, College Station, TX).

## Results

In all, 596 women who had a LEEP and subsequent pregnancy in the study period met inclusion criteria. The LEEP to pregnancy interval was shorter than 12 months for 56 women (9.4%), and 12 months or more in 540 women (90.6%). The overall rates of the primary outcomes were 6% for SAB, 8.7% for preterm birth prior to 34 weeks, and 18.1% for preterm birth before 37 weeks. Baseline characteristics of the study groups were only significantly different with respect to age and BMI. Women with a LEEP to pregnancy interval of shorter than 12 months were younger and thinner compared to those with an interval of 12 months or more. Rates of prior preterm birth, smoking, and African American race were not significantly different between the two groups. (Table 1)

The median time to pregnancy for the entire cohort was 30.8 months (interquartile range 18.4–50.7). Overall, women with SAB had a shorter median time interval from LEEP to pregnancy compared to women without SAB (20.3 months, interquartile range 11.2–40.9 vs. 31.2 months, interquartile range 18.7–51.2, p-value 0.01). There were 35 reported and confirmed SABs before 20 weeks: 30 before 12 weeks and five at 12–19 weeks. When stratifying the analysis by these two gestational age range categories, we continue to find a significantly shorter LEEP to pregnancy median time interval for women with SAB before 12 weeks (17.9 months, interquartile range 8.9–40.9 vs. 31.2 months, interquartile range 18.7–51.2, p-value <0.01). However, there was no difference in time interval for women with SAB 12–19 weeks compared to women without SAB (33.0 months, interquartile range 23.4–40.6 vs. 31.2 months, interquartile range 18.7–51.2, p-value 0.85). On the other hand, median time intervals were not significantly different for preterm birth before 37 weeks and before 34 weeks compared to term births. (Table 2)

Compared to women with a LEEP to pregnancy interval of 12 months or more, a time interval of shorter than 12 months was associated with more than a fivefold increased risk for SAB (17.9% vs. 4.6%, aOR 5.6, 95% CI 2.5–12.7), but not preterm birth before 37 weeks (26.2% vs. 19.1%, aOR1.5, 95% CI 0.7–3.1) or before 34 weeks (16.2% vs. 9.7%, aOR1.8, 95% CI 0.7–4.5). The initial logistic regression models for SAB and preterm birth were adjusted for age, BMI, prior SAB (or prior preterm birth), race (for preterm birth only), and smoking. However, only age remained significant for adjustment in the final regression models. (Table 3)

In secondary analyses, women were further stratified into interval strata of less than 6 months, 6–11 months, 12–23 months, and compared to those women with a LEEP to pregnancy interval of 24 months or more. There was an inverse dose-response relationship between category of LEEP to pregnancy interval and SAB (p trend=<0.01). Women with a time interval less than 6 months from LEEP to pregnancy had a significantly increased risk for SAB (42.9% vs. 4.3%, OR 16.8, 95% CI 3.5–81.6), but not preterm birth. Similarly, women with a time interval of 6–11 months were also found to have an increased risk for SAB compared to the reference interval of 24 months or more (14.3% vs. 4.3%, OR 3.7, 95% CI 1.4–9.6). However, the increased risk of SAB in women with a time interval of 12–23 months compared to those with an interval of 24 months or more was not statistically significant (5.5% vs 4.3%, OR 1.3, 95% CI 0.6–3.0). (Table 4)

## Discussion

We found that women with a time interval from LEEP to subsequent pregnancy occurring in less than 12 months are at significantly increased risk for SAB, but not preterm birth. Women who became pregnant within 12 months of the LEEP procedure were at over fivefold increased risk compared to those who got pregnant after 12 months, even after adjusting for potential confounding factors.

Prior studies have been performed investigating the time interval from LEEP to pregnancy and the effect on preterm birth. While some of the studies have reported an increased risk for preterm birth with a shorter interval (7–9), others have found no such association. (10–12) Himes et al performed a retrospective study examining the effect of time interval from LEEP to pregnancy on spontaneous preterm birth. (7) They found a significantly increased risk for spontaneous preterm birth for women with an interval shorter than 12 months compared to 12 months or more. However, this study had a limited sample size, reducing the precision of their risk estimates and did not examine the risk of SAB. Other studies that found a link between preterm birth and short interval from LEEP to pregnancy did not adjust for prior preterm birth, which could have confounded their results. (8–9) In the most recent study that investigated the role of time interval in preterm birth risk, Heinonen et al found no association, a result strengthened by their large numbers and adjusted analysis. (12)

While the effect of LEEP to pregnancy interval on risk of preterm birth has been investigated to an extent in the literature, only two studies to our knowledge reported rates of SAB in women with a history of cervical excision. (13–14) In 1979, Weber et al reported higher rates of SAB in women with a history of a conization compared to age matched controls (20.4% vs. 9.0%). (13) Later, Tan et al reported similar rates of SAB in women with a history of LEEP compared to controls. (14) Despite these limited reports, there are no studies that investigate the risk of SAB as it relates to the LEEP to pregnancy interval.

Compared to previous studies on this subject, our study offers unique strengths. Importantly, our study is the first to examine the effect of LEEP to pregnancy interval on risk for SAB. Our study was a secondary analysis of a multicenter cohort which included both tertiary and community centers, increasing the generalizability and providing large numbers of women with history of LEEP for analysis. In addition, the meticulous data gathering through patient interview and confirmation with medical records increased our study's interval validity by decreasing recall bias and allowed us to collect data on multiple confounding factors. By performing secondary analysis after further stratifying by time interval, we were able to more precisely identify the interval most at risk for SAB. Another strength of our study was the small amount of missing data; only 3% of our cohort was excluded for missing data with regards to time interval from LEEP to pregnancy outcome.

The potential limitations of our study must be considered as well. By definition, the retrospective nature of our study limited the available data to that which was already collected. However, the amount of data collected was robust and allowed us to evaluate relevant baseline maternal characteristics and adjust for known confounders. Additionally, it is important to note that the number of SABs in the 12-months-or-more group were lower than expected. Patients with an interval of 12 months or more had a SAB rate of 4.6%, much lower than would be anticipated in the general population, versus the SAB rate of 17.9% in patients with an interval of less than 12 months, possibly reflecting a degree of recall bias. Due to the relatively small number of women in the cohort with a LEEP to pregnancy interval of <6 months (n=7), although we were able to demonstrate a possible dose response relationship with intervals shorter than 12 months, the confidence intervals are wide and risk estimates should be interpreted with caution. Therefore, while women with an interval shorter than 12 months are at over fivefold increased risk for SAB, those with intervals less than 6 months may be at even higher risk. Another important consideration is that our negative findings with respect to preterm birth, as well as SAB 12–19 weeks, may be secondary to inadequate power.

Our study found that women with a shorter LEEP to pregnancy interval are at increased risk for SAB, but not preterm birth before 37 weeks or before 34 weeks. The exact mechanism which would lead to SAB after LEEP is unknown, but may be related to structural changes, and the pathogenesis deserves future study. The negative findings with respect to preterm birth are not unexpected, and confirm earlier rigorously performed studies on the subject. (12) From the results of our study, we have identified multiple potential areas for further research. Some may question why interval from LEEP to pregnancy would influence risk of SAB, but not preterm delivery. We postulate that SAB and preterm birth occur through different mechanisms and have differing risk factors, however this hypothesis merits future research. In addition, by definition, the further a patient progresses in gestation, the more time the cervix has had to heal from the LEEP. Therefore, the pathogenesis could potentially be investigated as it relates to cervical length or inflammation. Another potential area for future investigation involves the relationship between size of LEEP specimen excised and risk for SAB, given that previous studies have demonstrated that cervical regeneration after LEEP is dependent on size of prior excision. (15–16) Our findings indicate that time interval from LEEP to pregnancy could potentially impact the risk of SAB, and an interval of 12 months or more appears to be associated with the lowest risk. Additionally, if confirmed in other studies, patients can be reassured that the time interval from LEEP to pregnancy does not increase the risk for preterm delivery.

## Acknowledgments

Supported by NIH grant (#5R01CA10918604, PI Macones). Dr. Conner is also supported by the NICHD T32 grant (#22-3125-77026E) and the Washington University Institute of Clinical and Translational Sciences grant (#UL1TR000448).

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**Table 1**

Baseline Characteristics of the Study Cohort

| **Variable** | **LEEP <12 months (n=56)** | **LEEP ≥ 12 months (n=540)** | ***P*** |
|---|---|---|---|
| Age (years) | 26.6 ± 5.4 | 28.3 ± 5.0 | 0.02 |
| Nulliparity | 21 (37.5%) | 246 (45.6%) | 0.26 |
| African American race | 17 (30.4%) | 187 (34.6%) | 0.56 |
| Prior preterm birth | 6 (10.7%) | 59 (10.9%) | 0.99 |
| Smoking | 8 (16.3%) | 89 (17.3%) | 0.99 |
| BMI ($kg/cm^2$) | 29.5 ± 6.2 | 31.7 ± 6.7 | 0.04 |
| Pregnancy-induced hypertension | 5 (8.9%) | 59 (10.9%) | 0.82 |
| Gestational diabetes | 4 (7.1%) | 32 (5.9%) | 0.77 |

LEEP, loop electrosurgical excision procedure; BMI, body mass index; BMI, body mass index.

## Table 2

Median Time From Loop Electrosurgical Excision Procedure to Pregnancy for the Primary Outcomes

| **Outcome** | **n** | **Months to Pregnancy Median (Interquartile Range)** | ***P*** |
|---|---|---|---|
| Overall | 596 | 30.8 (18.4–50.7) | |
| Spontaneous abortion | | | |
| <20 weeks | 35 | 20.3 (11.2–40.9) | 0.01 |
| <12 weeks | 30 | 17.9 (8.9–40.9) | <0.01 |
| 12–19 weeks | 5 | 33.0 (23.4–40.6) | 0.85 |
| No spontaneous abortion (reference) | 561 | 31.2 (18.7–51.2) | |
| Preterm birth <37 weeks | 108 | 29.7 (18.2–47.2) | 0.31 |
| Term birth (reference) | 442 | 32.5 (19.1–53.4) | |
| Preterm birth <34 weeks | 52 | 30.7 (19.1–50.2) | 0.92 |

**Table 3**

Primary Outcomes for Women With Time Interval Shorter Than 12 Months Compared to 12 Months or More From Loop Electrosurgical Excision Procedure to Pregnancy

| Outcome | LEEP <12 months | LEEP ≥ 12 months | Odds Ratio (95% CI) | Adjusted Odds Ratio* (95% CI) | *P* |
|---|---|---|---|---|---|
| Overall | 56 (9.4%) | 540 (90.6%) | | | |
| Spontaneous abortion <20 weeks | 10 (17.9%) | 25 (4.6%) | 4.5 (2.0–9.9) | 5.6 (2.5–12.7) | <0.01 |
| Spontaneous abortion <12 weeks | 10 (17.9%) | 20 (3.7%) | 5.7 (2.5–12.8) | 7.3 (3.1–17.1) | <0.01 |
| Spontaneous abortion 12–19 weeks | 0 (0%) | 5 (0.9%) | - | - | - |
| Preterm birth <37 weeks | 11 (26.2%) | 97 (19.1%) | 1.5 (0.7–3.1) | 1.5 (0.7–3.1) | 0.31 |
| Preterm birth <34 weeks | 6 (16.2%) | 44 (9.7%) | 1.8 (0.7–4.6) | 1.8 (0.7–4.5) | 0.25 |

LEEP, loop electrosurgical excision procedure.

*Adjusted for age. Body mass index, prior spontaneous abortion (or prior preterm birth), race (for preterm birth only), and smoking dropped out of the model.

## Table 4

Primary Outcomes Stratified by Time Interval From Loop Electrosurgical Excision Procedure to Pregnancy

| Outcome | LEEP <6 Months | LEEP 6–11 Months | LEEP 12–23 Months | LEEP ≥ 24 Months | *P* |
|---|---|---|---|---|---|
| Overall | 7 (1.2%) | 49 (8.2%) | 165 (27.7%) | 375 (62.9%) | |
| Spontaneous abortion | 3 (42.9%) | 7 (14.3%) | 9 (5.5%) | 16 (4.3%) | <0.01 |
| OR (95% CI) | 16.8 (3.5–81.6) | 3.7 (1.4–9.6) | 1.3 (0.6–3.0) | Ref | - |
| Preterm birth <37 weeks | 1 (33.3%) | 10 (25.6%) | 27 (17.4%) | 70 (19.8%) | 0.46 |
| OR (95% CI) | 2.0 (0.18–22.6) | 1.4 (0.6–3.0) | 0.9 (0.5–1.4) | Ref | - |
| Preterm birth <34 weeks | 0 (0.0%) | 6 (16.2%) | 11 (7.9%) | 33 (10.4%) | 0.39 |
| OR (95% CI) | - | 1.8 (0.7–4.6) | 0.7 (0.4–1.5) | Ref | - |

LEEP, loop electrosurgical excision procedure. OR, odds ratio; CI, confidence interval.