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Loop Electrosurgical Excision Procedure and Risk of Vaginal Infections During Pregnancy: An Observational Study

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Abstract

Objective—To investigate the risk for preterm birth associated with vaginal infections in pregnancies after loop electrosurgical excision procedure (LEEP) compared to women with no prior LEEP.

Study Design—Multicenter retrospective cohort study

Setting—United States

Population—Women with LEEP between 1996 and 2006 were compared to two unexposed groups who had cervical biopsy or Pap test without any other cervical procedure in the same calendar year.

Methods—The first pregnancy progressing beyond 20 weeks of gestation in women with prior LEEP was compared to women without LEEP. Stratified analysis according to presence or absence of vaginal infection during pregnancy was used to investigate whether risk for preterm birth differed according to presence or absence of infection. Interaction between LEEP and vaginal infection was investigated using multivariable logistic regression with interaction terms as well as the Mantel-Haenszel test for homogeneity.

Main Outcome Measures—Spontaneous preterm birth (<37 and <34 weeks).

Results—Of 1727 patients who met inclusion criteria, 34.4% (n=598) underwent LEEP prior to index pregnancy. There was no increased risk for vaginal infections among women with LEEP compared to women without LEEP. Chlamydia infection and LEEP demonstrated significant

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interaction suggesting that the presence of chlamydia infection in women with history of LEEP augments the risk for preterm birth compared to women with no history of LEEP.

Conclusions—Vaginal infections during pregnancy in women with a history of LEEP may be associated with an increased risk for preterm birth compared to women with no history of LEEP.

Keywords

Loop Electrosurgical Excision Procedure; Preterm Birth; Vaginal Infection

Introduction

Deaths from cervical cancer have been declining in the United States, predominantly due to improved screening and treatment for precancerous cervical lesions¹. Currently treatment for high-grade cervical dysplasia relies on cervical excision procedures. In the United States more than 400,000 women are diagnosed with cervical dysplasia annually with 2-35 per 1000 women having high-grade dysplasia². Loop electrosurgical excision procedure (LEEP) is the most common cervical excision that is considered both diagnostic (providing a tissue specimen for pathologic review) and therapeutic (with the intent of removing all dysplastic tissue prior to progression to invasive cancer). Because cervical dysplasia occurs most commonly during a woman's reproductive years, the impact of cervical excision procedures on obstetric outcomes must be considered.

Several previous studies have examined the risk for preterm birth (PTB) after LEEP with varied results³⁻⁹. Two meta-analyses from 2006-2011 incorporating mounting observational data, reported an increased risk for PTB and/or preterm rupture of membranes associated with cervical excision procedures^{10, 11}. Putative mechanisms for the increased risk for preterm birth in women with a prior LEEP reported in some studies include disruption in collagen strength due to tissue removal, underlying demographic and sexual risk factors associated with development of severe dysplasia, and disruption of normal cervical immune defenses^{5, 7, 8, 12-14}. After LEEP the transition zone of the cervix is excised and the normal antimicrobial barrier of cervical gland mucus is altered, possibly facilitating acquisition of ascending infections^{12, 13, 15}.

On the other hand other observational studies have shown no increased risk for preterm delivery^{16, 17} and another meta-analysis suggested increased risk for PTB after cervical excision but not for the LEEP procedure specifically¹⁸. A recent meta-analysis suggested that LEEP is associated with a higher risk for preterm birth, although this risk was attenuated if compared to women with cervical dysplasia but no LEEP¹⁴. This suggests that the LEEP itself may not be the causative agent, but instead the combination of LEEP and other confounders together may augment the risk for preterm birth. Given previous conflicting results regarding association with LEEP and PTB, and the well-established association between infection and PTB, we aimed to test whether the risk for PTB in women with prior LEEP is modified by the presence or absence of vaginal infections during pregnancy.

Methods

This is a secondary analysis of a multicenter retrospective cohort study. The parent study compared women with prior LEEP to age-matched LEEP unexposed patients to assess the association between LEEP and spontaneous preterm birth before 34 weeks. Women who underwent LEEP between 1996 and 2006, and controls who underwent screening cervical cytology or cervical punch biopsy performed the same calendar year were identified from several tertiary and community hospitals electronic pathology databases using the following key words: “Pap (papanicolaou) smear”, “cervical cytology”, “cervical biopsy” and “LEEP”. The unexposed groups were identified based on having undergone cervical biopsy after colposcopy or Pap test without any other cervical procedure and were matched to the LEEP exposed women based on hospital site, age, and calendar year of cervical procedure (Pap test or biopsy). Treating physicians were contacted and eligible women were contacted by phone and offered enrollment in the study. For women who were not at the last documented phone number, a commercial service was used to obtain contact information. Women who agreed to participate underwent a structured phone interview by trained research staff to gather detailed information regarding prior pregnancies as well as on medical, gynecologic and sexual history. Medical records were then requested, reviewed by trained research staff, and abstracted in detail. Both pre- and post-LEEP obstetric and medical information was collected to adjust for characteristics pertinent to outcomes in the index pregnancy. Pathology and cytology reports were acquired from all prior cervical procedures. If there were inconsistencies between patient history report and medical record reports, the medical record information was preferentially used. If a subject reported a cervical excision procedure at an institution outside our hospital system they were excluded.

Because women with severe cervical dysplasia may differ from women without dysplasia with respect to important health risk factors, data from two unexposed comparison groups were collected. The two unexposed control groups were: women with cervical dysplasia who underwent a cervical biopsy but no LEEP and, second, women who underwent only routine cervical cytology. Because a cervical biopsy does not fully interrupt the transition zone mucosal barrier, for this investigation those with a prior LEEP were compared to a no-LEEP group with transition zones intact (cytology only and cervical biopsy groups combined). The exposure for this analysis was vaginal infections and prior LEEP. The first singleton pregnancy progressing beyond 20 weeks of gestation after the date of cervical procedure (LEEP, biopsy, or Pap test) LEEP was considered the index pregnancy for this analysis. The primary outcome was spontaneous preterm birth at less than 37 and less than 34 weeks gestation.

Spontaneous preterm birth was defined as delivery secondary to spontaneous preterm labor or preterm premature rupture of membranes at less than 37 weeks. Medically indicated preterm deliveries (e.g. pre-eclampsia, intrauterine growth restriction, non-reassuring fetal testing) were not included in the primary outcome. Gestational age was assigned based on routine obstetric criteria involving last menstrual period and earliest ultrasound dating available. Vaginal infections considered were bacterial vaginosis (BV), Chlamydia trachomatis (CT), Neisseria gonorrhea (GC), Trichomonas vaginalis, and composite outcomes of any vaginal infection and multiple vaginal infections (defined as two or more

vaginal infections). Infections were classified as present if they were confirmed during the index pregnancy. Because this was a multicenter retrospective cohort study, diagnosis of vaginal infections was based on standard clinical care in the prenatal setting for each center and were classified as present or absent at any time during the index pregnancy by medical record review. Generally, standard prenatal care in the United States includes universal chlamydial and gonococcal cervical nucleic acid tests at the time of presentation for prenatal care. Wet prep is performed if the patient has complaints of vaginitis symptoms. These tests are repeated later in pregnancy only for symptomatic complaints or concerns for exposure.

Baseline medical and demographic characteristics in women with a prior LEEP were compared to those without a LEEP. Associations between LEEP and vaginal infections, and PTB and vaginal infections were assessed using univariable analysis to obtain relative risk with 95% confidence intervals. Backward stepwise logistic regression was performed to adjust for pertinent confounding variables for each individual outcome to obtain adjusted odds ratios with 95% confidence intervals. The likelihood ratio test was used to assess the effect of removing covariates from the model. Stratified analysis defined by the presence or absence of each individual infection type was performed for PTB <34 and <37 weeks. Interaction of vaginal infection with LEEP on the risk of PTB was tested in the stratified analysis using the Mantel-Haenszel test for homogeneity and in adjusted logistic regression models that included interaction terms. A subgroup analysis of only patients with dysplasia (prior LEEP versus those with cervical biopsy) was performed to ensure that findings were not exaggerated due to differences between women with and without cervical dysplasia.

The institutional review boards at each participating hospital granted approval for the study. All statistical analyses were performed using Stata 12.0 (College Station, Texas).

Results

From the parent study of 1,839 patients, those without a post-LEEP pregnancy progressing beyond 20 weeks and without gestational age of delivery recorded were excluded. In addition, patients with history of cold knife cone (n=11) were excluded, leaving a total of 1,727 singleton pregnancies for this analysis. Of 1,727 women, 34.6% (n=598) had a LEEP preceding their index pregnancy and 65.4% (n=1129) with no history of LEEP comprised the unexposed group (n=549 with cervical biopsy and n=580 with cervical cytology). Baseline medical and demographic characteristics of the two study groups are compared in Table 1. Table 2 describes the demographic characteristics of women with LEEP compared to the two control groups (biopsy and Pap) individually. Women who had a prior LEEP were more likely to be >35 years old, and more likely to endorse tobacco use. Women with prior LEEP were less likely to be black than those in the control group. The study groups did not differ with respect to prior preterm birth, nulliparous status, alcohol use, obesity (defined as body mass index ≥ 30 kg/m²), or human immunodeficiency virus during the index pregnancy.

The association between infections and LEEP are assessed in Table 3. The absolute risk for common vaginal infections including bacterial vaginosis, GC, CT, and *Trichomonas* was lower in women with LEEP compared to women without LEEP, although these differences

were not statistically significant. When the infections were combined into a single variable (“any vaginal infection”) it was not statistically different in women with LEEP compared to those without LEEP. The presence of multiple vaginal infections (two or more) during pregnancy was also not statistically different in LEEP and no LEEP groups. Associations between vaginal infections and PTB are shown in Table 4. There was no statistically significant association between any single infection, or multiple vaginal infections and the risk for preterm birth <37 weeks after controlling for confounders. In women without LEEP there was no significant increased risk for PTB based on the presence or absence of any vaginal infection (15.8% vs. 15.6%, $p=0.9$).

The interaction analysis examining the effect LEEP with and without infection on the risk of PTB is shown in Table 5. The presence of any vaginal infection significantly modified the effect of LEEP for the risk of PTB <37 weeks suggesting that women with history of LEEP and vaginal infection are at significantly increased risk for preterm birth compared to those with LEEP but without vaginal infection. An even greater effect size was noted for the association between LEEP and multiple vaginal infections during pregnancy with a 2.5 fold increased risk for PTB <37 weeks compared to LEEP without multiple vaginal infections. When infections were examined individually, only chlamydia demonstrated significant interaction with LEEP for the risk for preterm birth less than 37 weeks. No vaginal infection individually or collectively demonstrated significant interaction with prior LEEP for the risk of early PTB <34 weeks.

Results of the subgroup analysis including only women with history of cervical dysplasia were consistent with the univariable and interaction analyses described above (data not shown).

Discussion

Main Findings

Among this large cohort of more than 1700 women, we found that vaginal infection during pregnancy is no more common in women with a prior LEEP, but the presence of infection, particularly chlamydial infection, may augment the risk for preterm birth compared to women with LEEP alone.

Strengths and Limitations

Because confounding is a pertinent issue in the assessment of the effect of LEEP on pregnancy outcomes, the inclusion of women with a prior cervical biopsy for suspected dysplasia (thought to be more similar in measured and unmeasured confounders to those who underwent LEEP) in the control group is more appropriate than a control group including only women with no history of dysplasia. Because this study sought to evaluate the interaction between infection and preterm birth after complete removal of the transition zone, the two comparison groups both with intact transition zones were combined. This risked biasing our results toward the null, but inclusion of women with cervical dysplasia seems a more appropriate comparison to those women with a prior LEEP. Furthermore, the subgroup analysis including only women with cervical dysplasia demonstrated similar

findings to the main analysis. In addition, the data for this study were collected by trained research personnel including contacting providers and patients for complete and accurate data collection for the primary purpose of investigation of the effect of LEEP on pregnancy outcomes. Lastly, the size of this cohort allowed for interaction analysis that smaller cohorts do not. Race plays a complex role in the risk for dysplasia as well as for preterm birth. We controlled for race (and other potentially important confounders such as maternal age and smoking) in regression models, however the possibility for residual confounding remains.

As with any retrospective study, there is the possibility for misclassification in the medical record. If information on the presence of vaginal infections was not recorded, they were classified as having no vaginal infection. Thus, only symptomatic or routine screen positive infections were captured. This would result in the potential misclassification of subjects with an undetected, undiagnosed, or undocumented infection into the no-infection group. However, this would risk biasing our results toward the null rather than produce spurious associations. The actual effect of vaginal infections with prior LEEP may in fact be greater than what is reported in this study. These data demonstrate that infection modifies the risk for preterm birth at <37 weeks but not at <34 weeks in women with prior LEEP. Some may suggest that whatever effect is seen at 37 weeks should also be present at earlier gestational ages. Despite the large cohort available for analysis, we may have been underpowered for early preterm birth. However, one explanation may be that earlier in gestation the cervix remains closed and unripened, and only after cervical ripening begins later in pregnancy does the risk for preterm birth in women with LEEP and vaginal infections increase. Unfortunately we are unable to capture the timing of infection during pregnancy as it relates to the risk for preterm birth.

Infection rates in our population were very high. This likely reflects the high rate of sexually transmitted infections generally in the greater urban Saint Louis region and is consistent with other high-risk populations in the United States with high prevalence of sexually transmitted infections^{19, 20}. Additionally because patients have access to clinical care during pregnancy and routine prenatal screening includes testing for infection we may be capturing otherwise asymptomatic infection. Lastly HPV positivity is not routinely captured during pregnancy. The years of this study included years when HPV specific genotyping was not routinely performed even in the context of dysplasia. Thus we are unable to comment on whether HPV persistence mediates the effect of LEEP and preterm birth risk.

Interpretation

The transition zone of the cervix, where the squamous cells of the ectocervix meet the glandular mucus secreting cells of the endocervix, is the area most susceptible to precancerous changes related to human papilloma virus²¹. The intended purpose of LEEP is to remove the dysplasia and, in doing so, the transition zone is also disrupted. LEEP has been associated with preterm birth and preterm rupture of membranes^{3, 5-7, 9, 16}. One potential mechanism for this association could be the loss of antimicrobial action of the endocervical mucus normally present in the transition zone. The cervical mucus is thought to provide both a mechanical and chemical antimicrobial barrier^{12, 13, 15} and the loss of

matrix metalloproteinases and other innate immune modulators present in the cervical transition zone could alter the risk of ascending infection.

Based on the results of this study, prior LEEP did not increase the risk for infection. In fact, the absolute incidences of vaginal infection were uniformly less in the LEEP group than the control group. Nonetheless, the presence of chlamydial infection in women with a prior LEEP doubled the risk for preterm birth compared to women with LEEP without chlamydial infection. In addition, any single vaginal infection as well as multiple vaginal infections demonstrated a significant interaction with prior LEEP for the risk of preterm birth. These findings may be driven mostly by the association noted with chlamydial infection. Given the observational nature of these data we are unable to know whether these findings suggest a specific biological plausibility associated with Chlamydia or alternatively whether this observation is seen due to Chlamydial infection being the most prevalent infection.

Prior studies investigating the association between LEEP and adverse obstetric outcomes have used comparison groups of otherwise healthy women as the non-LEEP comparison group^{4, 5, 8, 9, 17}. The weakness of that methodology is women with cervical dysplasia requiring LEEP may have inherent differences in infection risk, demographic characteristics, or immune characteristics than women who have not had severe cervical dysplasia warranting an excision procedure. Noehr and colleagues found that LEEP was associated with a 2-fold increased risk for PTB but additionally reported that women who underwent biopsy only (no LEEP) also had a significantly increased risk for PTB, suggesting that in fact women with dysplasia are the best control group for comparison⁵. Thus, confounding may exaggerate differences seen in the study groups. In fact, when only women with cervical dysplasia were included in a recent meta-analysis, the risk for preterm birth was not significantly increased suggesting that factors associated with cervical dysplasia mediate the increased risk for preterm birth¹⁴. Consistent with the suggestion of the most recent data that the effect of LEEP on the risk of preterm birth may be modified by other risk factors, our findings demonstrate that the risk for preterm birth is significantly higher with LEEP and infection compared to either risk factor alone.

Conclusion

In summary, this study suggests that vaginal infections in women with LEEP modify the risk for preterm birth. In particular, women with a prior LEEP and chlamydial infection may have an exaggerated risk for preterm birth compared to women with LEEP without infection. Preventing infection acquisition may be even more important when managing pregnancies in women with prior LEEP.

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Table 1

Comparison of baseline characteristics at time of index pregnancy of women who underwent loop electrode excision procedure (LEEP) compared to controls.

Characteristic	LEEP (n=598)	Control (n=1129)	p-value
Maternal age >35 years	13.7	8.6	<0.01
Nulliparous	50.2	47.9	0.2
Black race	34.4	63.3	<0.01
Body mass index>30	57.0	59.0	0.4
Smoking	16.2	12.8	0.05
Alcohol Use	2.0	2.2	0.9
Chronic hypertension	4.8	2.7	0.02
Diabetes Mellitus	3.2	2.3	0.3
Human Immunodeficiency Virus	1.3	1.7	0.5
Prior preterm birth	11.0	13.3	0.2

Table 2

Comparison of baseline characteristics at time of index pregnancy of women who underwent loop electrode excision procedure (LEEP) compared to cervical biopsy or Pap test.

Characteristic	LEEP (n=598)	Cervical Biopsy (n=549)	Pap test (n=580)	p-value
Maternal age >35 years	13.7	8.4	6.3	<0.01
Nulliparous	50.2	45.7	48.1	0.3
Black race	34.4	60.3	66.2	<0.01
Body mass index>30	57.0	63.9	54.5	0.01
Smoking	16.2	12.9	12.7	0.2
Alcohol Use	2.0	1.6	2.6	0.5
Chronic hypertension	4.8	2.2	3.1	0.04
Diabetes Mellitus	3.2	2.5	2.0	0.1
Human Immunodeficiency Virus	1.3	3.1	0.5	<0.01
Prior preterm birth	11.0	14.0	12.6	0.3

Table 3

Infection outcomes in index pregnancy in women with LEEP compared to women without LEEP

Infection	LEEP (n=598)	No LEEP (n=1129)	Relative Risk (95%CI)	Adjusted Odds Ratio (95%CI)	p-value
Bacterial Vaginosis	8.7%	12.9 %	0.7 (0.5-0.9)	0.9 ^a (0.7-1.2)	0.7
Chlamydia	15.6 %	24.2%	0.3 (0.1-0.5)	0.9 ^b (0.7-1.2)	0.5
Gonorrhea	7.5 %	9.4 %	0.8 (0.5-1.1)	1.3 ^c (0.9-1.9)	0.1
Trichomonas	8.0 %	12.9 %	0.6 (0.5-0.9)	1.1 ^c (0.7-1.5)	0.6
Any Vaginal Infection	25.7 %	39.1%	0.7 (0.5-0.8)	0.8 ^c (0.6-1.1)	0.3
Multiple Vaginal Infections	12.4%	20.6%	0.6 (0.5-0.8)	1.0 ^b (0.7-1.5)	0.9
Pyelonephritis	1.8 %	2.1%	0.9 (0.5-1.8)	0.9 ^d (0.4-1.7)	0.8

^a Adjusted for: prior preterm birth, advanced maternal age, black race, tobacco use, diabetes^b Adjusted for: prior preterm birth, black race, tobacco use, human immunodeficiency virus^c Adjusted for: black race, tobacco use, human immunodeficiency virus^d Adjusted for: tobacco use

Table 4

Infection outcomes in index pregnancy in women with preterm birth compared to term birth.

Infection	Preterm Birth <37 weeks (n=1434)	Term Birth (n=293)	Relative Risk (95%CI)	Adjusted Odds Ratio (95%CI)	p-value
Bacterial Vaginosis	9.9%	11.8%	0.8 (0.6-1.2)	0.8 ^a (0.5-1.2)	0.3
Chlamydia	25.6%	20.2%	1.3 (1.0-1.6)	1.2 ^b (0.8-1.5)	0.4
Gonorrhea	11.6%	8.2%	1.4 (1.0-2.0)	1.2 ^b (0.7-1.8)	0.4
Trichomonas	12.6%	10.9%	1.2 (0.8-1.6)	0.9 ^b (0.6-1.4)	0.7
Any Vaginal Infection	38.6%	33.6%	1.1 (1.0-1.3)	1.0 ^b (0.7-1.4)	0.1
Multiple Vaginal Infections	20.7%	17.0%	1.2 (0.9-1.6)	0.9 ^b (0.6-1.4)	0.6
Pyelonephritis	1.3%	2.1%	0.6 (0.2-1.8)	0.6 ^a (0.2-1.7)	0.3

^a Adjusted for: black race, diabetes

^b Adjusted for: black race, tobacco use, HIV infection

Table 5

Preterm birth outcomes stratified by presence or absence of vaginal infections.

	Preterm Birth <37 (n=293)			Preterm Birth <34 (n=91)		
	n (%)	RR (95%CI)	Test of Interaction* (p-value)	n (%)	RR (95%CI)	Test of Interaction* (p-value)
LEEP	115 (9.2)	1.4 (1.1-1.8)	--	40 (6.7)	1.6 (0.9-2.8)	--
LEEP + any vaginal infection	43 (38.1)	1.8 (1.1-3.2)	0.01	15 (38.5)	1.7 (0.9-3.3)	0.5
LEEP – any vaginal infection	72 (40.0)	1.0 (0.8-1.4)		25 (48.1)	1.4 (0.8-2.4)	
LEEP + multiple vaginal infections	22 (46.8)	2.5 (1.5-4.1)	<0.01	7 (43.8)	2.2 (0.9-5.4)	0.4
LEEP – multiple vaginal infections	93 (37.8)	1.0 (0.8-1.4)		33 (44.0)	1.4 (0.8-2.4)	
LEEP + BV	10 (34.5)	1.3 (0.5-3.2)	0.5	3 (25.0)	0.9 (0.3-3.3)	0.3
LEEP – BV	105 (39.8)	1.2 (0.9-1.5)		37 (46.8)	1.5 (1.0-2.4)	
LEEP + CT	30 (40.0)	2.0 (1.1-3.9)	0.01	11 (44.0)	1.4 (0.5-3.6)	0.2
LEEP –CT	85 (39.0)	1.1 (0.8-1.4)		29 (43.9)	1.3 (0.8-2.1)	
LEEP + GC	15 (44.1)	1.8 (0.7-4.2)	0.2	5 (41.7)	1.0 (0.2-3.2)	0.8
LEEP –GC	100 (38.6)	1.2 (0.9-1.4)		35 (44.3)	1.5 (0.9-2.3)	
LEEP + trichomonas	14 (37.8)	1.7 (0.7-3.8)	0.2	3 (33.3)	0.7 (0.2-3.1)	0.9
LEEP – trichomonas	101 (39.5)	1.2 (0.9-1.2)		37 (45.1)	1.5 (0.9-2.2)	

* From Mantel-Haenszel test for homogeneity

LEEP= loop electrode excision procedure

BV= bacterial vaginosis

CT= Chlamydia trachomatis infection

GC= Neisseria gonorrhea infection