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Cervical Surgery for Cervical Intraepithelial Neoplasia and Prolonged Time to Conception of a Live Birth: A Case-Control Study

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Abstract

Objective—To determine whether women with a history of surgery for cervical intraepithelial neoplasia (CIN) are at increased risk of sub-fertility, measured as time to pregnancy of more than 12 months.

Design—Case-control study

Setting—Iowa Health in Pregnancy Study (IHIPS), a population-based case-control study of preterm and small-for-gestational-age (SGA) live birth outcomes (5/2002–5/2005), United States.

Sample—Women with an intended pregnancy and a history of either one prior cervical surgery (n=152), colposcopy-only (n=151), or no prior cervical surgery or colposcopy (n=1021).

Methods—Cervical treatment history, pregnancy intention, time to pregnancy, and other variables were self-reported by computer-assisted telephone interviews. Odds ratios were calculated using logistic regression to estimate the risk of prolonged time to pregnancy among women with a history of cervical surgery or colposcopy alone compared to untreated women (referent group).

Main Outcome Measure—Prolonged time to pregnancy (ie, >1 year)

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Disclosure of Interests BJS is employed by Merck & Co., Rahway, NJ. The work was completed prior to her employment and the opinions expressed do not necessarily reflect the opinions of Merck & Co.

Contribution to Authorship AFS was responsible for the concept and design of the study. AFS and KKH oversaw the data acquisition. CNS, AFS, and KKH were responsible for the overall analysis. All authors contributed to the interpretation of data, drafting, and approval of the manuscript.

Details of Ethics Approval All protocols and informed consent procedures were approved by the University of Iowa Institutional Review Board [IRB ID: 200003008; July 2012].

Results—Prolonged time to pregnancy was most prevalent among treated women (16.4%) compared to untreated women (8.4%) and women with colposcopy only (8.6%) ($p=0.039$). After adjusting for covariates, women with prior cervical surgery had more than a two-fold higher risk of prolonged time to pregnancy compared to untreated women ($aOR=2.09$, 95% CI 1.26-3.46). In contrast, women with a history of colposcopy-only had a risk equivalent to that among untreated women ($aOR=1.02$, 95% CI 0.56-1.89).

Conclusions—Women with a history of cervical treatment for CIN are at increased risk of sub-fertility, measured as time to pregnancy of more than 12 months.

Keywords

Fertility; Sub-fertility; Cervical Intraepithelial Neoplasia/surgery; Loop Electrosurgical Excisional Procedure; Pregnancy

Introduction

When premalignant cervical lesions are found in reproductive-aged women, several surgical treatment modalities are available to remove these lesions, including conization, cryosurgery, laser vaporization, and loop electrosurgical excision procedure (LEEP). The goal of these procedures is to remove dysplastic tissue; however, varying amounts of healthy endocervical tissue are also removed. The endocervix contains a large number of mucus-producing glands and crypts (ie, secretory cells) that facilitate sperm transport from the vagina to the uterus. Loss of these structures may lead to a reduction in cervical mucus production or alterations in the composition of cervical mucus, which could inhibit sperm penetration and result in sub-fertility or infertility.¹ Removal of healthy tissue may also lead to changes in cervical architecture such as cervical stenosis, which can also lead to infertility.²⁻³

Although previous publications have reported little to no effect of cervical surgery on fertility outcomes²⁻¹⁶, several of these were case series studies^{4,6,8,14,15} and only two examined time to pregnancy.^{5, 13} Of these two studies, only the study by Bigrigg et al.⁵ had a comparison group of untreated women. This study reported on 72 women who had a LEEP and 62 control women who could recall their time to pregnancy. There was no difference between the two groups on time to conception, but the study only had enough power to detect a threefold difference in infertility rates.⁵ Very little information regarding the effect of other modalities of cervical treatment on time to pregnancy is available.

As treatments for CIN typically occur in young, reproductive-aged women, it is important to fully understand the potential fertility impact of cervical surgeries. With such limited data currently available, healthcare providers are unable to fully counsel their patients on the long-term outcomes of their treatment options. Understanding the impact of cervical surgeries for cervical dysplasia on future fertility can guide women and their providers in selecting the most appropriate procedure.

The objective of this study is to determine whether women with a history of excisional or ablative cervical surgery are at increased risk of sub-fertility, assessed as time to conception of a live birth.

Methods

We examined the association of cervical surgery with subsequent time to pregnancy within the Iowa Health in Pregnancy Study (IHIPS), a population-based case-control study of preterm and small-for-gestational-age (SGA) birth outcomes among residents of four Iowa

counties who delivered a live birth over the period, May 2002 through June 2005.¹⁸ All potential case and control subjects were identified and selected from the Iowa electronic birth certificate file and sent an introductory letter inviting them to participate in the study (n=7,202). The letter was followed up with a phone call inviting them to be screened for eligibility. Excluded from the study were women under the age of 18 years at delivery; those with twins and higher order births; non-English speakers, and women with a diagnosis of pre-gestational type-1 or type-2 diabetes, systemic lupus, or chronic renal disease. A total of 4,250 (59%) potential subjects selected from live-birth records were reached by telephone; of these, 836 (19.7%) refused to participate and 548 (12.9%) were ineligible. All protocols and informed consent procedures were approved by the University of Iowa Institutional Review Board.

Eligible women who provided verbal consent responded to a 45-minute computer-assisted telephone interview (CATI) (n=2,709). Over 90% of participating women provided signed consent allowing the research team to review their prenatal and hospital delivery records and to validate the preterm delivery and SGA outcomes (n=2,308). As excisional cervical surgery was an emerging risk factor for preterm delivery,¹⁸ all women were asked a series of nine questions regarding their history of positive pap smears, colposcopy with punch biopsy, and excisional surgery for the treatment of CIN (Table S1). Because very few studies had evaluated the effect of cervical surgery on subsequent fertility, we also asked women who had a planned pregnancy to report on how many months they took to conceive upon cessation of contraceptive use: “How many months of having sex without using birth control did it take for you to get pregnant?”

To determine the influence of a history of cervical surgery on time to pregnancy, we restricted the analysis to the subgroup of women who completed the interview, had an intended pregnancy (and, therefore, could provide data on time to pregnancy), and who had their medical chart data abstracted (n=1,632). Excluded from the final analysis were women who met any of the following criteria: received fertility treatment to conceive the index pregnancy (n=216); a history of two or more cervical surgeries (n=24); could not recall the type of cervical treatment (n=11); or missing data on time to pregnancy (n=57). This left a total of 1,324 women for analysis. Of these, 1,021 (77.1%) women had never received any form of cervical treatment, 151 (11.4%) women had a history of colposcopy or punch biopsy only, and 152 (11.5%) had cervical surgery for CIN (46 cone biopsies, 45 LEEPs, 44 cryosurgeries, and 17 laser vaporizations). Due to the small number of women receiving the individual treatment modalities, we analyzed cone biopsy, LEEP, cryosurgery, and laser vaporization as a single treatment category.

Twelve months of intercourse with no contraception is defined as the lower reference limit for infertility by the World Health Organization and many other countries.¹⁹ For this reason, we defined sub-fertility among those who required at least 12 months of sexual intercourse with no contraception in order to conceive.

Covariates

Information was also collected on a wide variety of demographic, reproductive, lifestyle, and characteristics, including maternal age, maternal race (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander and other), education (less than or equal to high school, some college, college graduate-bachelor degree, masters or professional degree), household income, pre-pregnancy body mass index (<24.9, 25-29.9, 30+), gravidity, and parity. Pregnancy intention was measured using a question from the Pregnancy Risk Assessment Monitoring System 2000-2003 Core Questionnaire (“Thinking back to just before you became pregnant, which of the following best describes how you felt about becoming pregnant?”).²⁰

Analysis

To identify study factors associated with increased time to pregnancy, we compared the characteristics of participants stratified by time to pregnancy (≤ 12 months versus > 12 months) and tested for statistical significance using chi-square tests for categorical variables and the Student's t-test for continuous variables.

To estimate the association of treatment for cervical surgery (colposcopy/punch biopsy only, cervical surgery, untreated referent group) with risk of prolonged time to pregnancy, we calculated crude and adjusted odds ratios using logistic regression analysis. Covariates that changed the odds ratios by at least 10% were retained in the final regression model. All data analysis was conducted using SAS® software, Version 9.3 of the SAS System for Microsoft, SAS Institute Inc., Cary, NC, USA.

Results

A total of 9.4% (n=124) of women with an intended pregnancy required more than 12 months to conceive. The comparable proportion among women treated with excisional or ablative surgery was 16%, which is nearly two times higher than the rate observed in the untreated (8.4%) and the colposcopy only (8.6%) groups. Characteristics of the study population stratified by time to conception of greater than one year (yes/no) are shown in Table 1. Compared to women who had a longer time to pregnancy, those who required less than 12 months to conceive were significantly more likely to have a college degree, a normal pre-pregnancy BMI, to have been a non-smoker prior to pregnancy, and less likely to have had cervical surgery for the treatment of CIN. There were no significant differences between the two groups according to maternal age, household income, race, parity, and case-control status (i.e., preterm, SGA, control).

As shown in Table 2, even after adjustment for confounding variables, the risk for subfertility was similar between women who had a colposcopy or punch biopsy and untreated women (aOR= 0.91, 95% CI (0.49-1.70)). In contrast, women treated with excisional or ablative therapy had a significantly increased risk of longer time to pregnancy compared to women in the referent group (aOR=2.09, 95% CI 1.26-3.46). Specifically, LEEP and laser vaporization were associated with a significantly increased time to pregnancy (aOR=2.47, 95% CI 1.10-5.55 and aOR=3.81, 95% CI 1.17-12.37, respectively). Women treated with cone biopsy or cryosurgery were also at an increased risk for longer time to pregnancy, though this association was not statistically significant (aOR=1.64, 95% CI 0.70-3.86 and aOR=1.72, 95% CI 0.69-4.25, respectively). Parity was also examined as a possible confounder, but it did not alter the risk estimates.

As LEEP and other excisional or ablative cervical surgery is more frequent among women who deliver preterm¹⁸ and because IHIPS was a case-control study of preterm delivery (PTD) and small-for-gestational age (SGA) births, we tested for an interaction between cervical treatment and case status (PTD, SGA, and normal grown) on the risk of a longer time to pregnancy and found none ($p=0.86$). As a further check of our findings, we restricted the analysis of cervical treatment to the subgroup of control women who delivered normally-grown (non-SGA), term infants (delivered at ≥ 37 completed weeks gestation) (n=790) to determine if the increased risk of sub-fertility associated with cervical treatment was due primarily to the high proportion of women at high obstetric risk in the study population. Findings from this analysis were comparable to those observed in full analysis sample: treated women had a significantly greater risk (aOR=3.33, 95% CI 1.66-6.67) of longer time to pregnancy than untreated women, while the colposcopy-only group had a risk similar to that of untreated women (aOR=1.12, 95% CI 0.47-2.62).

Discussion

Our findings suggest that cervical treatment for CIN is associated with a longer time to pregnancy, even after adjusting for important confounding factors. Women who had a history of any type of excisional or ablative cervical treatment had a two-fold higher risk of a longer time to pregnancy than untreated women. Women who had colposcopy or punch biopsy were not at increased risk of a time to pregnancy of more than one year.

Several potential mechanisms may account for a longer time to pregnancy following cervical treatment. The endocervix contains a large number of mucus-producing glands and crypts, which promote fertility by filtering, capturing, and storing sperm, and by facilitating sperm transport from the vagina to the uterus.²¹ The mucus producing cells are most highly concentrated in the lower portion of the endocervix next to the external os.²² Thus, even the shallowest excisional or ablative procedures are likely to remove some quantities of mucus producing tissue. Loss of these structures may alter the quality (e.g., pH, viscosity, salinity), quantity, levels of cervical mucus types (ie, L-, G-, P-, and S-mucus), and its immunologic composition. These changes may impair effective sperm-mucus interactions and resistance to upper and lower genital tracts infections, which could, in turn, lead to an increased risk of sub-fertility or infertility.¹ The impact of mucus gland destruction on the subsequent quality, immunologic composition, and quantity of cervical mucus, and on the subsequent risk of infertility, is not well established.

Cervical stenosis, or the narrowing of the endocervical canal, is a fairly infrequent sequelae of cervical surgery and another possible mechanism.^{23,24} This loss of cervical architecture could impair the sperm-mucus interaction and prevent sperm from entering the uterine cavity, resulting in subfertility. Finally, the possibility that the mechanism of sub-fertility is related to the presence of higher grades of CIN in treated women cannot be ruled out.

Although previous studies reported no association between cervical surgery and time to pregnancy²⁻¹⁶, most were case series reports based on small numbers of treated women^{4,6,8,14,15} with incomplete follow-up^{4-6,13,14} and no comparison group of untreated women.^{6,8,9,15} In a prospective design, Ferenczy et al. monitored the time to conception from the date of a large loop excision of the transformation zone (LLETZ) procedure. They did not, however, include a comparison group of untreated women and followed women for just 3 years, during which most women did not attempt to conceive.¹³ Bigrigg et al, conducted an age-matched retrospective cohort to evaluate the association of LLETZ and an increased time to pregnancy, but was greatly underpowered and had incomplete follow-up.⁵ Our study reports on the subfertility experience of a much larger group of women than previous studies, none of whom received fertility treatments to conceive the index pregnancy. We also conducted a more rigorous analysis by adjusting for confounding variables.

As our study may be the first to report that women with a history of cervical surgery have a significantly longer time to pregnancy, further research is needed to confirm and define the risks. A key limitation of this study is the self-reported nature of the exposure and outcome data and small numbers of women in each of the specific treatment modality groups. We did, however, perform analyses according to specific treatment and found an increased risk associated with each of the treatment types when compared to untreated women. Because we did not have access to study subjects' treatment and pathology records, we were unable to verify the type of cervical treatment or the cervical pathology findings. However, all but two treated women knew the type of procedure they had received. We also minimized bias by excluding women who received fertility treatment. Of note, none of the women in our

sample reported having a diagnosis of pelvic inflammatory disease within the six months prior to conception.

Recall bias is another potential threat to validity. Women were also asked to recall their exposure to cervical treatment and time to pregnancy an average of 9.6 months following delivery. Recall bias would be most likely to occur among women who had SGA and PTD births than among women with normally-grown, term infants. If present, recall bias would lead to an overestimation of the risk associated with excisional or ablative treatments. To test for this bias, we examined for an association of cervical treatment with sub-fertility within the control group of women who delivered term and adequate-for-gestational age infants. These results are similar to those within the full study sample, indicating that recall bias is unlikely to be differential because the association of treatment for cervical dysplasia with time to pregnancy is as strong in control subjects as it is in case subjects.

The fact that women treated for cervical dysplasia are advised to abstain from sexual activity for 2-4 weeks is another possible factor that could bias results towards a longer time to pregnancy in these women. To take this delay into account, we reran the analyses and provided treated women with a 'handicap' of an additional 4 weeks to meet the definition of prolonged time to pregnancy; however, the odds ratios remained statistically significant.

Conclusion

Women with a history of cervical treatment for CIN are at increased risk of sub-fertility, measured as time to pregnancy of more than 12 months. Understanding the impact of cervical surgeries on future fertility could be an important factor when deciding upon cervical treatment protocols, especially in young women. For women under evaluation for infertility, a history of destructive cervical therapies may indicate a need for earlier use of fertility treatments such as intrauterine inseminations that bypass the cervix altogether. Therefore, better understanding of the implications of cervical damage on future fertility is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table1

Characteristics of the 1,324 study participants by time to pregnancy in the Iowa Health in Pregnancy Study, Iowa City, IA, 2002-2005

	12 Months to pregnancy (n=1200)	> 12 Months to pregnancy (n=124)	p-value ^a
Age			
18-19	63 (5.3)	8 (6.5)	0.36
20-24	134 (11.2)	9 (7.3)	
25-29	450 (37.5)	41 (33.1)	
30-34	389 (32.4)	43 (34.7)	
35-45	164 (13.7)	23 (18.6)	
Education			
High school graduate or less	136 (11.3)	30 (24.2)	0.0002
Some college, vocational education, or Associate's degree	343 (28.6)	30 (24.2)	
College graduate (Bachelor's degree)	494 (41.2)	37 (29.8)	
One or more years graduate/professional school	227 (18.9)	27 (21.8)	
Household income			
< \$30,000	144 (12.5)	21 (17.7)	0.06
\$30,000-50,000	190 (16.5)	29 (24.4)	
\$50,000-75,000	350 (30.4)	32 (26.9)	
\$75,000-100,000	255 (22.1)	21 (17.7)	
> \$100,000	214 (18.6)	16 (13.5)	
Race			
White	1071 (89.3)	107 (86.3)	0.32
Non-white	129 (10.8)	17 (13.7)	
Parity			
0	542 (45.2)	61 (49.2)	0.83
1	440 (36.7)	42 (33.9)	
2	157 (13.1)	16 (12.9)	
3-6	61 (5.1)	5 (4.0)	
Pre-pregnancy BMI			
Underweight (<18.5)	76 (6.3)	10 (8.1)	0.03
Normal (18.5-25)	682 (56.8)	55 (44.4)	
Overweight (25-30)	251 (20.9)	28 (22.6)	
Obese (>30)	191 (15.9)	31 (25.0)	
Pre-pregnancy smoking			
Yes	216 (18.0)	34 (27.4)	0.01
No	984 (82.0)	90 (72.6)	
Cervical surgery			
No cervical surgery	935 (77.9)	86 (69.4)	0.04
Colposcopy or punch biopsy	138 (11.5)	13 (10.5)	
Cone biopsy	39 (3.3)	7 (5.7)	
LEEP/LLETZ	37 (3.1)	8 (6.5)	

	12 Months to pregnancy (n=1200)	> 12 Months to pregnancy (n=124)	p-value ^a
Cryosurgery	38 (3.2)	6 (4.8)	
Laser vaporization	13 (1.1)	4 (3.2)	
Case status			
Preterm delivery	316 (26.3)	37 (29.8)	
Small-for-gestational-age	192 (16.0)	24 (19.4)	0.33
Normal delivery (control group)	692 (57.7)	63 (50.8)	

Abbreviations: IHIPS, Iowa Health in Pregnancy Study; BMI, body mass index; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone

^aChi-square p-value for the group difference 12 months to conception versus > 12 months to conception

Table 2

Prior cervical excisional treatment associated with crude and adjusted odds of > 12 months to conception, Iowa Health in Pregnancy Study, Iowa, 2002-2005

	<u>Unadjusted</u>		<u>Full model^b</u>	
	OR	95% CI^a	OR	95% CI^a
Cervical treatment (n=1408)				
No cervical treatment	1.00	(Ref)	1.00	(Ref)
Colposcopy or punch biopsy	1.02	(0.56-1.89)	0.91	(0.49-1.70)
Any cervical surgery ^c	2.14	(1.32-3.47)	2.09	(1.26-3.46)

Abbreviations: IHIPS, Iowa Health in Pregnancy Study; OR, odds ratio; CI, confidence interval

^aWald statistic

^bFull model includes household income, education (categorical), age, pre-pregnancy BMI, smoking (y/n), and case status (PTD, SGA, Control)

^cCervical surgeries includes cone biopsy, loop electrosurgical procedure (LEEP), cryosurgery, and laser vaporization