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Investigating the Treatment of Cervical Intraepithelial Neoplasia With the Loop Electrosurgical Excision Procedure and its Association With Preterm Pregnancy

Ariel R. MacMahon
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Investigating the Treatment of Cervical Intraepithelial Neoplasia With the Loop Electrosurgical Excision Procedure and its Association With Preterm Pregnancy

Abstract

Background: Cervical intraepithelial neoplasia (CIN) can be a precursor to the development of invasive cervical cancer. There are two ways to approach the treatment of CIN, observation or immediate treatment. For women with CIN1, most often observation is the best choice. Women diagnosed with CIN2 or CIN3 typically undergo immediate treatment, due to the increased likelihood of progression. LEEP is currently the procedure of choice, and its association with preterm delivery has been a topic of debate. Many studies have been done analyzing the LEEP in an attempt to investigate the association, and while this is a promising tool in the treatment of cervical cancer, more research needs to be done to reach a definitive conclusion.

Methods: A comprehensive search of the medical literature published within the last five years was conducted using MEDLINE, CINAHL, and EBM Multifile. Search terms used were: cervical intraepithelial neoplasia, loop electrosurgical excision procedure, and pregnancy complications. Web of Science was used in a secondary search to locate articles of interest from the references of the included articles. Each article was filtered based on strict inclusion and exclusion criteria, and then critically appraised. The validity of each article was assessed using the criteria located in Table I.

Results: A total of seven articles were critically appraised. These articles are addressed in Table II. After the appraisal, one article was eliminated due to receiving a validity score less than 3. In Acharya et al the rate of preterm delivery was observed at 9/79 (11.4%) in the study group and 17/158 (10.8%) in the control group. In Samson et al the rates of preterm delivery were 44/558 (7.9%) and 14/558 (2.5%) in the study and control groups respectively. In Nohr et al (2007) the rate of preterm delivery following LEEP was identified at 6.6%, with an adjusted odds ratio of 1.8 and 95% CI of 1.1-2.9. The preterm delivery rate among the comparison group was 3.5% with an OR of 1.0. In Michelin et al the rate of preterm delivery was 1/18 (5.5%). The comparison group was those who were submitted to cold knife conization, in which the preterm delivery rate was 4/17 (23.5%). In Nohr et al 2009 the preterm delivery rate was 530/8180 (6.5%) with an OR of 2.11 and 95% CI of 1.9-2.3. The rate of preterm delivery after no procedure was 17,106/510,841 (3.3%) with an OR of 1.0. In Jakobsson et al the rate of preterm delivery after LEEP was 75/624 (12%), with an OR of 2.61.

Conclusion: Treatment of cervical intraepithelial neoplasia with the LEEP does appear to be associated with and increased risk of preterm delivery, ranging from two to three and a half times greater than that of the general population. Increase in cone height of removed tissue also reflects a greater risk for preterm delivery. More research needs to be done in order to clarify whether the presence of cervical neoplasia alone is a risk factor for adverse outcomes on future pregnancy.

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Ariel R. McMahon

A Clinical Graduate Project Submitted to the Faculty of the
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Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 14, 2010

Faculty Advisor: Mark Pedemonte M.D.
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Ariel McMahon was raised in Wasilla, Alaska. She spent her childhood camping and fishing the rivers of south central Alaska, and learning how to preserve the numerous “fruits of the land.” In 2002 she moved to Bozeman, Montana to attend Montana State University. She was involved in numerous campus organizations, and worked in a biology research laboratory. She went on to publish her research shortly after she graduated with honors in 2006. After earning her bachelor’s degree she remained in Bozeman and worked for Bozeman Deaconess Hospital. She also worked part time as a teaching assistant in developmental biology at the university, and volunteered as a snowboard instructor for children with disabilities. Her life changed drastically when she was accepted to Pacific University School of Physician Assistant Studies in January 2008. She uprooted her life from Montana and moved to Oregon in May 2008. Since then, she has been working vigorously and is looking forward to beginning the next chapter of her life after graduation from Pacific University in August 2010.
Abstract

Background: Cervical intraepithelial neoplasia (CIN) can be a precursor to the development of invasive cervical cancer. There are two ways to approach the treatment of CIN, observation or immediate treatment. For women with CIN1, most often observation is the best choice. Women diagnosed with CIN2 or CIN3 typically undergo immediate treatment, due to the increased likelihood of progression. LEEP is currently the procedure of choice, and its association with preterm delivery has been a topic of debate. Many studies have been done analyzing the LEEP in an attempt to investigate the association, and while this is a promising tool in the treatment of cervical cancer, more research needs to be done to reach a definitive conclusion.

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Keywords: Cervical intraepithelial neoplasia, Loop electrosurgical excision procedure, Preterm delivery
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To Shawn, I cannot express in words how much your continued support has meant to me. You have sacrificed so much of your life, in order to help mine prosper. There is no way that I could have done this without you by my side. You have brought me joy, laughter, and comfort throughout some of the most challenging times of my life. You are my rock, my love, and I am so excited to continue our journey together.
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List of Abbreviations

CIN .......................................................... Cervical Intraepithelial Neoplasia
HPV .......................................................... Human Papillomavirus
COC .......................................................... Combination Oral Contraceptives
RR .......................................................... Relative Risk
LEEP ..................................................... Loop Electrosurgical Excision Procedure
ACOG ..................................................... American College of Obstetrics and Gynecology
EBM ........................................................ Evidence Based Medicine
OR .......................................................... Odds Ratio
CI .......................................................... Confidence Interval
SPR ........................................................ Standardized Prevalence Ratio
Investigating the Treatment of Cervical Intraepithelial Neoplasia With the Loop Electrosurgical Excision Procedure and its Association With Preterm Pregnancy

BACKGROUND

Cervical intraepithelial neoplasia (CIN) is a precancerous change to the epithelium of the cervix. There are three categories of CIN. CIN1 is considered to be low grade, and reflects mild dysplastic changes to the lower third of the epithelium. CIN2 reflects a high grade lesion, and involves dysplasia limited to the basal two thirds of the epithelium. CIN3 is also high grade, and is present when dysplasia encompasses from greater than two thirds, to the full thickness of the epithelium. CIN can be a precursor to the development of invasive cervical cancer.

“The estimated annual incidence in the United States of CIN among women who undergo cervical cancer screening is 4 percent for CIN 1 and 5 percent for CIN 2,3.” Not all CIN lesions will progress to invasive cancer. Low grade lesions (CIN 1) have a relatively low likelihood of progression to invasive cancer, while high grade lesions (CIN 2 and CIN 3) have an increased risk of progression. The diagnosis of high-grade CIN typically occurs between 25 and 35 years of age, while the diagnosis of cervical cancer is often after the age of 40. This allows roughly a decade between the time of diagnosis with CIN, and the development of cervical cancer. Multiple risk factors are associated with the development and progression of CIN.

Some of the common risk factors for the development of CIN include: Human papillomavirus (HPV) infection, multiple sexual partners, early coitarche, tobacco smoking, and combination oral contraceptives (COC) use, and ethnicity. Multiple sex partners and early coitarche are behavioral factors that are associated with an increased
risk of developing HPV infection. In women who smoke tobacco, nicotine and its metabolites, are found in the cervical mucus. The presence of the chemicals, especially in combination with HPV infection, can advance cellular transformation and neoplasia.\textsuperscript{3} A study of HPV positive women revealed a two to four-fold increase in cervical cancer in smokers compared to non-smokers.\textsuperscript{5} There is evidence supporting the association of an increased risk of cervical cancer among women who take COC that directly correlates with length of use. Women who have been on COC for 5 or more years have a relative risk (RR) of 1.90 compared to non-users.\textsuperscript{6} The incidence of cervical cancer in the United States, is 66 percent higher among Hispanics, and 50 percent higher in African Americans as compared to Caucasian women.\textsuperscript{7} The most notable and influential risk factor is considered infection with HPV.

HPV infection has a strong correlation with the development of cervical neoplasia. It is found in 99.7 percent of cervical malignancies.\textsuperscript{8} Over 100 different strains of HPV exist, of which 15 are known to cause cancer.\textsuperscript{4} Not all women with HPV infection develop CIN or cervical cancer. HPV infection is considered to be common, in fact, “it is likely that >50% of sexually active adults have been infected with ≥ 1 genital HPV type.”\textsuperscript{9} HPV infection is most often transient, asymptomatic, and self limiting. The two most important factors in determining whether the infection will lead to neoplasia are HPV subtype and persistence. HPV subtypes 16 and 18 are found in 50 to 60 percent of CIN2 and CIN3 cases, and 25 percent of CIN1 cases.\textsuperscript{10} Persistence of the infection for greater than 12 months increases the risk of neoplasia. “In one prospective population based cohort study, 21 percent of patients with highly oncogenic HPV infections
Management of CIN depends on the grade of neoplasia and persistence.

There are two approaches to the management of CIN, observation or immediate treatment. For women with CIN1, most often observation is preferred. This involves repeat cytology and HPV retesting in 12 months, with referral for colposcopy if the woman’s cytology remains HPV positive or shows atypical squamous cells. If CIN1 persists for longer than 24 months it is acceptable to treat it. Women diagnosed with CIN2 or CIN3 typically undergo immediate treatment, due to the increased likelihood of progression. There are two major treatment modalities, ablation and excision. Ablative treatments include cryosurgery, carbon dioxide laser, and electrofulguration. Ablative procedures destroy local tissue and do not produce specimens available for further evaluation. Due to the nature of the treatment, ablative modalities are suitable for women who do not have invasive squamous or glandular disease, and are compliant to follow up. Excisional modalities include cold knife conization, laser conization, and loop electrosurgical excision procedure (LEEP). These procedures allow for a specimen that can be examined to ensure negative margins. Excisional treatment is appropriate for women who have suspected microinvasion, unsatisfactory colposcopy, or lesions that extend into the endocervical canal.

Of the excision modalities the LEEP has become the procedure of choice because it is cost effective, and can be performed in an outpatient setting. The LEEP utilizes a thin wire loop that is charged with electrical current, allowing for instant coagulation as it cuts the tissue. The loop type can be adjusted according to the size and shape of the lesion, or loop types of various sizes can be used in sequence. The LEEP procedure is
considered to be a safe and effective procedure for the treatment of CIN. Complications include cramping, bleeding, cervical stenosis, and effects on future pregnancy outcome.

**Purpose of the Study**

On November 20, 2009 the American College of Obstetrics and Gynecology (ACOG), released new guidelines on cervical cancer screening recommendations. These guidelines increased the age of initial screening from 18 to 21, and increased the intervals between screenings for most women. Some of the changes were implemented in an attempt to decrease unnecessary exposure to some of the treatment procedures. Most women who undergo these procedures are of child bearing age, and some procedures have been implicated in causing adverse effects on future pregnancy. LEEP is a commonly used outpatient procedure, and its association with adverse pregnancy outcomes has been a topic of some debate. The primary adverse event documented is preterm delivery. Many studies have been done analyzing the LEEP in an attempt to investigate the association. Some researchers have reported that the amount of tissue removed (cone height) plays an important role, while others state the presence of cervical neoplasia alone can affect future pregnancy outcome. LEEP is a promising tool in the treatment of cervical cancer; however, more studies need to be done in order to reach a definitive conclusion on the efficacy of the procedure.

**METHODS**

**Search Strategy**
A comprehensive search of the medical literature published within the last five years was conducted using MEDLINE, CINAHL, and EBM Multifile. Search terms used were: cervical intraepithelial neoplasia, loop electrosurgical excision procedure, and pregnancy complications. Web of Science was used in a secondary search to locate articles of interest from the references of the included articles.

**Inclusion/Exclusion Criteria**

Articles that were eligible for further analysis were those in which the study population included women of reproductive age who underwent LEEP for the treatment of CIN, and with the primary outcome of assessing the rate of pre-term delivery. Articles were excluded if there was no distinction between LEEP and other conization procedures, and if they were not published in the English language.

A total of seven articles fulfilled the inclusion and exclusion criteria. Each article was critically appraised using standard EBM techniques. Due to the nature of the topic all articles were retrospective cohort studies. Therefore, the appraisal included careful attention to the methods used in selecting the study population, and ensuring that confounding variables were taken into consideration. The validity of each article was assessed using the criteria located in Table I. Each article was given a validity rating with four points being the maximum possible score.

**RESULTS**

The search of Medline using the terms cervical intraepithelial neoplasia, loop electrosurgical excision procedure, and pregnancy complications yielded 19 results. Of the 19 articles 6 met the inclusion and exclusion criteria. The search of CINAHL and
EBM Multifile, using the same search terms, yielded 11 and 15 articles respectively. No new articles were obtained from these searches. After a comprehensive review of the included articles references, one additional article was located using the Web of Science database.

A total of seven articles were critically appraised. These articles are addressed in Table II. After the appraisal, one article was eliminated due to receiving a validity score less than 3. The results of the remaining six articles were valid. A summary of the findings of these articles is displayed in Table III.

**Review Articles**

The article by Acharya et al\textsuperscript{17} was a matched retrospective cohort study. The study population included women of reproductive age who underwent the LEEP procedure between December 1995 and December 2000. The women then must have subsequently delivered at the University Hospital of Northern Norway. Women had to be under age 45 at the time of the LEEP and only the first pregnancies following the procedure were included. Two controls were matched per case by age, parity, previous obstetric history, and smoking habit. The primary outcomes of this study were duration of pregnancy and birth weight. A total of 79 women were included in the study group, and there were 158 matched controls. The rate of preterm pregnancy was observed at 9/79 (11.4%) in the study group and 17/158 (10.8%) in the control group. The study did not show a statistically significant increase in preterm birth after treatment by the LEEP.

Samson et al\textsuperscript{18} performed a retrospective cohort study. The researchers began by identifying all women who submitted to the LEEP in Halifax County, Nova Scotia, between 1992 and 1999. The study population then included the women who still lived in
Halifax County, and delivered at the IWK Health Centre. Only the first pregnancies after the procedure were analyzed. The comparison group information was gathered from the same database and the controls were matched for age, parity, smoking status, and date of delivery. Women were excluded if they had known major risk factors for preterm delivery. The primary outcome was rate of preterm delivery. The rates of preterm delivery were 44/558 (7.9%) and 14/558 (2.5%) in the study and control groups respectively. The odds ratio (OR) was 3.5 with a 95% confidence interval (CI) of 1.9-6.95. This study concluded that there was a notable increase in the rate of preterm delivery after LEEP exposure. Cone height of tissue removed was analyzed as a secondary outcome. Samson et al\textsuperscript{18} concluded “no difference in rate of preterm delivery based on characteristics of the LEEP, including depth.”

Nohr et al\textsuperscript{19} (2007) was a population based retrospective cohort study. Women included in the study population were those already participating in a Danish population-based study investigating the natural history of HPV infection. Women in this study were between 20-29 years of age. Investigators linked the information of 11 088 women in the Danish study with the National Patient Registry, Medical Birth Register, and the Pathology Data Bank. They found 14 981 deliveries among 8134 women that were eligible for the study. The primary outcomes measured were rate of pre-term delivery and cone height. Confounding factors such as maternal age, parity, obstetric history, schooling, smoking during pregnancy, and date of delivery were adjusted for. Of the 14 981 deliveries 541 were preterm. The rate of preterm delivery following LEEP was identified at 6.6%, with an adjusted odds ratio of 1.8 and 95% CI of 1.1-2.9. The preterm delivery rate among the comparison group was 3.5% with an OR of 1.0. This suggests
almost a two-fold increase in pre-term delivery among the women treated with LEEP. Women who underwent LEEP with a cone height of 14-16mm had a 7.4% rate of preterm delivery (compared to 3.5% in the control group), with an OR of 2.1. If the cone height was equal to or greater than 17mm the preterm delivery rate was 20%, with an OR of 5.6. This implies an increased risk in preterm delivery that correlates with an increase in cone height.

Michelin et al\textsuperscript{20} conducted a retrospective study. The study group was collected by analyzing the surgical specimens of women who submitted to LEEP or cold knife conization from January 1991 to December 2004 at the Research Institute of Oncology – IPON/UFTM in Brazil. The included patients were women 18 to 45 years of age. The primary outcomes were preterm birth, low birth weight, and miscarriage. Of the 199 patients who met the inclusion criteria, 95 were LEEP cases. Of the 95, 18 women went on to deliver. The rate of preterm delivery was 1/18 (5.5%). The comparison group was those who were submitted to cold knife conization, in which the preterm delivery rate was 4/17 (23.5%). This article concluded that preterm delivery was much greater among cold knife conization.

Nohr et al\textsuperscript{21} (2009) completed a retrospective population-based study. All deliveries in Denmark between 1997 and 2005 were considered. Data was gathered using the National Patient Registry, Medical Birth Register, and the Danish Registry of Pathology databases. A total of 552 678 deliveries were eligible for statistical analysis. Confounding factors including year of delivery, maternal age, smoking during pregnancy, and marital status during pregnancy were adjusted for. The primary outcome of interest was preterm delivery. Of the eligible deliveries 8180 were after LEEP. The preterm
delivery rate was 530/8180 (6.5%) with an OR of 2.11 and 95% CI of 1.9-2.3. The rate of preterm delivery after no procedure was 17,106/510,841 (3.3%) with an OR of 1.0. This reflects a two fold increase in preterm delivery after LEEP.

Jakobsson et al\textsuperscript{22} performed a retrospective cohort study. The study population included 672 women having outpatient treatment for CIN from 1997-2003 and subsequent delivery at the Department of Obstetrics and Gynaecology, Helsinki University Hospital and at the Maternity Hospital, Helsinki, Finland until 2006. The primary outcome assessed was rate of pre-term delivery. Age and parity were adjusted for. The rate of preterm delivery after LEEP was 75/624 (12%), with an OR of 2.61. This rate was compared to a calculated pre-term delivery rate of 4.6%. This study concluded a nearly three-fold increase in pre-term delivery.

**DISCUSSION**

**Preterm Delivery**

Of the six articles reviewed, five concluded that there was an increase in preterm delivery among women treated with the LEEP\textsuperscript{18-22}. There were four articles that received the maximum possible validity score: Acharya et al\textsuperscript{17}, Samson et al\textsuperscript{18}, Nohr et al\textsuperscript{19} (2007), and Nohr et al\textsuperscript{21} (2009). The increase in preterm delivery cited in these studies ranged from no statistically significant increase to an over three fold increase. The studies by Acharya et al and Samson et al were performed in a very similar manner. Both matched cases and controls before analysis, controlled for the same variables, and analyzed only the first pregnancies after the procedure. The results however, were strikingly different, with Acharya et al concluding no statistically significant increase and Samson et al concluding that there was an over three fold increase in preterm delivery. The methods in
both of the Nohr et al papers were also quite similar. Unlike Samson et al and Acharya et al, the study population was composed of a cohort of deliveries, not a cohort of women. In both studies multiple deliveries per woman were considered, and they included the deliveries in those who underwent more than one procedure. These methods are still valid, but limited. Both concluded roughly a two-fold increase in preterm delivery. Based on the results of a majority of the studies, the LEEP does appear to be associated with an increase in preterm delivery. The exact rate of this increase is still unclear, and will continue to be a topic of discussion.

Cone Height

An issue of debate concerning the LEEP is whether or not the height of the cone of removed tissue is associated with the rate of preterm delivery. Many of the reviewed studies were analyzing this as a secondary outcome. Samson et al concluded that the cone height did not have an effect on the rate of preterm delivery, while Nohr et al concluded that the cone height significantly increased the rate of preterm delivery. However, both of these studies were limited by the amount of data available in the pathology reports. There is no standard in place regarding how to report specimen dimensions, therefore, data was missing in some cases. In a study published by Nohr et al in December 2009, researchers consulted with pathologists to compose standardized guidelines for registration of the specimens. With these standards in place they were able to analyze accurate data. They concluded there was a “significant increase in preterm delivery with increasing cone depth, with an estimated 6% increase in risk per each additional millimeter of tissue excised (OR 1.06, 95% CI 1.03-1.09).” This is an extremely important and surprising development. Providers who perform the LEEP
should be informed of these recent findings and take precautions, to remove the minimum amount necessary to ensure negative margins. Standards on information gathering will need to be a major focus in future studies.

**Risks of Cervical Intraepithelial Neoplasia**

Some studies have suggested that the presence of CIN alone is a risk factor for adverse outcomes in pregnancy, including preterm birth, regardless of the treatment modality.\(^{24,25}\) A study conducted by Bruinsma et al\(^{24}\) published in 2006, reported that women who were diagnosed with precancerous changes to the cervix, and not treated, were at an increased risk of preterm delivery as compared to the general population (standardized prevalence ratio (SPR) 1.5, 95% CI 1.4-1.7). A second study by Shanbhag et al\(^{25}\) published in October 2009, compared excisional treatments to no treatment. The excisional group had a preterm delivery rate of 12%, while the no treatment group showed a 15% preterm delivery rate, however, these values were not proven to be statistically significant. This study did show a separate and interesting finding that was statistically significant. They found that the risk of perinatal mortality in the untreated group was seven and a half times that of the excisional group (the 95% CI was wide, but the p-value was .005). This statistic is quite shocking, and illustrates that the risks associated with the procedure may be far less than the risks associated with no treatment. The findings in both studies suggest that the presence of CIN may be an independent risk factor for preterm delivery, however, more research needs to be done on this topic to reach a definitive conclusion.

**Study Limitations**
Due to the nature of the topic the ideal randomized controlled trial will never be done to assess the effects of the LEEP on pregnancy outcomes. It would be unethical to assign women to a no treatment group with the presence of precancerous cervical changes. Most of the available literature on this topic is thus retrospective, and carries with it the inherent limitation of retrospectively analyzed data. The research is limited to the available data, and often, records are missing information. There are numerous cases in which there is no standard in place for how to chart patient information, as it is unclear what may become important to researchers at some later date, they are often left to interpret weak or unclear information. Retrospective cohort studies also leave the door open for introduction of bias when selecting study populations. To address these issues, the ideal solution would be to conduct a prospective observational study. This would allow standards to be developed for gathering and recording information before the study begins, and to fix criteria on the selection of the population to be studied, in order to decrease bias.

All of the studies were able to control for confounding variables. In Acharya et al\textsuperscript{17} and Samson et al\textsuperscript{18} confounding variables were controlled for when selecting the study groups. The others adjusted the results for confounding variables. It would have been ideal if all studies controlled for the confounding variables in a similar fashion.

Study populations were different among the articles. Nohr et al\textsuperscript{19,21} considered the data on actual deliveries. With the research performed in this manner, it allowed for multiple deliveries per woman to be considered, and did not focus on the woman’s outcome after the procedure. In Acharya et al\textsuperscript{17} and Samson et al\textsuperscript{18} the study analyzed only the first pregnancies of specific women following the procedure. Conducting the
study in this manner is more appropriate to clinical practice, as it is the patient that should be the focus rather than data on anonymous deliveries.

**CONCLUSION**

Treatment of cervical intraepithelial neoplasia with the LEEP does appear to be associated with an increased risk of preterm delivery. Of the studies reviewed, five out of six reported that there was an increased risk for pre-term delivery after the LEEP.\textsuperscript{18-22} The increase in risk was anywhere from two to three and a half times greater than that of the general population. Cone height of the tissue removed also proved to be an important factor. The more cervical stroma disrupted, the greater the risk for preterm delivery. Further research needs to be done to clarify whether the presence of cervical neoplasia alone is a risk factor for adverse outcomes in future pregnancy. LEEP is still a safe and effective procedure for the treatment of CIN, but providers should educate their patients on the available treatment options and the risks associated with each.

The LEEP has been used in the treatment of CIN for over a decade. As the years have passed, research has been uncovering the risks and side effects associated with the procedure. In order to accurately calculate these risks, there needs to be a focus on meticulous record keeping. Factors such as loop size, number of passes, and the length, width, and weight of tissue excised, need to be charted accurately. Maternal characteristics before and after delivery, as well as, perinatal outcomes must be reported correctly. This concept is essential in paving the way for future research.

New cervical cancer screening guidelines were established by the ACOG in November 2009. They suggested an increase in the age of the patient at initial screening
and lengthened the time between screenings for most women. The fear was, that too many women of childbearing age were being exposed to procedures such as the LEEP, which may be associated with adverse outcomes in future pregnancy. Due to the nature of CIN and its slow progression to cervical cancer, these new guidelines are appropriate. They will decrease the exposure to procedures such as the LEEP. As long as women adhere to the guidelines and undergo the recommended screenings, even with the increased intervals, the CIN will be diagnosed with adequate time to treat before it progresses to cervical cancer. Providers should reassure any patients with concerns about the safety of the new guidelines.
REFERENCES


## TABLES

Table I. Validity Criteria

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<thead>
<tr>
<th>Criteria</th>
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<td>Quality of Methods</td>
<td>Study and control groups treated similar, All cases accounted for, Clearly reproducible methods</td>
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Table II. Matrix of Reviewed Literature

<table>
<thead>
<tr>
<th>Study/ Design</th>
<th>Population</th>
<th>Comparison</th>
<th>Primary Outcomes</th>
<th>Validity/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya et al (2005) 17</td>
<td>Matched Cohort</td>
<td>79 Women 158 Controls</td>
<td>LEEP vs No LEEP</td>
<td>Duration of pregnancy, Birth weight</td>
</tr>
<tr>
<td>Samson et al (2005) 18</td>
<td>Matched Cohort</td>
<td>571 Women 571 Controls</td>
<td>LEEP vs No LEEP</td>
<td>Pre-term delivery</td>
</tr>
<tr>
<td>Nohr et al (2007) 19</td>
<td>Retrospective Cohort</td>
<td>349 Deliveries 14,567 Controls</td>
<td>LEEP vs No LEEP</td>
<td>Pre-term delivery, Cone height</td>
</tr>
<tr>
<td>Michelin et al (2008) 20</td>
<td>Retrospective Cohort</td>
<td>18 Women 17 Controls</td>
<td>LEEP vs Cold knife</td>
<td>Pre-term delivery, Birth weight, Miscarriage</td>
</tr>
<tr>
<td>Patrelli et al (2008) 26</td>
<td>Retrospective Cohort</td>
<td>45 Women General population</td>
<td>LEEP or Cold knife vs General Population</td>
<td>Duration of pregnancy, Pregnancy outcomes, Mode of delivery, Excision parity</td>
</tr>
<tr>
<td>Nohr et al (2009) 21</td>
<td>Retrospective Cohort</td>
<td>8180 Deliveries 510,814 Controls</td>
<td>LEEP vs No LEEP</td>
<td>Pre-term Delivery</td>
</tr>
</tbody>
</table>
Table III. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Number</th>
<th>% Preterm</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya et al (2005)</td>
<td>LEEP</td>
<td>79</td>
<td>11.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Samson et al (2005)</td>
<td>None</td>
<td>158</td>
<td>10.8</td>
<td>1.8</td>
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<tr>
<td>Nohr et al (2007)</td>
<td>LEEP</td>
<td>558</td>
<td>7.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Michelin et al (2008)</td>
<td>None</td>
<td>558</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Nohr et al (2009)</td>
<td>LEEP</td>
<td>95</td>
<td>6.6</td>
<td>2.11</td>
</tr>
<tr>
<td>Jakobsson et al (2009)</td>
<td>None</td>
<td>14,564</td>
<td>3.5</td>
<td>2.61</td>
</tr>
<tr>
<td></td>
<td>LEEP</td>
<td>18</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>8180</td>
<td>3.3</td>
<td>3.3</td>
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<tr>
<td></td>
<td>LEEP</td>
<td>510,841</td>
<td>12</td>
<td>12</td>
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<tr>
<td></td>
<td>None</td>
<td>624</td>
<td>4.6*</td>
<td>4.6*</td>
</tr>
</tbody>
</table>

* Singleton preterm pregnancy rates from 97”- 06”, calculated from Medical Birth Register, Finland.