

Reduction of Recurrent Cervical Intraepithelial Neoplasia: Cold Knife Conization versus Loop Electrosurgical Excision Procedure

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Abstract

Introduction: Surgical options for cervical intraepithelial neoplasia vary in the reduced risk of recurrence. This systematic literature review investigated the effectiveness of cold knife conization and loop electrosurgical excision procedure for the reduction of neoplastic recurrence in women with cervical intraepithelial neoplasia.

Methods: A literature search of PubMed, the Cochrane Database of Systematic Reviews, and Turning Research Into Practice between January and March 2019 resulted in two systematic reviews, one meta-analysis, and two retrospective cohort studies for analysis. Studies included women with cervical intraepithelial neoplasia, compared cold knife conization and loop electrosurgical excision procedure, reported neoplastic recurrence and were published in English within the past ten years. Critical appraisal was performed utilizing the Centre for Evidence-Based Medicine's Critical Appraisal Worksheets.

Results: Four of five included studies favored cold knife conization over loop electrosurgical excision procedure for reduction of recurrence. One article was considered to be of moderate-to-high quality, two of moderate quality, one of low-to-moderate quality, and one of low quality.

Conclusion: The data provided weak but pertinent evidence supporting the use of cold knife conization over loop electrosurgical excision procedure for reduction of recurrence. Further research is advised to affirm the findings of this review and to explore additional treatment options.

Keywords

Cervical intraepithelial neoplasia (CIN), Cold knife conization (CKC), Loop electrosurgical excision procedure (LEEP), Neoplastic recurrence

Introduction

The frequency of cervical intraepithelial neoplasia and invasive cervical cancer have fluctuated in recent decades, concurrent with changes in screening practices and more recently, the introduction of a vaccine directed towards the human papilloma virus.¹ Incidence of high-grade cervical intraepithelial neoplasia (2 or 3) was estimated as 1 to 2% yearly in 2012 with diagnosis historically occurring between the ages of twenty-five and twenty-nine, most prevalent in Hispanic and Black ethnic groups and those with human immunodeficiency virus.^{2, 3, 4, 5}

Human papilloma virus, commonly affecting young females, is the cause of precancerous cervical cell changes and is identified in over 95% of pre-invasive and invasive squamous carcinomas of the cervix.⁵ Human papilloma virus infection for prolonged periods, especially with subtypes 16 and 18, is associated with an increased risk of cervical intraepithelial neoplasia. Women can often clear the human papilloma virus naturally; however, with the interference of immune response, the progression of precancerous lesions to invasive carcinoma can occur, typically developing over ten or more years.^{6, 7, 8, 9} Additionally, other risk factors for cervical intraepithelial neoplasia pathogenesis include immunosuppression, smoking, coexisting infection, oral contraceptive use, and lack of screening measures.^{6, 10, 11}

Cervical intraepithelial neoplasia is generally diagnosed without symptoms during routine screening measures; however, more severe lesions can present as intermenstrual bleeding or weight loss and fatigue in more advanced stages.¹¹ Clinical assessment of the uterine cervix is performed using the Papanicolaou smear. Current recommendations suggest initiation of screening at age twenty-one with repetition at appropriate intervals dependent on findings; screenings average every three years until age sixty-five.¹ Colposcopy, microscopic visualization of the lower genital tract, and application of acetic acid or iodine to the cervix can allude to neoplastic changes and warrant biopsy upon cellular response with abnormal color or pattern.^{6, 12}

Cervical intraepithelial neoplasia 1 is generally managed on a watch-and-wait basis due to the minimal risk of transformation to carcinoma.^{3, 7, 13} Risk of progression to invasive carcinoma increases with higher grade classification: the natural history of CIN 2 suggests 50% of lesions regress spontaneously, and one in five progress to cervical intraepithelial neoplasia 3 or worse within two years.³ Therefore, treatment is generally recommended with a diagnosis of cervical intraepithelial neoplasia 2 or greater.^{3, 13} Additionally, patients with mild cervical intraepithelial neoplasia which persists for two or more years may be recommended to pursue treatment.^{6, 14} Active management typically includes ablation or surgical excision; however, pregnant women or those aged twenty-one to twenty-four may be considered for alternative treatment options.¹⁴

The loop electrosurgical excision procedure is generally used in lower-grade neoplasia and younger women with cold knife conization reserved for more extensive lesions in females of more advanced age due to concern of adverse reproductive outcomes.^{6, 7, 12} Additionally, cold knife conization is preferred in cases when minimal damage to margins is essential or the presence of microinvasion cannot be ruled out.^{6, 12} The cone depth requirement can increase with age, as post-menopausal women have squamocolumnar junctions which migrate cephalad into the endocervical canal. Women who have completed childbearing or those with comorbid uterine conditions may consider hysterectomy as a definitive option. These interventions are evaluated for efficacy using techniques of follow-up Papanicolaou smear and colposcopic examination. Cold knife conization and the loop electrosurgical excision procedure were investigated in this review to improve understanding of the relationship between either option and the recurrence rate of cervical intraepithelial neoplasia.

Materials and Methods

An electronic literature search in PubMed, the Cochrane Database of Systematic Reviews, and Turning Research Into Practice were conducted from January to March 2019. To address the research question, studies that included adult women with cervical intraepithelial neoplasia, a comparison of treatment with loop electrosurgical excision procedure to cold knife conization, and a primary outcome of recurrent neoplastic rates were selected. An initial search resulted in 321 studies, primarily consisting of retrospective cohort studies, meta-analyses, systematic reviews, and literature reviews.

To isolate the most relevant evidence on the topic, studies greater than ten years old were excluded. Studies not published in the English language were further excluded. The remaining studies were independently reviewed and included if the methods compared the loop electrosurgical excision procedure to cold knife conization in women with cervical intraepithelial neoplasia with a reported outcome of recurrence. Exclusion criteria were applied to reject studies with restricted populations, such as those exclusively including women with or without HIV or HPV, pregnant women, patients with narrowed stages of cancer (IA1 or AIS), or women determined to have persistent positive margins, as this restricted the applicability of results to clinical practice. Pilot or prospective studies, as well as literature reviews, were excluded from selection due to lesser quality and a higher risk of bias. Following the removal of duplicates and application of the stated inclusion and exclusion criteria, 316 studies were eliminated. A total of five studies were selected for final review, consisting of two systematic reviews with meta-analysis, one meta-analysis, and two retrospective cohort studies.

Review of the Literature

A 2017 systematic review and meta-analysis by El-Nashar et al., “Loop Electrosurgical Excision Procedure Instead of Cold-Knife Conization for Cervical Intraepithelial Neoplasia in Women With Unsatisfactory Colposcopic Examinations: A Systematic Review and Meta-Analysis,” aimed to compare the efficacy and safety of the two treatment options.¹⁵ The primary outcome investigated in this review was the combined endpoint of persistent (less than six months post-procedure) or recurrent (greater than six months post-procedure) cervical intraepithelial neoplasia following an intervention. This outcome was assessed in nineteen of the twenty-six studies; the data regarding combined persistent and recurrent cervical intraepithelial neoplasia following the loop electrosurgical excision procedure or cold knife conization indicated a significant difference in efficacy of the two treatments, favoring cold knife conization ($p=0.05$). In the subgroup analysis, which included assessment solely of recurrence, the loop electrosurgical excision procedure resulted in a significantly higher rate of recurrent cervical intraepithelial neoplasia compared to cold knife conization (pooled RR, 2.07; 95% CI = 1.26-3.40). The incidence of persistent disease for loop electrosurgical excision procedure and cold knife conization were comparable in the subgroup analysis (pooled RR, 1.01; 95% CI = 0.81-1.35). A secondary outcome of positive surgical margins did not show significance in endocervical (pooled RR 1.14; 95% CI = 0.86-1.51) or ectocervical (pooled RR 1.08; 95% CI = 0.63-1.86) specimens.

A valid research question was posed examining the efficacy of the loop electrosurgical excision procedure compared to cold knife conization for the treatment of women with cervical intraepithelial neoplasia, two treatments previously regarded as equally efficacious. The authors systematically explored several appropriate medical databases with pertinent search terms to identify relevant studies, with neither language nor sample size used as exclusion criteria. An increased number of pertinent studies and a broader population of women were included due to the lack of these exclusion criteria, expanding the applicability of the results.

Limitations of this study included the use of studies with small sample sizes, which may have skewed results secondary to small-study bias or chance findings. Additionally, specific terms utilized in the search were not indicated, increasing the possibility relevant studies were not identified. In the eighteen cohort studies included, treatment group sizes ranged from relatively equal to having differences of nearly 800 patients. Furthermore, heterogeneity of study populations was indicated by the corresponding Chi-square value ($p=0.03$), decreasing the statistical power of results, as well as the applicability of the study to the general population. Of the few studies reporting follow-up data, attrition rates ranged from zero to forty-eight percent. Therefore, the quality of the studies was questionable due to notable attrition rates and heterogeneity of included studies in conjunction with the lack of data regarding follow-up. Additionally, the authors

expressed limitations in data due to the retrospective design of included studies which could have influenced levels of bias.

The detailed methodology demonstrated a comprehensive search that accumulated a large number of valuable studies of appropriate quality representing an extensive collection of relevant data. Subgroup analyses afforded further investigation of relationships of each treatment choice with persistence and recurrence which identified the superiority of cold knife conization at reducing recurrent cervical intraepithelial neoplasia. The precise methodologic execution, large number of studies included, subgroup analyses, and adequate quality of studies included were important strengths to be noted in this systematic review.

A 2016 meta-analysis by Jiang et al., “Meta-analysis of cold-knife conization versus loop electrosurgical excision procedure for cervical intraepithelial neoplasia” compared surgical complications and treatment efficacy in women who had received either option.¹⁶ There was no statistical significance between treatments about the positive margin rate ($p= 0.17$) or residual disease rate ($p= 0.48$). However, some adverse pregnancy outcomes were shown to be higher with cold knife conization compared to the loop electrosurgical excision procedure, such as preterm premature rupture of membranes ($p= 0.03$), preterm delivery ($p= 0.04$), and low birth weight ($p= 0.04$). Two RCT’s, one prospective, and four retrospective studies reported recurrence rates of cervical intraepithelial neoplasia, and a meta-analysis based on these seven studies demonstrated a lower recurrence rate with cold knife conization as compared to loop electrosurgical excision procedure (RR= 1.75); however, the difference was not statistically significant ($p= 0.06$). Subgroup analyses supported these findings. After analysis, the Cochran Q was not statistically significant, although the ratio of Cochran Q to degrees of freedom was greater than one, indicating possible heterogeneity. Authors stated the design of included studies or the exclusion of missing or unpublished data could have led to bias in the effect.

The study posed an answerable and valid question to distinguish a superior option between the two treatments. Studies were screened by the authors to determine relevance, and scales were used to determine the quality of each study. The inclusion criteria required studies to compare both procedures in women with cervical intraepithelial neoplasia, as well as publication in English or Chinese. For the studies included in the meta-analysis of the recurrence rate of cervical intraepithelial neoplasia, there was a lack of balanced study groups and variance or absence of follow-up and retention data, which may not have adequately represented the rate of recurrence in each specified cohort. As previously stated, there was possible heterogeneity between the seven studies included for assessment of recurrence rate, which could make results less reliable. The inclusion of prospective and retrospective studies is not desirable, as there were likely confounders in the studies which were unrecognized and uncontrolled.

Limitations of the study included uneven cohorts, lack of or inconsistent length of follow-up, lack of reported retention rates, the inclusion of retrospective studies, and the possible presence of

heterogeneity among studies involved. The inconsistent or lack of data could have contributed to skewed or inaccurate results. The heterogeneity between studies and inclusion of studies with a retrospective design may have resulted in decreased quality of the study.

The strengths of the study included a systematic search for articles through several databases, a large number of studies and total participants, and subgroup analyses, which allowed for a detailed collection of data and thorough investigation of the relationships and superiorities of cold knife conization or the loop electrosurgical excision procedure for each of the primary outcomes. The quality of the RCT's, prospective, and retrospective studies according to the modified Jadad and Newcastle-Ottawa scales was determined to be moderate.

A 2016 systematic review and meta-analysis by Santesso et al. "Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia," aimed to assess the efficiency and safety of the listed methods to inform decision-makers on how to best manage cervical intraepithelial neoplasia in women.¹⁷ The results of this systematic review and meta-analysis demonstrated a lower recurrence rate of cervical intraepithelial neoplasia with cold knife conization (pooled RR, 1.431; 95% CI = 0.8323-2.030) when compared to the loop electrosurgical excision procedure (pooled RR, 5.312; 95% CI = 3.702-6.922) based on data from two RCT's and seven non-RCT's. A secondary outcome of premature delivery was assessed including data from two non-randomized studies and showed increased risk with cold knife conization (RR 1.31; 95% CI 0.55-3.12). One RCT measured an additional outcome of spontaneous abortion and found that fewer occurred with cold knife conization compared to LEEP (RR 0.73; 95% CI -0.35-1.51). Neither of these pregnancy outcomes showed statistical significance. Heterogeneity between studies was high, with I^2 of 84-93%. The quality of all evidence was low to very low.

The study presented a justified and important question to identify the benefits and harms of three treatment options for cervical intraepithelial neoplasia to better aid women and their providers in selecting appropriate management, with which to update the World Health Organization guidelines. It is uncertain as to why the authors selected a minimum study population size of 100 for non-RCT study designs with single cohorts or determined that 90% of patients in the included studies were required to have histologically confirmed disease. These parameters appear arbitrary and may have excluded well-conducted studies with relevant data of smaller sizes or percentages. The precise sizes and characteristics of the studies involved were not explicitly outlined; therefore, it was unknown if they were appropriate for the aim of this study. However, the authors state most of the outcomes reported included between 3,000 and 20,000 women, a sufficient size that would have positively affected the quality and reliability of results. Several databases were searched with keywords specific to each, there were no language or study design restrictions, and independent reviewers selected articles based on appropriate inclusion and exclusion criteria.

Limitations of the study included the absence of reported study characteristics listed above, the inclusion of non-RCT's, high heterogeneity, and the inclusion of studies without direct

comparisons. These limitations may have led to lower quality of evidence and lack of direct comparison, and heterogeneity could have contributed to less reliable results. Notable strengths of this study included the rigorous methodology and a large number of studies and participants, which helped to establish the dependability of the data obtained.

A 2012 retrospective cohort study by Serati et al., “Risk factors for cervical intraepithelial neoplasia recurrence after conization: a 10-year study,” aimed to evaluate the risk factors associated with the development of cervical intraepithelial neoplasia recurrence after cervical conization during a ten-year follow-up period.¹⁰ Among variables assessed, the conization methods of loop electrosurgical procedure and cold knife conization were compared for efficacy. The results of this study demonstrated histologically-confirmed persistent/recurrent disease in sixty-four (22.7%) women. Women were distributed into groups of “recurrence” or “no recurrence” for further analysis of variables. In the recurrence group, the positive surgical margin rate was significantly higher ($p=0.016$) and was determined to be the most important independent predictor of recurrent cervical intraepithelial neoplasia. The univariate analysis of surgical conization techniques indicated a two-fold increased risk of recurrence with the loop electrosurgical excision procedure compared to cold knife conization which was statistically significant ($p=0.009$). However, multivariate analysis did not show significance ($p=0.06$).

The authors posed a valid question in the study by pursuing possible risk factors for the recurrence of cervical intraepithelial neoplasia. For inclusion, participants were required to have a diagnosis of cervical intraepithelial neoplasia, undergo either the loop electrosurgical excision procedure or cold knife conization, and have an initial colposcopy. These criteria narrowed the population to those with the disease and interventions of interest. Women were excluded if they failed to complete six months of follow-up, followed up outside of study parameters, or had more severe diagnoses requiring hysterectomy, which aided in the elimination of missing or skewed data.

The limitations of the study included a restricted study population, uneven treatment groups, lack of criteria separating persistent and recurrent disease, follow-up variability, combined outcomes, and retrospective design. The combination of cervical intraepithelial neoplasia 2 and 3 inhibited the ability to make direct correlations between specific stages and associated outcomes. These factors contributed to decreased reliability of results, restriction of applicability, and possible bias, all of which adversely impacted the quality of the study. The study quality was strengthened by the reasonable size of the cohort, the meticulous methodology and statistical analysis, and the assessment of a diverse set of variables to determine possible risk factors for recurrent disease, which support the precision of the results. Assessment of multiple variables provided the study a diverse range of applicability, affording increased value of the results.

A 2013 retrospective cohort study by Simões et al., “Post-cervical conization outcomes in patients with high-grade intraepithelial lesions,” investigated rates of residual, recurrent, and invasive disease after women with cervical intraepithelial neoplasia grades 2 and 3 underwent treatment with either the loop electrosurgical excision procedure or cold knife cone.¹⁸ Several outcomes were

explored for relevance including conization type, margin status, and histological results. The results of the study demonstrated no association between post-conization outcome (absence of disease, persistence, recurrence, or evolution into invasive carcinoma) and procedure type (loop electrosurgical excision procedure versus cold knife conization), with a p-value of 0.198. However, a significant correlation existed between post-conization outcome and type of margins ($p = 0.011$), as well as final cone result ($p = 0.030$). A significant relationship was established between patients with an outcome of residual disease with positive margins compared to negative margins ($p = 0.005$). Additionally, there was a correlation between outcomes of persistence or invasion with a diagnosis of cervical intraepithelial neoplasia grade 3 as compared to grade 2 ($p = 0.006$).

A valid question was proposed in the study, which was both answerable and significant for future practice. Inclusion criteria consisted of women from a single hospital in Brazil with a diagnosis of cervical intraepithelial neoplasia 2 or 3 and treatment with one of the aforementioned procedures. These conditions were appropriate to restrict participants to those with the disease and interventions of interest; however, the narrowed population of a single facility limited the applicability of results. Exclusion criteria eliminated women with previous treatment and those who did not achieve at least six months of follow-up. These exclusions may have eliminated important data obtained before six months or data from previously treated women but are adequate to normalize the study methods and as a precaution to ensure results weren't skewed by prior treatment or lack of follow-up.

Limitations of the study included the retrospective design, narrowed population studied, the potential for lack of data, and variability of follow-up. The retrospective design resulted in a study suspect to selection bias and confounding variables, which could have negatively affected the outcome data. The narrow population studied contributed to results that were less applicable to the general population. Unknown group sizes of the loop electrosurgical excision procedure versus cold knife conization and the lack of accessible data during retrospective collection may have contributed to an incomplete or uneven data set, which could have skewed outcomes. Lastly, the variability of follow-up harmed the quality of the study, as results from patients not seen for the same length of time may have been excluded.

The positive features of the study consisted of nearly 300 participants, assessment of many variables, and inclusion of several subgroups. The relatively large number of women included in the study allowed for improved reliability of the results. The many variables assessed provided information regarding risk factors associated with cervical intraepithelial neoplasia which could be used to guide decisions made by women and their providers. The inclusion of many subgroups of women contributed to a study population more representative of the general population, and therefore the results applicable to a wider span of patients.

Discussion

The purpose of this review was to identify relationships between the loop electrosurgical excision procedure or cold knife conization and rates of recurrent cervical intraepithelial neoplasia to determine a superior option for women requiring treatment. Two systematic reviews with meta-analysis, one meta-analysis, and one retrospective cohort study supported the use of cold knife conization to achieve a reduction in recurrent cervical intraepithelial neoplasia.^{10, 15, 16, 17}

The characteristics of four of the five included studies were sufficient to determine the outcomes of this review, as they all had study population sizes greater than 100 and included variable ages and disease states of women to accurately represent the population.^{10, 15, 16, 18} The systematic review and meta-analysis by Santesso et al. did not disclose demographic details of the study; therefore, adequacy of patient characteristics was unknown.¹⁷ Furthermore, two studies were limited to women from a single institution, narrowing the relevance of outcomes.^{10, 18} The systematic review and meta-analysis by El-Nashar et al. specifically excluded pregnant women; thereby excluding important population data.¹⁵ These discrepancies may have negatively impacted the results due to the possibility of incomplete or inaccurate data to represent the whole population. There were inconsistencies between studies regarding the proportions of life states included in the study as well, and not every study assessed outcomes with demographics. Varying percentages of the populations assessed between studies may not have accurately encompassed all women with cervical intraepithelial neoplasia.

Results were similar among the studies reviewed; two of the five studies included data significantly favoring treatment with cold knife conization as compared to the loop electrosurgical excision procedure due to decreased risk of recurrence.^{10, 15} Of the remaining three studies, two favored cold knife conization lacking statistical significance, and the other reported no difference between treatments regarding recurrence.^{16, 17, 18} Although variation in measurements existed among study outcomes, the data obtained afforded comparison of results across multiple studies.

Limitations of this review included article selection restricted to publications in English, exclusion of pilot and prospective studies, lack of statistical tools to compare data between studies, use of retrospective cohort studies, and nonspecific cervical intraepithelial neoplasia grades of included patients. The exclusion of pilot and prospective studies may have circumvented relevant articles during the initial search; however, the detrimental quality of these articles outweighed the risk of exclusion. The use of retrospective studies subjected this review to potential bias or confounding

variables which may have skewed results; however, it was necessary to include such articles as they represented much of the data encompassing this subject.

The strengths of this review consisted of the inclusion of the most up-to-date data, a thorough search of multiple credible medical literature databases, adequate quality of the majority of studies, large population sizes, and relative homogeneity of findings. Up-to-date data and a thorough initial search assured the most recent and pertinent evidence was included. The adequate quality of the majority of the studies supported the dependability of results acquired. The study was strengthened by the homogeneity of data, as consistent outcomes between the various studies promoted reliability. All studies in this review had adequate population sizes which positively affected the precision and statistical power of outcomes.

The main findings of this review consisted of four out of five articles favoring treatment of cervical intraepithelial neoplasia with cold knife conization in comparison to the loop electrosurgical excision procedure for reduction of recurrent CIN, as exhibited in Figure 1.^{10, 15, 16, 17} The subgroup analysis performed by El-Nashar in a moderate-to-high quality study demonstrated a significantly higher rate of recurrent cervical intraepithelial neoplasia after the loop electrosurgical excision procedure as compared to cold knife conization (pooled RR, 2.07; 95% CI = 1.26-3.40).¹⁵ A low-to-moderate quality univariate analysis by Serati et al. indicated a two-fold increased risk of recurrence with the loop electrosurgical excision procedure compared to cold knife conization ($p=0.009$); however, the same significance was not repeated in the multivariate analysis.¹⁰ A moderate-quality study by Jiang et al. favored treatment with cold knife conization over the loop electrosurgical excision procedure to reduce risk of recurrence; however, the difference was not significant ($p=0.06$).¹⁶ The systematic review with meta-analysis of moderate quality by Santesso et al. revealed an insignificant decrease in recurrence rates with cold knife conization when compared to the loop electrosurgical excision procedure.¹⁷ The low-quality study by Simões et al. indicated no association between post-conization outcome and procedure type for treatment of cervical intraepithelial neoplasia.¹⁸

Secondary outcomes reported by two or more studies included persistent disease, positive margins, and pregnancy outcomes. One moderate-to-high and one moderate-quality study exhibited no significant difference between the loop electrosurgical excision procedure and cold knife conization in post-procedural persistent or residual disease rates.^{15, 16} The risk of positive margins after surgical conization by either procedure was assessed by one moderate-to-high and one moderate quality study, which indicated no statistical difference between cold knife conization and the loop electrosurgical excision procedure for post-procedural positive margins.^{15, 16} Regarding each surgical treatment's effect on pregnancy outcomes, one moderate-quality study demonstrated no significant difference between procedure type and pre-term delivery.¹⁷ However, a separate moderate-quality study reported rates of pre-term delivery were significantly higher with cold knife conization compared to the loop electrosurgical excision procedure.¹⁶ It was notable this statistic was obtained from a single study within the meta-analysis. A moderate-quality study

demonstrated no significant difference in surgical excision type regarding spontaneous abortion.¹⁷ There was insufficient evidence to support a claim of superiority of one procedure for the incidence of pre-term delivery or spontaneous miscarriage.

By performing the best evidence synthesis, it was concluded four of the five studies favored treatment with cold knife conization when compared to the loop electrosurgical excision procedure; however, the evidence was weak.^{10, 15, 16, 17} Secondary outcomes studied resulted in minimal evidence supporting the superiority of one procedure. Two studies noted a statistically significant reduction of recurrence in women who received cold knife conization as compared to the loop electrosurgical excision procedure, primarily from moderate-quality studies with a weak-evidence foundation.^{10, 15}

Women requiring a surgical excision procedure for cervical intraepithelial neoplasia may elect cold knife conization over the loop electrosurgical procedure if prevention of recurrence is of the highest priority. Further investigation should be conducted with randomized controlled trials to affirm the relationship between cold knife conization and the reduction of recurrent disease. There was weak or minimal evidence about secondary outcomes for each procedure which should be explored in greater depth. In particular, pregnancy outcomes are a focus for many practitioners during the decision-making process; statistical evidence evaluating the efficacy of surgical techniques and the impact on pregnancy is warranted. Conduction of further studies exploring other routes of cervical intraepithelial neoplasia treatment would assist in the formulation of first-line recommendations for women with various comorbidities or reproductive states and desires. If the main priority of a woman undergoing treatment for cervical intraepithelial neoplasia is to decrease the rate of recurrence, cold knife conization displayed notable efficacy and should be recommended for treatment.

Conclusion

In adult women diagnosed with cervical intraepithelial neoplasia pursuing conservative surgical management, cold knife conization demonstrated a reduction in the incidence of recurrence when compared to the loop electrosurgical excision procedure; however, evidence was weak.^{10, 15, 16, 17} Secondary outcomes such as persistent disease and positive surgical margins were insignificant, while pregnancy outcomes had controversial results.^{15, 16, 17} Based on the results of this review, patient preference should be considered regarding whether the reduction of neoplastic recurrence or reduction of pregnancy complications is of highest priority; practitioners should recommend CKC or LEEP, respectively, to achieve optimal care.

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LEEP versus CKC for Reduction of CIN Recurrence

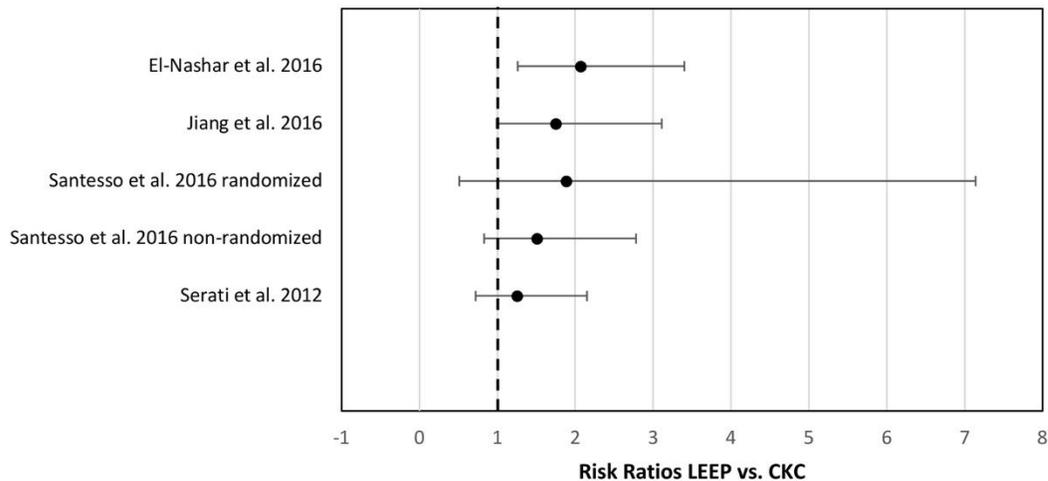


Figure 1: Forest plot of four of the articles selected for this review comparing results of LEEP vs. CKC for reduction of CIN recurrence.^{10, 15, 16, 17} The fifth article by Simões et al. did not report the risk ratios and confidence intervals necessary to compare data.¹⁸ It is of note that the data from Serati et al. reflects the multivariate analysis rather than the univariate analysis, which is why the data appears insignificant in contrast to previous discussion.¹⁰