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REVIEW ARTICLE

Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia

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ABSTRACT

Background: Cervical intraepithelial neoplasia (CIN) stage 2–3 is a premalignant lesion that can progress to cervical cancer in 10–20 years if untreated. *Objectives:* To conduct systematic reviews of randomized and nonrandomized studies for effects of cryotherapy, loop electrosurgical excision procedure (LEEP), and cold knife conization (CKC) as treatment for CIN 2–3. *Search strategy:* Medline, Embase, and other databases were searched to February 2012 for benefits, and to July 2012 for harms. Additionally, experts were contacted. Keywords for CIN, cervical cancer, and the treatments were used. *Selection criteria:* Studies of nonpregnant women 18 years or older not previously treated for CIN were included. *Data collection and analysis:* Two investigators independently screened and collected data. Relative risks and proportions were calculated and evidence assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation). *Main results:* Recurrence rate was 5.3% 12 months after cryotherapy or LEEP, and 1.4% after CKC. There seemed to be little or no differences in frequency of complications after LEEP or cryotherapy, but they occurred more often after CKC. Evidence suggests premature delivery is most common with CKC, but it also occurs after LEEP and cryotherapy. *Conclusions:* Despite a comprehensive search, there is very low quality evidence and often no evidence for important outcomes, including reproductive outcomes and complications. Studies assessing these outcomes are needed.

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that can be confirmed histologically from a biopsy sample and divided into three stages (1, 2, and 3). It is estimated that, in 70% of affected women, CIN 2–3 can persist or progress to cervical cancer after 10–20 years [1,2]. For this reason, treatment is typically provided to women with histologically confirmed CIN 2–3. There are three principle treatment options available in low- and middle-income countries: cryotherapy, loop electrosurgical excision procedure (LEEP; including large loop excision of the transformation zone or cone biopsy with loop excision), and cold knife conization (CKC).

In 2012, WHO committed to updating recommendations for the treatment of precancerous cervical lesions. Although a body of data from randomized controlled trials (RCTs) comparing the effects of these treatments would provide the best evidence about the benefits and harms to support these recommendations, a recently updated and comprehensive Cochrane systematic review of all surgical options confirmed that there are few RCTs available [3]. These RCTs also do not include data for important patient outcomes, such as adverse effects on maternal and fetal outcomes. However, nonrandomized studies could provide complementary information, particularly for adverse effects or complications [4].

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To inform the updated WHO guidelines, a systematic review was conducted of the best available evidence for the benefits and harms of the three treatment options for histologically confirmed CIN 2–3. It includes RCTs and nonrandomized studies and presents the evidence and an assessment of its quality for important outcomes. The objective was to assess the benefits and harms of cryotherapy, LEEP, and CKC for treatment of CIN. More specifically, the aim was to search for and compare the benefits and harms of the treatments (and also no treatment) to inform decision makers who are faced with decisions about how to treat CIN. When comparative studies were not available, noncomparative studies were identified to assess the benefits and harms. Benefits included a reduction in recurrence rates of CIN 2–3 in nonpregnant women aged at least 18 years not previously treated for CIN; and harms included major and minor bleeding and infection, premature delivery, pelvic inflammatory disease (PID), HPV clearance, and damage to other organs. Harms could be reported in nonpregnant women with CIN 1–3 receiving treatment, because the harms would probably be similar irrespective of CIN stage.

2. Materials and methods

Medline, Embase, the Cochrane Library, the Chinese Biomedicine Literature Database, the Chinese Scientific Journal Full-text Database, the Chinese Journal Full-text Database, and the Wanfang Database were searched up to February 2012 for benefits, and up to July 2012 for harms. The search strategy consisted of keywords specific to the database and text words for the treatment options, CIN, and cervical cancer (Supplementary Material S1). The search was not restricted by language or study design. The reference lists of relevant studies were also reviewed and clinical experts in the specialty (e.g. members of the WHO Guideline Development Group panel for the Recommendations on Treatment and Screen and Treat Strategies for Cervical Cancer Prevention [5]) contacted for additional references.

Two investigators independently screened titles, abstracts, and the full text of relevant articles. A third investigator resolved disagreements. Inclusion and exclusion criteria were defined a priori. Studies had to include nonpregnant women aged 18 years or older who had not been previously treated for CIN. RCTs and nonrandomized controlled trials comparing women who received cryotherapy, LEEP, CKC, or no treatment were included. Nonrandomized studies with one group were also included but a minimum of 100 women had to receive cryotherapy, LEEP, or CKC. Systematic reviews of these studies were also included. For studies reporting benefits, at least 90% of the participants had to have histologically confirmed CIN 2–3; for studies reporting harms, participants could have been diagnosed with CIN 1–3. Studies had to report data for at least one outcome identified by the WHO guideline panel as important to decision making. The important outcomes were residual/recurrent CIN 2–3 (at 12 months), damage to other organs/other surgery required (e.g. injury to bladder or urethra), major bleeding (requiring hospitalization/blood transfusion), maternal death, HPV clearance (after 6, 12, and 24 months), major infections (requiring hospitalization and antibiotics), premature delivery, spontaneous abortions, PID, infertility, and minor bleeding (requiring packing or suturing).

Two investigators independently collected data for patient characteristics, diagnosis, treatments, setting, follow-up, and outcomes using a pretested data abstraction form. The quality/risk of bias was assessed for each outcome from the studies using the Cochrane risk of bias tool for RCTs [6] and the domains of the Newcastle-Ottawa Scale for observational studies [7]. Data were analyzed using RevMan 5.2 (The Nordic Cochrane Center, Copenhagen, Denmark). Relative risks (e.g. risk ratios [RRs] and odds ratios) were calculated by pooling results from RCTs and from observational studies comparing treatments. When no direct comparisons between treatments (e.g. cryotherapy vs CKC) within a study were available, the risk of an event (or proportion) in a study (e.g. recurrence of CIN 2–3 for cryotherapy) was calculated and then the proportions from each study weighted by the generic inverse variance were combined. The relative effect between two treatments was then calculated by dividing the overall proportion for one treatment (e.g. cryotherapy) by the overall proportion for the other treatment (e.g. CKC). All results were normalized to effects over a period of 1 year, with the exception of adverse events, most of which would be likely to occur and be reported within the first year. Exploration of moderate to high heterogeneity ($I^2 > 50\%$) and a subgroup analysis for HIV-positive women were planned, but identified data were inadequate.

Two investigators evaluated the quality of the evidence for each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, and a third investigator helped to resolve any discrepancies [8]. The quality of the evidence/confidence in the results of the present systematic review were assessed as high, moderate, low or very low. The effects and quality of evidence were summarized in GRADE Evidence tables for the WHO guideline update [5].

3. Results

3.1. Search results

Among 2703 nonduplicate records identified from the electronic database search and from other sources, 611 articles in full text were retrieved after title and abstract screening (Fig. 1). After exclusion of articles that were not relevant, 167 studies were included. They were either RCTs or nonrandomized studies (comparing two or more treatments, or following one group receiving treatment).

3.2. Cryotherapy, LEEP, or CKC versus no treatment

None of the RCTs identified compared any of the three treatments with no treatment. One nonrandomized study compared cryotherapy with no treatment for prevention of CIN 2–3 recurrence [9] and one systematic review compared all treatments with no treatment for premature delivery [10]. All other outcomes were assessed by pooling proportions from studies of one group receiving treatment.

Detailed results are shown in Table 1 and the study data are available in Supplementary Material S2. Briefly, the recurrence rate of CIN 2–3 seems to be similar with cryotherapy or LEEP (~5%), but are lower with CKC (~1%). However, there was high heterogeneity across studies for each treatment ($I^2 = 84\%–93\%$). Major and minor adverse events seem to occur in less than 1% of women, with the exception of minor bleeding when receiving CKC (affecting ~2.4%). Generally, there were more adverse events with CKC than with LEEP, and more with LEEP than with cryotherapy.

The systematic review of premature delivery (<37 weeks) [10] found that the relative risk of premature delivery was greater with any treatment than with no treatment. The highest risk of premature birth was with CKC, and the lowest with LEEP. HPV clearance was not measured in cryotherapy studies, but was assessed in one small study of LEEP and one of CKC providing little data to make conclusions.

Maternal mortality was not measured. Infertility and spontaneous abortions due to earlier treatment among nonpregnant women were selectively measured and reported. The available data suggested that there are few events with treatment (Table 2).

The quality of the evidence for all outcomes was low to very low, because there were no randomized studies that compared the treatments with no treatment. When data could be pooled, heterogeneity among studies was high.

3.3. Comparisons between treatments

Few RCTs and nonrandomized studies were found that compared one treatment with another treatment. When direct comparisons within studies were available, relative risks and risk differences were calculated (Supplementary Material S3).

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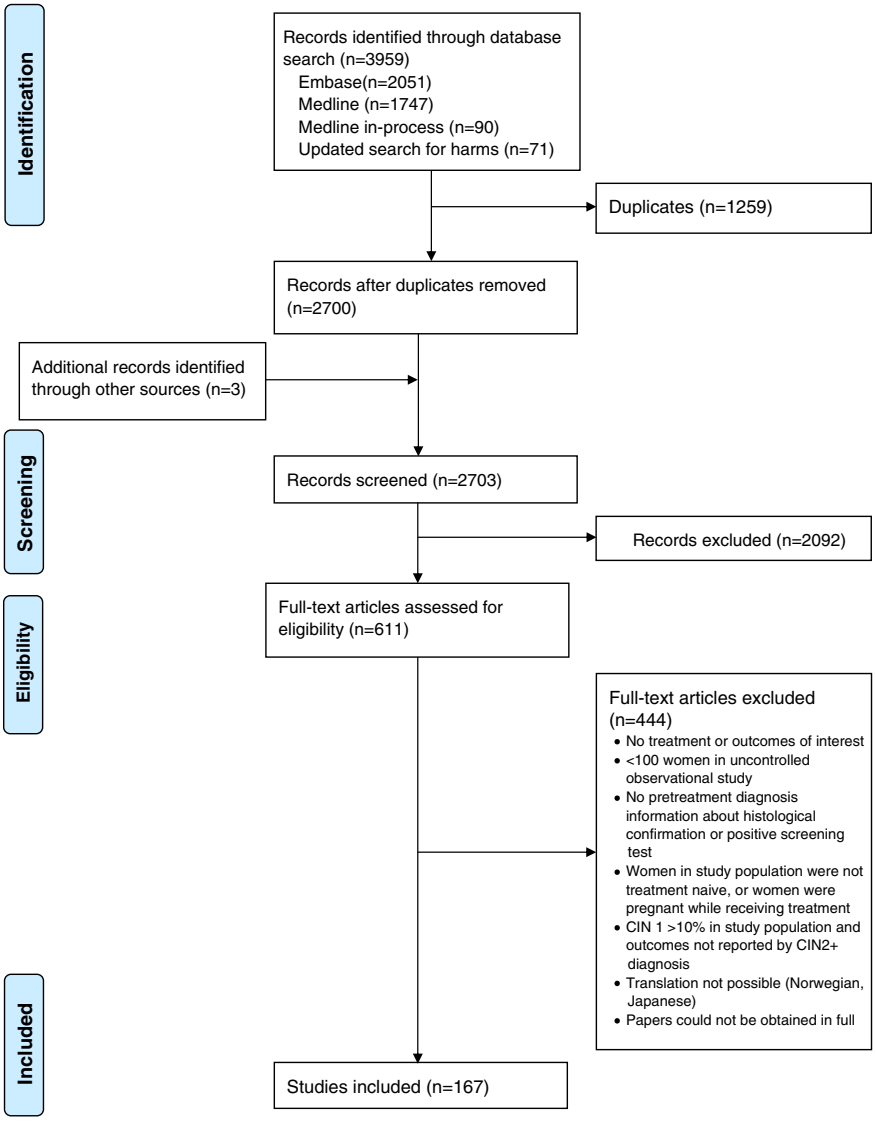

Fig. 1. Flow diagram of study selection.

One RCT was identified that directly compared cryotherapy with LEEP [25]. This RCT showed greater recurrence rates of CIN 2–3 at 12 months after cryotherapy, irrespective of HIV status (RR 3.00; 95% confidence interval [CI] 0.98–9.14). The opposite effect was shown in a non-randomized study comparing the two treatments (RR 0.78; 95% CI 0.12–5.07) [26], although the confidence intervals did include the potential for greater recurrence.

There were no episodes of major bleeding or major infections reported in the RCT, but an indirect comparison between studies evaluating cryotherapy or LEEP showed that fewer major infections (including PID) might occur with cryotherapy (RR 0.12; 95% CI 0.06–0.28). The RCT reported fewer minor bleeds in women receiving cryotherapy (RR 0.46; 95% CI 0.37–0.56).

An indirect comparison was conducted for premature delivery by comparing the risks from the systematic review of studies comparing LEEP with no treatment and cryotherapy with no treatment [10], and showed that there could be a greater risk of premature birth with cryotherapy (RR 1.22; 95% CI 0.08–19.30). However, only one small study contributed to the results for cryotherapy versus no treatment. There were no direct comparisons for spontaneous abortions or infertility, and no data to compare HPV clearance or maternal mortality.

There was moderate-quality evidence for CIN 2–3 recurrence, and major and minor bleeding after cryotherapy or LEEP because of imprecise results (few events and participants in the studies). Evidence for other outcomes was very low quality, primarily because effects were estimated using indirect comparisons between studies which evaluated only one treatment.

For cryotherapy versus CKC, no randomized controlled trials were identified. Six nonrandomized studies comparing treatments [26–31] showed a greater frequency of recurrence of CIN 2–3 among women receiving cryotherapy than among those receiving CKC (RR 3.23; 95% CI 2.63–3.96). Indirect comparisons between up to 44 studies evaluating harms for cryotherapy or CKC showed that there could be fewer major bleeds requiring hospital admission or blood transfusion (RR 0.15; 95% CI 0.10–0.20), fewer major infections (including PID; RR 0.17; 95% CI 0.07–0.43), fewer women with damage to other organs requiring surgery (RR 0.11; 95% CI 0.03–0.38), and fewer minor bleeds (RR 0.03; 95% CI 0.02–0.06) with cryotherapy than with CKC.

Indirect evidence from a systematic review of premature delivery [10] also showed that there may be a lower risk of premature delivery (<37 weeks) with cryotherapy than with CKC (RR 0.70; 95% CI 0.05–4.16). There were no studies that provided a direct comparison

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Table 1
Effects of cryotherapy, LEEP, and cold knife conization at 12 months.[a]

Outcomes	Percentage/RR (95% CI)[b]	Number of studies	Number of events/number of participants
Cryotherapy			
Recurrence of CIN 2–3	5.342 (3.879 to 6.805)	12	562/13 907
Major bleeding	0.034 (−0.030 to 0.098)	17	39/11 570
Major infection	0.014 (−0.038 to 0.065)	18	7/11 938
PID	0.006 (−0.48 to 0.060)	13	3/10 995
Damage to organs	0.022 (−0.056 to 0.100)	7	3/4974
Minor bleeding	0.006 (−0.051 to 0.064)	17	12/8757
Premature delivery	2.25 (0.14 to 34.98)[c]	1	2/117
HPV clearance	–	–	–
LEEP			
Recurrence of CIN 2–3	5.312 (3.702 to 6.922)	19	391/8269
Major bleeding	0.226 (0.131 to 0.320)	40	121/16 423
Major infection	0.128 (0.011 to 0.245)	19	37/7796
PID	0.139 (0.005 to 0.273)	12	33/5913
Damage to organs	0.221 (0.070 to 0.371)	12	21/5727
Minor bleeding	0.363 (0.281 to 0.444)	53	308/19 861
Premature delivery	1.85 (1.59 to 2.15)[c]	8	26 352/656 581
HPV clearance	64.706 (56.242 to 73.169)	1	77/119
Cold knife conization			
Recurrence of CIN 2–3	1.431 (0.8323 to 2.030)	11	228/17 616
Major bleeding	0.859 (0.651 to 1.066)	26	216/9311
Major infection	0.089 (−0.082 to 0.260)	11	12/3443
PID	0.138 (−0.032 to 0.309)	6	9/3003
Damage to organs	0.276 (0.057 to 0.494)	8	17/3180
Minor bleeding	2.450 (2.084 to 2.816)	27	324/7638
Premature delivery	3.41 (2.38 to 4.88)[c]	3	2009/30 216
HPV clearance	72.269 (64.322 to 80.216)	1	86/119

Abbreviations: LEEP, loop electrosurgical excision procedure including large loop excision of the transformation zone; RR, risk ratio; CIN, cervical intraepithelial neoplasia; PID, pelvic inflammatory disease.
[a] On the basis of evidence of low to very low quality.
[b] Percentage unless otherwise indicated.
[c] RR.

between treatments for HPV clearance, infertility outcomes, or spontaneous abortions. One nonrandomized study [30] reported that no deaths occurred in mothers at childbirth with either treatment.

The quality of the evidence was low for recurrence of CIN 2–3 after cryotherapy or CKC because of a lack of randomization in studies; and very low for other outcomes as a result of imprecise results and indirect comparisons.

For CKC versus LEEP, there were four RCTs [21,32–34]. Recurrence rates of CIN 2–3 at 12 months seemed to be lower with CKC than with LEEP on the basis of two RCTs [32,33] (RR 0.53; 95% CI 0.14–1.98), and also on the basis of data from seven nonrandomized studies [23,26,31,35–38] (RR 0.66; 95% CI 0.36–1.20).

Three RCTs [21,32,38] showed a probable reduction of major bleeds with CKC (RR 0.79; 95% CI 0.24–2.60). However, pooled results from two non-randomized studies comparing the two treatments [39,40] showed an RR of 3.42 (95% CI 0.14–50.49). Two RCTs [32,33] showed a probable reduction in minor bleeds with CKC (RR 0.89; 95% CI 0.39–2.01), but data from three nonrandomized studies [23,40,41] showed that minor bleeds could be increased with CKC (RR 3.91; 95% CI 1.02–15.04). The risk of major infection (including PID) was increased with CKC in one nonrandomized study [40] (RR 2.34; 95% CI 0.13–43.18). In an indirect comparison of 20 studies evaluating CKC or LEEP, the risk of damage to other organs requiring surgery was increased with CKC (RR 1.46; 95% CI 0.77–2.76).

There were two non-randomized studies comparing premature delivery after CKC and LEEP [22,42]. The risk was increased with CKC (RR 1.31; 95% CI 0.55–3.12). One RCT [21] measured spontaneous abortion and found that there were fewer with CKC than with LEEP (RR 0.73; 95% CI 0.35–1.51). There were no direct comparisons for infertility or HPV clearance.

There was moderate-quality evidence for major and minor bleeding after CKC and LEEP because of imprecise results. The evidence for other outcomes was of low to very low quality as a result of imprecise results and indirect comparisons.

4. Discussion

The present systematic review of the literature was conducted to inform decision making about effective and safe treatments for CIN 2–3. Unfortunately, although not unexpectedly, only a few small RCTs were found

Table 2
Narrative summary of results for reproductive and fertility outcomes.

Outcome	Cryotherapy	LEEP	CKC
Infertility	4 nonrandomized studies reported 65/439 women with infertility [11–14]	1 non-randomized study of 134 women reported no difference in time to conceive at ≥3 years when compared with no treatment [15]	1 nonrandomized study found no difference in time to conceive in 36 women ≤24 months [16]; another found no infertility ≤12 months in 166 women [17]
Spontaneous abortions	7 nonrandomized studies reported 12 spontaneous abortions in 210 pregnancies with a range of 0%–15% (follow-up 6 months to 10 years) [11–14,18–20]	3 nonrandomized studies of 207 women reported 12 spontaneous abortions [21–23]	3 nonrandomized studies found 10 spontaneous abortions in 1090 women [22–24]

Abbreviations: LEEP, loop electrosurgical excision procedure; CKC, cold knife conization.

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that compared these treatments and measured the outcomes important to decision making. Thus, to fill the gaps in the evidence, the search also included nonrandomized studies. Most of those reported results of one group of women who received one type of treatment. Therefore, these data were pooled together to determine the proportion of women who experience benefits and harms when provided with the treatments.

Moderate-quality evidence comparing cryotherapy with LEEP was found for some outcomes. This evidence suggests that recurrence of CIN 2–3 is probably reduced with LEEP, although there are probably fewer or similar rates of major and minor complications with cryotherapy. Low- to very-low-quality evidence was identified from indirect comparisons between LEEP and no treatment, and cryotherapy and no treatment; the data suggested that there are few differences in reproductive-related outcomes.

Moderate- to low-quality evidence was identified for the comparison of CKC with LEEP for some outcomes. Recurrence of CIN 2–3 is probably reduced with CKC, as is major and minor bleeding. One explanation for the reduction in bleeding is that conditions could be better controlled during CKC surgical procedures. However, for other complications, low- to very-low-quality evidence was found from indirect comparisons between LEEP and no treatment, and between CKC and no treatment, that suggests that major infections, damage to other organs requiring surgery, and premature delivery could be increased with CKC when compared with LEEP.

Not surprisingly, evidence from indirect comparisons between cryotherapy and CKC suggested that recurrence of CIN 2–3 could be greater with cryotherapy but there are fewer complications with cryotherapy than with CKC. The evidence was of low to very low quality.

Overall, insufficient data were identified to draw conclusions about outcomes that have been identified as critical when making decisions about treating CIN 2–3 to prevent cervical cancer. There was very-low-quality evidence and often no evidence at all from studies for reproductive outcomes, such as infertility, spontaneous abortions, and maternal mortality. However, the evidence does suggest that premature delivery could be increased with treatment, which could be a concern to women undergoing treatment and their partners.

The present review has many strengths and some limitations. Current reviews of the literature have restricted the search to randomized controlled trials that can potentially provide the highest quality of evidence. Given the dearth of RCTs in the area, the present search included nonrandomized controlled trials. The search was systematic and comprehensive, and consisted of searches in multiple electronic databases and requests to experts in the field. When searching, a plethora of studies following one group of women who received one intervention were identified, some with fewer than 100 participants. The present study excluded these nonrandomized studies with fewer than 100 women; although this cutoff was arbitrary, it was felt that studies with larger groups of women would have more rigorous design methods to follow up participants and measure outcomes. Despite this restriction, most outcomes included between 3000 and 20 000 women. Additionally, the review did not rely solely on direct comparisons. Instead, risk differences and relative risks were calculated for outcomes between studies in which women received one intervention and studies in which women received another intervention. Although these indirect comparisons provide a lower quality of evidence because of the potential for selection bias, it was felt that low- or very-low-quality evidence would be more informative to decision makers than would no evidence.

In conclusion, the present review provides a summary of the benefits and harms of cryotherapy, LEEP, and CKC to treat CIN among nonpregnant women to prevent progression to cervical cancer. This information has been used to inform the development of WHO recommendations for the treatment of CIN 2–3 to prevent cervical cancer. The benefits and harms of the treatments found in the present review can be considered along with the values and preferences of patients, resources, and feasibility issues to decide which treatment to provide. The data were also used to inform recommendations about screen-and-treat strategies to prevent cervical cancer. It is hoped that additional research into the outcomes important to decision makers will be done to fill the gaps identified in the current literature.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijgo.2015.07.026.

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Conflict of interest

The authors have no conflicts of interest.

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