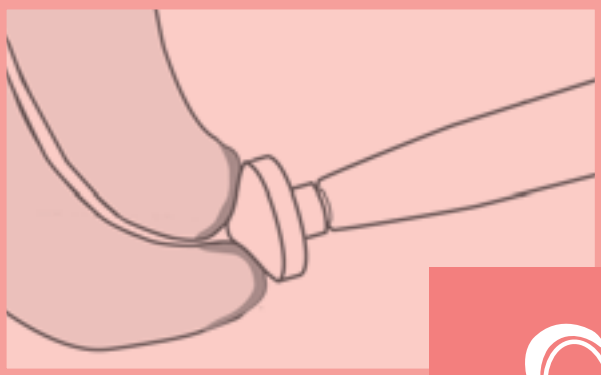
WHO guidelines

Use of cryotherapy for cervical intraepithelial neoplasia



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Declarations of interest

All experts who participated in the development of *World Health Organization guidelines: use of cryotherapy for cervical intraepithelial neoplasia*, were required to complete the WHO Declaration of Interests form. Out of all the experts who participated in this work, three experts declared an interest in the subject related to cervical cancer prevention, as follows:

Dr Lynette Denny: from 2006 to 2010, she has spoken on HPV vaccination at various speaker's fora organized by the companies MSD and GSK. The total honorarium received by Dr Denny from both companies combined was approximately US$ 3000 per year."

Dr Swee Chong Queck: over the past four years, he has participated in medical advisory boards and speakers' bureaux relating to cervical cancer prevention strategies, HPV vaccine efficacy studies and clinical relevance of HPV vaccination for the prevention of cervical cancer and other HPV related diseases. The total income received by Dr Queck from both companies combined was approximately 5000 Singapore dollars per year over the past four years.

Dr Vivien Tsu: her employer PATH, an international nonprofit organization operating in the field of health, has received large-scale donations of HPV vaccines and test kits, as well as equipment, for use in demonstration projects aimed at promoting public health, including in particular in low-resource countries.

Contents

Executive Summary

In 2008, cervical cancer was responsible for 275 000 deaths, of which about 88% occurred in low- and middle-income countries. In 2009, the World Health Organization (WHO) committed to updating the recommendations on the use of cryotherapy for cervical intraepithelial neoplasia (CIN), adhering to the WHO revision process of guideline development. This document summarizes the new evidence-based WHO recommendations about the use of cryotherapy in women with histologically confirmed CIN for low-, middle- and high-income countries.

The methods used to develop these guidelines follow the *WHO handbook for guidelines development*. An expert panel was established that included clinicians who provide cryotherapy services, researchers in cervical cancer prevention and treatment, programme directors and methodologists. An independentgroup of scientists at a WHO collaborating center conducted systematic reviews and produced evidence summaries following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

GRADE evidence profiles were created for 16 key questions about the effects of cryotherapy in the presence of histologically confirmed CIN compared to no treatment and to loop electrosurgical excision procedure (LEEP), as well as the use of different techniques of cryotherapy. Conflict of interests were managed according to WHO rules.

The systematic reviews had very few randomized controlled trials or controlled observational studies, and therefore most of the recommendations are based on pooled results across observational studies in women receiving cryotherapy. Very few studies assessed outcomes that the expert panel had identified as critical to decision-making, including fertility and obstetrics outcomes, maternal morbidity, acceptability of the procedure to women or their health-care providers, referral rates for complications, and HIV acquisition and transmission. Thus, most of the resulting 14 recommendations are based on studies that included outcomes for recurrence rates of CIN, major and minor adverse events, and cervical cancer incidence and mortality rates.

Specific recommendations and their strength and quality of available evidence

Context	Recommendation		Quality of evidence	Strength
Use of cryotherapy for prevention of CIN	1a	The expert panel recommends cryotherapy over no treatment	⊕○○○	Strong
	1b.	In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy	⊕⊕○○	Conditional
Lesion size	2.	Among women with CIN lesions covering more than 75% of the ectocervix, or with lesions extending beyond the cryo tip being used, the expert panel suggests performing or referring for excisional therapy	⊕⊕○○	Conditional
Lesions extending into the endocervical canal	3a.	In settings where LEEP is available and accessible, and women present with CIN lesions extending into the cervical canal, the expert panel suggests treatment with LEEP over cryotherapy	⊕⊕○○	Conditional
	3b.	In settings where excisional procedures (e.g. LEEP, laser or CKC) or referral to additional treatment are not available, the expert panel suggests that women with lesions extending into the endocervical canal be treated with cryotherapy	⊕○○○	Conditional
Cryotherapy technique and procedure	4.	The expert panel suggests double freeze using a 3 minute freeze, 5 minute thaw, 3 minute freeze cycle over single-freeze cryotherapy	⊕⊕○○	Conditional
	5.	The expert panel recommends cryotherapy using either carbon dioxide (CO_2) or nitrous oxide (N_2O) gas	⊕⊕○○	Strong
		In settings where both gases are available, the expert panel suggests cryotherapy with CO_2 rather than with N_2O	⊕○○○	Conditional
	6.	The expert panel recommends that the "cough technique" *should not be used* during cryotherapy	⊕○○○	Strong
	7.	The expert panel suggests that prophylactic antibiotics *should not be used* when providing cryotherapy	⊕○○○	Conditional
Providers	8.	The expert panel recommends that health-care workers (including non-physicians) trained in cryotherapy perform the procedure for women when it is indicated	⊕⊕○○	Strong
		The expert panel also suggests that trained nurses or trained midwives rather than physicians may perform cryotherapy	⊕○○○	Conditional
Use of cryotherapy during pregnancy	9a.	In pregnant women, the expert panel suggests deferring cryotherapy until after pregnancy	⊕○○○	Conditional
	9b.	In women whose pregnancy status is unknown (or there is no clinical evidence of pregnancy), the expert panel suggests using cryotherapy	⊕○○○	Conditional
Retreatment of CIN lesions with cryotherapy	10a.	The expert panel recommends cryotherapy over no treatment for women who screen positive after prior cryotherapy treatment	⊕○○○	Strong
	10b.	In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy for women who screen positive after prior cryotherapy treatment	⊕⊕○○	Conditional

See page 7 for full details of recommendations and remarks.

Introduction

In 2008, cervical cancer was responsible for 275 000 deaths, of which about 88% occurred in low- and middle-income countries. Cervical cancer is the third most common cancer in women worldwide and the most common cancer in many low- and middle-income countries (*1*). Because it has a typically slow progression, from atypical cells to cervical intraepithelial neoplasia (CIN) and to invasive carcinoma, precancerous lesions can be treated and invasive cervical cancer prevented. The screening methods currently available in a wide range of settings include cytological smears (Pap smear), visual inspection with acetic acid (VIA), and human papillomavirus (HPV) testing. A diagnosis of CIN can be confirmed by histological interpretation of biopsies, either with or without colposcopy. Furthermore, a variety of treatment methods are available, including cryotherapy, loop electrosurgical excision procedure (LEEP)/large loop excision of the transformation zone (LLETZ)[1], cold knife conization (CKC), laser vaporization, cold coagulation, and hysterectomy. In 2004, the World Health Organization (WHO) and other international organiaations, developed and published *Comprehensive cervical cancer control: a guide for essential practice* (C4-GEP), as a comprehensive guide to assist health-care providers at multiple levels of the health system to prevent, detect and treat cervical precancer and cancer (*2*).

In 2009, WHO committed to updating these guidelines following the WHO revised process for guideline development (*3*). The C4-GEP currently includes recommendations on major treatment procedures for precancer of the cervix: cryotherapy, LEEP and CKC. Since many countries are moving towards marked revisions in their national programmes based on "single-visit" or "screen-and-treat" approaches using cryotherapy following a positive screening test, and because of the widespread use and ready availability of cryotherapy and limited availability of confirmatory colposcopy diagnosis, recommendation on the use of cryotherapy was therefore deemed a priority for the update of the C4-GEP, to support programme managers and clinicians to scale-up national programmes.

This document presents recommendations for the use of cryotherapy compared to no treatment, and to LEEP in the presence of histological confirmation of precancer lesion, CIN (CIN1, CIN2 or CIN3). The document also addresses the use of different techniques of cryotherapy for CIN and provides recommendations for treatment of CIN in women who are pregnant, as well as for women who are HIV infected. In keeping with WHO guideline terminology, the recommendations are either "strong" or "conditional" (*4*). For strong recommendations, we use the words "we recommend", and for conditional recommendations, "we suggest". We offer suggested interpretations of "strong" and "conditional" recommendations in Table 1. Understanding the interpretation of these two grades – either strong or conditional – is essential for health-care decision-making.

Methods

The methods to develop these guidelines followed the *WHO handbook for guidelines development* (*3*).

Formulating questions and determining outcomes

In March 2009, experts invited by WHO drafted a list of 45 general questions about the effects of cryotherapy in women with CIN. These experts were then asked to rank the questions by priority.

Expert guideline panel

WHO selected a multidisciplinary expert guideline panel comprising clinicians with cryotherapy experience, researchers in cervical cancer prevention and treatment, programme directors, epidemiologists, public health offi-

[1] Although two techniques are described, LEEP and LLETZ, these are the same and only LEEP will be referred to throughout the document.

Table 1. Interpretation of strong and conditional recommendations

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
	Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful for helping individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

cers and methodologists. The methodologists (evidence review team) were based at the McMaster University WHO Collaborating Center and had expertise in guideline development and evidence synthesis. A steering group of seven members was then created from the expert guideline panel, to guide the process.

Following a review of the suitability of the initial 45 general questions, these questions were refined to 16 questions for which an evidence review was deemed necessary. The steering group also decided to assess the evidence for the effects of cryotherapy in women with histologically confirmed CIN, to provide the best estimate of the benefits and side-effects of cryotherapy without the potential for confounding the outcomes due to false-positive screening tests or diagnoses.

To determine the outcomes, a scoping review of cryotherapy studies was conducted by the evidence review team. The expert guideline panel was also consulted. A list of outcomes to be considered when making the recommendations was compiled. Nineteen members of the expert guideline panel independently and anonymously scored the outcomes by importance for decision-making, via an electronic survey (*5*). The mean and median importance of each outcome (scale: 1 – least important to 9 – critical) was calculated, and 16 outcomes were identified as important or critical (see Box 1).

Preparation of the evidence profiles and grading of the evidence

The evidence review team conducted a series of systematic literature reviews following the methods of the Cochrane Collaboration, and prepared GRADE (Grading of Recommendations, Assessment, Development and Evaluation) evidence profiles for each question (*6*). During this process, the steering group held conference calls to discuss issues about the available evidence, the presentation of the results, and their impact on making recommendations.

MEDLINE, Embase, LILACS, The Cochrane Library and the WHO Clinical Trials Search Portal were searched up to July 2009, using key subject and text words for cryotherapy and cervical cancer, depending on the database (see appendix A for the MEDLINE search strategy). The search was not limited by language or by study type. The evidence review

Box 1. Outcomes identified as important or critical to making recommendations[a]

- Resource use (including cost, human resources and length of stay)
- CIN2–3
- Cervical carcinoma incidence
- Acceptability to women (e.g. satisfaction with process or provider)
- Referrals after cryotherapy for complications or follow-up treatment
- Acceptability according to providers
- HIV transmission (HIV acquisition, HIV shedding)
- All severe adverse events (including major bleeding, major infections, etc.)
- Mortality
- Fertility (e.g. conception)
- CIN (1 or 2–3)
- Spontaneous abortion
- Pain (requiring local treatment)
- Maternal morbidity
- Minor infection (requiring outpatient treatment only)
- CIN1

[a] In order of importance for cryotherapy versus no treatment or LEEP.

team screened titles, abstracts and full text of potentially relevant literature, in duplicate. The first screen was for controlled trials (randomized or non-randomized), but because only a few controlled trials were identified, observational studies without independent controls were also included as evidence. Authors in the field, and the expert guideline panel, were also contacted to identify missing studies, studies in progress or studies not yet published.

When possible, relative effects (such as relative risks and odds ratios of an event) were calculated from pooled data of controlled studies. When there were no data, indirect comparisons were made (e.g. randomized controlled studies of cryotherapy versus laser excision were compared to laser excision versus LEEP), and a network meta-analysis was conducted. In studies without independent controls, the risks of an event were pooled across studies (e.g. for cryotherapy and for LEEP), and a relative effect was then calculated to compare those pooled results. All results were normalized to effects over a period of one year, with the exception of adverse events, most of which would probably occur and be reported within one year. Cervical cancer rates in untreated CIN were obtained from McCredie et al. (2010), and annualized *(7)*. It was assumed that these risks were constant over time.

Evidence summaries and profiles, which were based on the evidence of the systematic reviews, were prepared for each question using the GRADEprofiler software *(8)*. GRADE evidence profiles present the effect of the intervention on each outcome (e.g. number of women with recurrent CIN), and the quality of the evidence for each outcome. The quality of a body of evidence is assessed based on the following criteria: risk of bias, imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and an assessment of the effect of residual confounding and bias. Quality is categorized into four levels, ranging from ⊕○○○, being the lowest quality, to ⊕⊕⊕⊕, being the highest quality. The GRADE evidence profiles allow the expert guideline panel to base its judgments on the same concisely summarized evidence when making recommendations. One week before the expert guideline panel met to develop the recommendations, panel members were able to review the evidence profiles for each question via a password-protected electronic SharePoint site.

Development of recommendations

The expert guideline panel met on 22 to 23 September 2010, to review the evidence and make recommendations. This meeting was chaired by a methodologist with experience in guideline development, and cochaired by a gynaecological oncologist. There were 32 panel experts, as well as WHO and International Agency for Research on Cancer (IARC) officers, who provided scientific input and guidance. The key objectives of the meeting were to formulate evidence-based recommendations for each of the priority questions, identify key research gaps and discuss a dissemination plan for the new guidelines.

During the September meeting, the panel developed recommendations based on the GRADE evidence profiles. For each recommendation, the panel considered and agreed on the following: the quality of the evidence; the balance of benefits and downsides; the assumptions about the values and preferences associated with the decision; and the extent of resource use. Recommendations were made by consensus. Before the meeting concluded, the panel used the evidence to classify each recommendation as “strong” or “conditional” and agreed on the wording and remarks for each recommendation.

Results

GRADE evidence profiles were created for 16 key questions about the effects of cryotherapy compared with no treatment or LEEP in women with histologically confirmed CIN1, 2 or 3 (see Appendix B for summary tables for each recommendation; GRADE tables are available from http://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/index.html). The systematic reviews found only a few randomized controlled trials or controlled observational studies (such as cohort or case–control studies) that fulfilled the inclusion criteria. Therefore, most of the recommendations are based on pooled results across observational studies of women who received cryotherapy. For these analyses, results were pooled across all CIN grades (CIN1, 2, 3), and, when possible, tested for differences between outcomes for CIN1 and CIN2/3. However, cryotherapy outcomes stratified by CIN grade at diagnosis were not different enough to make separate recommendations based on CIN grade. For this reason, these recommendations can apply to any CIN grade. There were few studies measuring outcomes that the panel identified as critical to decision-making: fertility and obstetrics outcomes; maternal morbidity; acceptability of the procedure to women or their health-care providers; referrals rates for complications; and HIV acquisition and transmission. Therefore, the recommendations are based primarily on studies that measured cryotherapy treatment failures for CIN (i.e. included any evidence of disease after treatment); major and minor adverse events; and mortality.

Recommendations

Use of cryotherapy for prevention of CIN

1a. The expert panel recommends cryotherapy over no treatment (strong recommendation, ⊕○○○ quality evidence)

Remarks: This recommendation is strong, despite the presence of very-low-quality evidence. The expected benefit of cervical cancer prevention is very high but there is uncertainty related to the occurrence of adverse outcomes. There was very low-quality evidence for the occurrence of spontaneous abortions and infertility but the risk appeared similar to that in the general population. Although neither the risk of HIV acquisition in HIV-negative women nor the risk of HIV transmission by HIV-infected women who undergo cryotherapy is known, the current limited data do not suggest that there is an increase in the risk of HIV acquisition/transmission. Additional data regarding the rate of HIV acquisition/transmission are pending and will need to be assessed in future. However, the panel agreed that the net benefit from cryotherapy outweighs the potential HIV risk.

1b. In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy (conditional recommendation, ⊕⊕○○ quality evidence)

Remarks: This recommendation applies to women regardless of HIV status. The benefits of LEEP when compared to cryotherapy were greater, and harms fewer or similar; therefore, LEEP was suggested. However, the panel recognized that there are greater resource implications for LEEP than with cryotherapy and therefore LEEP is not available in all settings. When LEEP is unavailable, cryotherapy is recommended (see recommendation 1a). Although the risk of HIV seroconversion in HIV-negative women, and the risk of transmission after LEEP or cryotherapy are unknown, the benefits of LEEP were felt to outweigh the harms, and, therefore, this recommendation applies to women regardless of HIV status.

Lesion size

2. Among women with CIN lesions covering more than 75% of the ectocervix, or with lesions extending beyond the cryo tip being used, the expert panel suggests performing or referring for excisional therapy (conditional recommendation, ⊕⊕○○ quality evidence)

Remarks: This recommendation includes considerations that cryo tips should cover the entire lesion and that the largest cryo tip typically only covers lesions that extend over up to 75% of the cervix. Since the quality of the evidence is low for recurrent CIN lesions and for lesions larger than 75% of the cervical surface, the panel made a conditional recommendation.

Lesions extending into the endocervical canal

In women with CIN lesions extending into the endocervical canal, prior guidelines recommend excisional procedures; this panel operated under this assumption (*2*).

3a. In settings where LEEP is available and accessible, and women present with CIN lesions extending into the cervical canal, the expert panel suggests treatment with LEEP over cryotherapy (conditional recommendation, ⊕⊕○○ quality evidence)

Remarks: The benefits of LEEP were greater than those of cryotherapy, and the harms were fewer in these women. However, since there are greater resource implications for LEEP than cryotherapy, and thus LEEP is not available in all settings, a conditional recommendation was made.

3b. In settings where excisional procedures (e.g. LEEP, laser or CKC) or referral to additional treatment are not available, the expert panel suggests that women with lesions extending into the endocervical canal be treated with cryotherapy (conditional recommendation, ⊕○○○ quality evidence)

Remarks: The risk of treatment failure is higher in women with CIN lesions extending into the cervical canal than in women whose lesion

margins are clearly demarcated or do not extend into the cervical canal. The rationale for treating these women is that women left untreated may be lost to follow-up (i.e. they may not receive further treatment and are at risk for developing cervical cancer). This recommendation should be considered in the context of recommendation 3a.

Cryotherapy technique and procedure

4. The expert panel suggests double freeze using a 3 minute freeze, 5 minute thaw, 3 minute freeze cycle over single-freeze cryotherapy (conditional recommendation, ⊕⊕◯◯ quality evidence)

Remarks: The evidence stems from studies in which a single-freeze technique was performed for up to 3 minutes. This recommendation takes into consideration that during a cryotherapy procedure, the iceball should extend beyond the edge of the cryo tip. Data from trials regarding the benefits and harms of single-freeze versus double-freeze techniques are pending and will be assessed in the future. The panel commented that randomized controlled trials should be performed to specifically address this issue.

5. The expert panel recommends cryotherapy using either carbon dioxide (CO_2) or nitrous oxide (N_2O) gas (strong recommendation, ⊕⊕◯◯ quality evidence); in settings where both gases are available, the expert panel suggests cryotherapy with CO_2 rather than with N_2O (conditional recommendation, ⊕◯◯◯ quality evidence)

Remarks: Due to the limitations in the available evidence, it is uncertain whether CO_2 provides better or worse health outcomes, but the existing evidence suggests that there is no difference. Laboratory studies suggest no difference in temperature at the cryo tip between different grades of CO_2 (e.g. medical or industrial). Although, N_2O gas is less available and requires more resources due to higher cost and additional requirements for ventilation, in settings where N_2O gas is more likely to be available or has other advantages, this conditional recommendation suggests that N_2O gas may be used. Studies addressing the use of CO_2 versus N_2O are being conducted.

6. The expert panel recommends that the "cough technique" should *not be used* during cryotherapy (strong recommendation, ⊕◯◯◯ quality evidence)

Remarks: The "cough" or "freeze–clear–freeze" technique was historically used because of technical deficiencies in a particular cryotherapy device from a single manufacturer, which caused instrument clogging. This device has been removed from the market, and so this is a strong recommendation despite very low-quality evidence.

7. The expert panel suggests that prophylactic antibiotics should *not be used* when providing cryotherapy (conditional recommendation, ⊕◯◯◯ quality evidence)

Remarks: While there may be fewer minor adverse events and fewer minor infections with prophylactic antibiotic use, there is a risk of increased antimicrobial resistance and allergic reactions that is unlikely to outweigh any potential benefits. Resources also appear to be increased with the use of antibiotics.

Providers

8. The expert panel recommends that health-care workers (including non-physicians) trained in cryotherapy perform the procedure for women when it is indicated (strong recommendation, ⊕⊕◯◯ quality evidence); the expert panel also suggests that trained nurses or trained midwives rather than physicians may perform cryotherapy (conditional recommendation, ⊕◯◯◯ quality evidence)

Remarks: The importance of cryotherapy training of the health-care worker was considered when making this recommendation. There appear to be better health outcomes when cryotherapy is performed by trained nurses or trained midwives rather than physicians. However, values and preferences for

cryotherapy performed by physicians versus midwives or nurses differ across settings. In many settings, the resources required for nurses and midwives are lower than for physicians.

Use of cryotherapy during pregnancy

9a. In pregnant women, the expert panel suggests deferring cryotherapy until after pregnancy (conditional recommendation, ⊕◯◯◯ quality evidence)

Remarks: Deferral means that cryotherapy is delayed until the postpartum period. The available limited evidence does not suggest that cryotherapy increases risk of adverse pregnancy outcomes when performed during pregnancy; however, an increased risk of pregnancy loss cannot be ruled out and evidence is required. If women with histologically confirmed CIN lesions are at a high risk of loss to follow-up, or if additional opportunities for treatment are unlikely, treatment during pregnancy may be considered. However, there is an opportunity for enforcing the need for postpartum visits (including opportunities for child vaccination) if lesions are identified during pregnancy. There also are possible negative perceptions if cryotherapy is (erroneously) associated with pregnancy loss by women.

9.b. In women whose pregnancy status is unknown (or there is no clinical evidence of pregnancy), the expert panel suggests using cryotherapy (conditional recommendation, ⊕◯◯◯ quality evidence)

Remarks: This is based on recommendation 1a.

Retreatment of CIN lesions with cryotherapy

10 a. The expert panel recommends cryotherapy over no treatment for women who screen positive after prior cryotherapy treatment (strong recommendation, ⊕◯◯◯ quality evidence)

Remarks: There was no evidence for use of cryotherapy over no treatment in women who screen positive after previous treatment with cryotherapy. Therefore, this recommendation is based on recommendation 1a.

10 b. In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy for women who screen positive after prior cryotherapy treatment (conditional recommendation, ⊕⊕◯◯ quality evidence)

Remarks: There was very-low-quality evidence for benefits of LEEP techniques over cryotherapy and no evidence for harm in women who screen positive after previous treatment with cryotherapy. This recommendation is directly related to recommendation 1b.

Education

As part of best practice, detailed counselling and education should be provided with informed consent, prior to performing cryotherapy. Specific involvement of a woman's partner post-treatment should be given special attention, and, in particular, the use of condoms post-cryotherapy. The reviewed evidence was judged by the expert panel as too indirect to make a recommendation for additional education and counselling beyond what would be part of best practice. Evidence from future interventions may inform this question.

Discussion

This document summarizes the recent WHO recommendations for the use of cryotherapy in women with histologically confirmed CIN. The methods recommended by WHO for guideline development were followed, and a series of systematic reviews were conducted to inform these recommendations. The panel, comprising experts from around the world, developed 14 recommendations, while considering the international audience and application of these guidelines in low-, middle- and high-income countries.

These guidelines are directly applicable to women with histologically confirmed CIN, but may be applicable to women who have been screened positive without histological confirmation. However, this review and the recommendations did not address the issue of "single-visit" or "screen-and-treat" approaches. We recognize that in many cervical cancer prevention and control programmes, treatment is commonly offered on the basis of a screening test result alone, such as VIA, most often because histological confirmation is not available or is programmatically feasible. Thus, although not all women who screen positive will have CIN, treatment by cryotherapy according to these present guidelines can be provided. In addition, the recommendations for cryotherapy using the double-freeze techniques and different gases (CO_2 versus N_2O) are directly applicable to any populations of women receiving cryotherapy who have positive screening test results without confirmatory histology diagnosis. These cryotherapy recommendations are also essential for the forthcoming development of the WHO "technical specification and procurement of cryotherapy equipment", and for programme managers wanting to scale-up national cervical cancer and prevention programmes.

As in most guidelines, many of these recommendations are conditional, due to the absence of moderate or high quality of evidence. Therefore, clinicians and policy-makers will need to consider available resources (including costs, equipment and human resources), and the presumed values and preferences of women presenting with precancerous lesions found at the time of screening. For suspicion of glandular disease, the evidence was considered too indirect or sparse to develop recommendations, and so the panel did not formulate recommendations. There is also little evidence for cryotherapy use among HIV-positive women and those who are pregnant. For recommendations in these populations, the panel agreed that the benefits of treatment to prevent cervical cancer outweighed the unknown or uncertain harms, but that future research will need to be considered for future updates of the recommendations.

A strength of these recommendations is the process used by the expert panel. Specifically, the recommendations were made considering the totality of the available evidence and using the transparent and rigorous methods recommended for all WHO guidelines. Thus, despite the frequently indirect evidence from studies that lacked independent control groups, the panel had at hand comprehensive evidence summaries when making decisions regarding recommendations. The WHO guideline process also provided a systematic approach to decision-making, and a method to transparently record the benefits, harms, values, preferences and resource use for each recommendation decision.

The limitations of these guidelines are inherent to the lack of available evidence to answer key questions. Guidelines in general, and for WHO in particular, should provide recommendations based on the *best* available evidence. Much of the best available evidence for these guidelines came from pooled data across observational studies, which did not include independent control or comparison groups. Because of this, the estimates of comparative effects were frequently based on *indirect* comparisons, that is, comparisons were made across studies rather than within studies, leading to considerable uncertainty about the best estimates of effect. More importantly, the efficacy estimates

of cryotherapy compared to no intervention are based on observational data that were not properly controlled. While trials comparing cryotherapy to no treatment to determine the effectiveness of cryotherapy are not ethically sound or feasible, studies comparing different techniques or equipment (e.g. a trial comparing women randomized to receive cryotherapy with N_2O versus CO_2, or different-shaped cryo tips) could, and should, be conducted. Moreover, randomized trials comparing the effects of providing additional counselling and education to standard best-practice counselling have not been performed. While most providers might assume that detailed education and counselling would be inherently effective, the cost–benefit analysis of the additional time spent, and measurement of potential harms, such as increased anxiety or treatment refusal, need to be explored.

These guidelines provide recommendations on the use of cryotherapy for cervical cancer prevention, and will be incorporated into the next update of *Comprehensive cervical cancer control: a guide for essential practice*. WHO has committed to updating the guide and will focus the next steps on reviewing the evidence to make recommendations for (1) health education; (2) HPV vaccines; (3) use of screening tests, including HPV testing as a primary stand-alone test; (4) treatment of precancerous lesions other than with cryotherapy; (5) "screen-and-treat" or "single-visit" approaches based on VIA of the cervix with and without HPV testing, followed by cryotherapy; and (6) additional guidance on prevention and management of positive screening tests in HIV-infected women.

References

1. Ferlay J et al. GLOBOCAN 2008. *All cancers (excluding non-melanoma skin cancer) incidence and mortality worldwide in 2008.* IARC CancerBase. Lyon, International Agency for Research on Cancer, 2010 (http://globocan.iarc.fr/factsheets/cancers/all.asp, accessed 20 April 2011).

2. World Health Organization. *Comprehensive cervical cancer control: a guide to essential practice*. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241547006_eng.pdf, accessed 20 April 2011).

3. World Health Organization. *WHO Handbook for guideline development*. Geneva, World Health Organization, 2010 (http://www.who.int/hiv/topics/mtct/grc_handbook_mar2010_1.pdf, accessed 4 May 2011).

4. Oxman AD, Fretheim A, Schünemann HJ; SURE. Improving the use of research evidence in guideline development: introduction. *Health Research Policy and Systems* 2006, 4:12.

5. Schünemann HJ et al. Transparent development of the WHO rapid advice guidelines. *PLoS Medicine* 2007, 4(5):e119.

6. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008 (www.cochrane-handbook.org, accessed 20 April 2011).

7. McCredie MR et al. Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2010, 50(4):363–370.

8. GRADE Working Group. GRADEpro. Version 3.5. (http://www.ims.cochrane.org/revman/gradepro, accessed 20 April 2011).

Appendix A: Search strategy for OVID MEDLINE

1. cervical intraepithelial neoplasia/
2. uterine cervical dysplasia/
3. uterine cervical neoplasms/
4. (precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer*).tw.
5. cin.tw.
6. 4 or 5
7. 6 and cervi*.tw.
8. 1 or 2 or 3 or 7

Appendix B: Summary tables for each recommendation

Recommendation 1a. Should cryotherapy versus no treatment be used in women with histologically confirmed CIN (cervical intraepithelial neoplasia)?

Recommendation: The expert panel recommends cryotherapy over no treatment.			
Population: Women with histologically confirmed CIN			
Intervention: Cryotherapy versus no treatment			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There is low- to very-low-quality evidence from both randomized and observational controlled studies for recurrence rates and adverse events. In general estimates of effect are obtained from single arm studies with no independent control. Outcomes, such as some fertility outcomes and acceptability were not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☒ Yes ☐ No	There is considerable benefit and relatively little harm	▪ Recurrence rates of CIN from observational studies with no independent control show • CIN II–III, 4% • CIN I, 2% • All CIN, 6% ▪ Absolute risk reduction in cervical cancer with cryotherapy was calculated as 18% over 30 years for baseline risk of 1%; 9% over 30 years for 0.5% • assumptions: from observational studies with no independent control the relative risk reduction with cryotherapy is 86%, but a spontaneous regression of 28% which gives the relative risk reduction with cryotherapy as 61% [86% – (28% × 86%)]. Using 1% baseline risk without cryotherapy, the absolute risk reduction with cryotherapy is 0.61% over 1 year or 18% over 30 years. Using 0.5% gives 0.3% over 1 year or 9% over 30 years. ▪ Major adverse effects occurred rarely with cryotherapy, but minor may occur more frequently. ▪ It is unclear whether cryotherapy affects fertility/ obstetric outcomes, or whether cryotherapy is unacceptable to women. ▪ Risk of HIV shedding or acquisition is not known, but this risk is unlikely to outweigh the benefits.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No		▪ A high value was placed on avoiding CIN recurrence, avoiding serious adverse events and acceptability to the patient ▪ A low value was placed on minor adverse events

Resource implications The lower the cost of an intervention compared with the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	Resources required for cryotherapy but they are generally affordable	▪ There are resources required to provide cryotherapy to prevent cervical cancer but these resources are worth the expected benefits and downstream treatment costs for cervical cancer are avoided. The treatment of adverse outcomes is also considered worthwhile.
Overall strength of recommendation	Strong		

References (see Appendix C)

4,4a,4b,6,7,8,10,11,15,16,16a,18,19,21–23,26,27,29–31,31a,31b,31c,34–38,40–44,48,52,53,55,57,58,63,64,66–70,72,75–77,81,82,82a,84–88,91–95

ADDITIONAL REFERENCES

McCredie MR, Paul C, Sharples KJ, Baranyai J, Medley G, Skegg DC, Jones RW. Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3. *Aust N Z J Obstet Gynaecol.* 2010, 50(4):363-70.

Michael Chung and colleagues. 2010. Unpublished data from personal communication.

Recommendation 1b. Should cryotherapy versus LEEP (loop electrosurgical excision procedure) be used in women with histologically confirmed CIN?

Recommendation: In settings where LEEP/LLETZ is available and accessible, the expert panel suggests treatment with LEEP/ LLETZ over cryotherapy.			
Population: Women with histologically confirmed CIN			
Intervention: Cryotherapy versus LEEP			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕⊕◯◯	There is moderate quality evidence from both randomized and observational controlled studies for recurrence rates. However, there is low quality evidence for other outcomes which were considered critical and important for decision-making (e.g. severe adverse events, cervical cancer). There is uncertainty for fertility and other obstetrical outcomes, and HIV acquisition/ transmission was not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Benefits of LEEP were greater, and harms were fewer or similar	▪ Recurrence rates of CIN I, CIN II–III and all CINs are probably greater with cryotherapy • CIN II–III, OR 3.3 (1.04 to 10.46) • CIN I, OR 2.74 (0.62 to 12.07) • All CIN, OR 2.14 (1.05 to 4.33) ▪ Cryotherapy may be less acceptable to patients than LEEP ▪ There may be little difference in serious adverse events between cryotherapy and LEEP, but there may be fewer minor adverse events (such as pain) with cryotherapy ▪ It is unclear whether there is a difference in fertility/ obstetric outcomes
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No	Similar values across women	▪ High value was placed on CIN recurrence, serious adverse events and acceptability to the patient ▪ Low value was placed on minor adverse events
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	More resources required for LEEP	▪ Need for more skilled providers to perform LEEP ▪ Need for more or expensive equipment/supplies for LEEP; electrical supply for LEEP ▪ Need for local anaesthesia with LEEP
Overall strength of recommendation	Conditional		

References (see Appendix C)

2,5,11,14,17,22,23,25,33,42,47,50,54,55,58,60,63,64,66,70,77,82,82a,83,89,95

Recommendation: In settings where LEEP/LLETZ is available and accessible, the expert panel suggests treatment with LEEP/ LLETZ over cryotherapy.			
Population: Women with histologically confirmed CIN *who are HIV-positive*			
Intervention: Cryotherapy versus LEEP			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕⊕◯◯	There is low quality evidence for recurrence rates. But very-low-quality evidence for other outcomes which were considered critical and important for decision-making (e.g. severe adverse events, cervical cancer). There is uncertainty around acceptability, fertility and other obstetrical outcomes, and HIV acquisition/transmission was not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Risks greater with cryotherapy	▪ Recurrence rates of CIN II–III and all CINs may be greater with cryotherapy • CIN II–III, OR 3.6 (0.85 to 15.32) • All CIN, OR 3.89 (1.54 to 9.85) ▪ The difference between cryotherapy and LEEP is uncertain for prevention of cervical cancer. ▪ It is uncertain whether there are differences in major or minor adverse events between cryotherapy and LEEP. ▪ There is uncertainty about fertility/obstetric outcomes, acceptability and HIV transmission.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No		▪ High value was placed on CIN recurrence, serious adverse events and acceptability to the patient ▪ Low value was placed on minor adverse events
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	More resources required for LEEP	▪ Need for more skilled providers to perform LEEP ▪ Need for more or expensive equipment/supplies for LEEP ▪ Need for local anaesthesia with LEEP
Overall strength of recommendation	Conditional		

References (see Appendix C)

1,17,24,39,45,46,51,56,59,78,89,97

Recommendation 2. In women who have histologically confirmed CIN, are there differences in recurrence of CIN by lesion size?

Small lesion defined as <25% covered, 1 quadrant or 1 degree. Moderate lesion defined as 25 to 75% covered, 2 quadrants, 2 degree or <25 to 30mm. Large lesion defined as >75% covered, large lesion, >2 quadrants, >25 to 30mm.

Meta-analysis of the proportion of women who had recurrence/persistence of CIN at 1 year shows a significant interaction among different lesion sizes.

At 1 year post cryotherapy, recurrence rate was greatest in women who had a large lesion. Recurrence rate of all grades of CIN in women with a

- small lesion is 6% (from 5 to 7%);
- moderate lesion is 7% (from 6 to 8%);
- large lesion is 18% (from 13 to 23%).

See the evidence summaries on the evidence base document at http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.11_eng.pdf?ua=1

Recommendation 3, a and b. In women who have histologically confirmed CIN, are there differences in recurrence of CIN when the lesion extends into the endocervical canal?

Summary

Meta-analysis of the proportion of women with a lesion that DOES or DOES NOT extend into the endocervical canal showed a significant interaction between these two groups for recurrence of all grades of CIN at 1 year.

At 1 year post cryotherapy, the recurrence rate in women was higher in women with endocervical canal extension. Recurrence of all grades of CIN at 1 year in women with a lesion that is:

- ECC positive is 16% (from 13 to 20%);
- ECC negative is 6% (from 5 to 6%).

There was however, inconsistency across studies in both groups of women which could not be explained and therefore decreases our confidence in these results.

References (see Appendix C)

Extends into canal: 4,4a,4b,6,19,30,35,38,44,48,66.

Does not extend into canal: 4,4a,4b,6,8,9,15–17,19,20,22,23,26,27,29,30,31,31a,31b,31c,34–38,40–44,48,52, 53,55,57,58,63,64,66–68,70,72,75,77,82,82a,84–88, 91–94.

See the evidence summaries on the evidence base document at http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.11_eng.pdf?ua=1

Recommendation 4. Should cryotherapy using a double versus single freeze technique be used in women with histologically confirmed CIN?

Recommendation: The expert panel suggests double freeze using a 3 minute freeze, 5 minute thaw, 3 minute freeze cycle over single freeze cryotherapy.			
Population: Women with histologically confirmed CIN			
Intervention: Double versus single freeze			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕⊕◯◯	There is moderate to low quality evidence from both randomized and observational controlled studies for recurrence rates. There is low quality evidence for other outcomes which were considered critical and important for decision-making (e.g. severe adverse events, cervical cancer). There is uncertainty for fertility and other obstetrical outcomes, and HIV acquisition/transmission was not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Risks may be reduced with double-freeze cryotherapy	▪ Recurrence rates of CIN I, CIN II–III and all CINs may be reduced with double-freeze technique • CIN II–III, OR 0.40 (0.22 to 0.75) • CIN I, OR 0.70 (0.21 to 2.28) • All CIN, OR 0.37 (0.21 to 0.63) ▪ There may be little difference in cervical cancer rates based on absolute risks ▪ There may be little difference in serious adverse events between double and single freeze cryotherapy, but there may be fewer people experiencing pain with double-freeze cryotherapy and more minor infections ▪ It is unclear whether there is little difference in fertility/obstetric outcomes
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No		▪ High value was placed on CIN recurrence, incidence of cervical cancer, serious adverse events, resource use, and acceptability to the patient and providers ▪ Low value was placed on minor adverse events and fertility
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	More resources for double freeze but benefits worth the resources	▪ Both interventions utilize the same equipment/ supplies ▪ Additional resources are required (provider time, patient time, more gas) for double freeze
Overall strength of recommendation	Conditional		

References (see Appendix C)

11,13,15,20,21,47,49,67,68,80,85,87,90,94

Recommendation 5. Should nitrous oxide versus carbon dioxide be used in cryotherapy to treat women with histologically confirmed CIN?

Conditional Recommendation: The expert panel recommends cryotherapy using either CO^2 or N^2O gas.			
Population: Women with histologically confirmed CIN			
Intervention: Cryotherapy using N^2O versus Cryotherapy using CO^2			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There is very-low-quality evidence from observational controlled studies for recurrence rates, cervical cancer, and severe adverse events which were considered critical for decision-making. HIV acquisition/transmission as well as fertility and other obstetrical outcomes were not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	It is uncertain whether risks differ between nitrous oxide and carbon dioxide	▪ It is uncertain whether recurrence rates of CIN I, CIN II–III and all CINs differ between nitrous oxide and carbon dioxide • CIN II–III, OR 0.67 (0.38 to 1.18) • CIN I, OR 1 (0.58 to 1.73) • All CIN, OR 1.2 (0.96 to 1.50) ▪ It is uncertain whether there is little or no difference in cervical cancer rates, as well as severe adverse events between nitrous oxide and carbon dioxide ▪ Minor infections may be lower with nitrous oxide, but this is uncertain.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No		▪ High value was placed on CIN recurrence, cervical cancer, and serious adverse events ▪ Low value was placed on minor adverse events
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☐ Yes ☒ No	More resources required for nitrous oxide	▪ Nitrous oxide is more costly than carbon dioxide ▪ Nitrous oxide requires more safety measures <(e.g. ventilation)
Overall strength of recommendation	Conditional		

References (see Appendix C)

3,4,4a,4b,6,8–12a,15,17,19,21,26,29–31c,34,41,44,48,52,53,55,57,58,66,67,70,75,77,82,82a,85-87,92,94

Recommendation 6. Should cryotherapy using cough technique be provided to women with histologically confirmed CIN?

Recommendation: The expert panel recommends to *not* use cough technique during cryotherapy.			
Population: Women with histologically confirmed CIN			
Intervention: cryotherapy using cough technique			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There is very-low-quality evidence for outcomes such as recurrence rates and adverse events. Outcomes, such as acceptability to women or providers, and fertility were not measured or could not be compared between studies using cryotherapy with cough technique or cryotherapy.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☒ Yes ☐ No	The risks may be higher when using the cough technique	▪ It is uncertain whether recurrence rates of CIN increase when using cough technique. • CIN II–III, OR 1.00 (0.58 to 1.73) • All CIN, OR 2.75 (1.89 to 4.00) • CIN I, OR 3.5 (2.22 to 5.51) ▪ The effects on acceptability according to women or their providers is not known. ▪ The risk of major infection and pain may be increased, but this is uncertain. ▪ There may be little difference in cervical cancer rates based on absolute risks. ▪ It is not known what the effects are on fertility outcomes, mortality.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No		▪ High value was placed on acceptability to the patient and provider, and adverse events ▪ Low value was on recurrence rates of CIN
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	Similar resource use	▪ Resource use may not be increased with use of the cough technique.
Overall strength of recommendation	Strong		

References (see Appendix C)

4,4a,4b,6–12,15–17,19,21,23,26,27,29,30,31,31a,31b,31c,34–38,40–44,48,52,53,55,57,58,66,68,70,72,75,77,82,82a, 84–88,91–95

Recommendation 7. Should antibiotics be provided prophylactically with cryotherapy in women with histologically confirmed CIN?

Recommendation: The expert panel suggests that prophylactic antibiotics *not* be used when providing cryotherapy.			
Population: Women who have a histologically confirmed CIN and being treated with cryotherapy			
Intervention: Prophylactic antibiotics			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	Indirect comparisons of observational studies with no control group provided very-low-quality evidence for the outcomes that were considered important for decision-making (e.g. major bleeding, major infection and minor adverse effects). Acceptability to providers or women was not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Major risks similar with antibiotic, but minor risks appear to be lower with antibiotics	▪ ▪ It is uncertain whether there is little difference with risks of major adverse events with or without antibiotics ▪ It is uncertain if the risk of minor infections, vaginal discharge and all minor adverse events are lower when prophylactic antibiotics are given
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No	Similar values	▪ ▪ Similar value was placed on major and minor adverse events ▪ Burden to women may be a consideration
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☐ Yes ☒ No	Increased cost with antibiotics	▪ ▪ Additional costs of antibiotics and burden on staff
Overall strength of recommendation	Conditional		

References

8,9,11,17,22,23,26,27,30,37,55,58,66,64,67,70,77,82,82a,85,92,94

Recommendation 8. Should cryotherapy be provided by a non-physician for women with histologically confirmed CIN?

Recommendation: The expert panel recommends that health-care workers (including non-physicians) who are trained in cryotherapy perform the procedure in women when indicated.			
Population: women who have a histologically confirmed CIN			
Intervention: cryotherapy performed by a non-physician			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There is very-low-quality evidence from observational studies (with no control) for the outcomes that were considered critical for decision-making (e.g. CIN 2-3, all severe adverse events, cervical carcinoma) or important for decision-making (e.g. minor infections and pain) Unacceptability to women or their providers, and HIV transmission were not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☒ Yes ☐ No	Appears to be benefits with non-physicians	▪ It would appear that CIN recurrence rates are reduced when cryotherapy is provided by non-physicians: • CIN II–III, OR 0.14 (0.05 to 0.38) • CIN I, OR 0.5 (0.32 to 0.78) • All CIN, OR 0.63 (0.49 to 0.73) ▪ It is uncertain if there is little or no difference in severe adverse events, or minor infections. ▪ Fewer women may have pain or minor infections when cryotherapy is provided by non-physicians, but this is uncertain. ▪ It is also unclear whether cervical cancer rates decrease when cryotherapy is provided by non-physician.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No	Similar values	▪ High value was placed on acceptability, recurrence of CIN II,III, severe adverse events and cervical cancer incidence. ▪ Low value was placed on fertility outcomes and minor adverse events.
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	Balanced costs	▪ Need for professional training and monitoring ▪ Less cost with fewer physicians performing cryotherapy ▪ Training non-physicians may increase the availability of cryotherapy
Overall strength of recommendation	Strong		

References (see Appendix C)

6,16,16a,17,21,35,38,41,58,70,82,82a,84,88,93

Recommendation 9. Should cryotherapy be used in women with histologically confirmed CIN who are pregnant?

Recommendation: In women who are pregnant, the expert panel suggests to defer cryotherapy until after pregnancy.			
Population: Women with histologically confirmed CIN who are pregnant			
Intervention: Cryotherapy versus LEEP or no treatment			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There were no randomized controlled trials or observational studies (with or without a control) that evaluated the effects of cryotherapy (only) compared with no treatment or LEEP. Results are from cryotherapy or laser, compared to no surgical procedure or conisation.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Suggests benefits over adverse effects	It is unclear whether cryotherapy reduces recurrence of CIN compared to no treatment or LEEP. Cryotherapy versus LEEP • OR 0.88 (0.05 to 16.98) Cryotherapy versus no treatment • OR 0.77 (0.04 to 14.86) It is uncertain whether adverse obstetrical outcomes (e.g. preterm delivery and complications) occur with cryotherapy.
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☐ Yes ☒ No	Uncertain	▪ High value was placed on CIN recurrence, serious adverse events and acceptability to the patient ▪ Low value was placed on minor adverse events ▪ It is unclear whether all women would want or not want treatment
Resource implications The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☐ Yes ☒ No	Lower resource use with cryotherapy versus LEEP	▪ Need for more resources to perform LEEP (e.g. skilled providers, more or expensive equipment/ supplies, local anaesthesia and electrical supply)
Overall strength of recommendation	Conditional		

References

20,23,26,28,32,65,71,73,79,96,98

Recommendation 10. Should cryotherapy versus conisation be used for treatment failures diagnosed >12 months after first cryotherapy treatment?

Recommendation: The expert panel recommends cryotherapy over no treatment for women who screen positive after treatment for a previous diagnosis of histologically confirmed CIN lesions. In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy for women who screen positive after previous cryotherapy treatment.			
Population: women who have been already treated with cryotherapy but screen positive or histologically diagnosed CIN at follow-up testing (>12 months)			
Intervention: retreatment with cryotherapy versus other intervention			
Factor	**Decision**	**Explanation**	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕◯◯◯	There is very-low-quality evidence from observational studies for recurrence rates between cryotherapy and conisation for retreatment. Other outcomes which are considered critical and important for decision-making (e.g. major adverse effects) were not measured in the studies.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Risks may be greater with cryotherapy	▪ It is uncertain whether the risk of CIN recurrence is greater with cryotherapy than conisation All CIN, OR 2.35 (0.82 to 6.7)
Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☐ Yes ☒ No	Uncertain	▪ High value was placed on CIN recurrence, acceptability and severe adverse events ▪ Low value was placed on minor events
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	Fewer resources with cryotherapy	▪ More resources needed for other follow-up treatment modalities
Overall strength of recommendation	Strong (cryotherapy to no treatment); Conditional (cryotherapy to LEEP)		

References (see Appendix C)

7,11,15,19,29,37,38,43,53,86,92,94

Appendix C: References used in creating the GRADE tables for the recommendations

GRADE tables can be downloaded from http://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/index.html

1. Alvarez R, et al. Prospective randomised trial of LLETZ versus laser ablation in patients with cervical intra-epithelial neoplasia. *Gynecologic Oncology,* 1994, 52:175–179.

2. Andersen ES, Thorup K, Larsen G. The results of cryosurgery for cervical intraepithelial neoplasia. *Gynecologic Oncology*, 1988, 30(1):21-25.

3. Andersen ES, Husth M. Cryosurgery for cervical intraepithelial neoplasia: 10-year follow-up. *Gynecologic Oncology*, 1992, 45(3): 240-242.

4. Arbyn M, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *British Medical Journal,* 2008, 18:337–1284.

    a. Noehr B, et al. Loop electrosurgical excision of the cervix and risk for spontaneous preterm delivery in twin pregnancies. *Obstet Gynecol*. 2009, 114(3):511-5.

    b. Werner CL et al. Loop electrosurgical excision procedure and risk of preterm birth. *Obstetrics & Gynecology,* 2010, 115(3):605-608.

5. Arof HM, Gerbie MV, Smeltzer J. Cryosurgical treatment of cervical intraepithelial neoplasia: four-year experience. *American Journal of Obstetrics & Gynecology*, 1984, 150(7):865-869.

6. Atad J, Bloch B. An evaluation of treatment modalities in cervical intra-epithelial neoplasia. *South African Medical Journal,* 1983, (14):522-525.

7. Benedet JL, Nickerson KG, Anderson GH. Cryotherapy in the treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1981, 58(6):725-729.

8. Benedet JL, et al. The results of cryosurgical treatment of cervical intraepithelial neoplasia at one, five, and ten years. *American Journal of Obstetrics & Gynecology,* 1987, 157(2):268-273.

9. Benedet JL, Miller DM, Nickerson KG. Results of conservative management of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1992, 79(1):105-110.

10. Berget A, et al. Outpatient treatment of cervical intra-epithelial neoplasia. The CO^2 laser versus cryotherapy, a randomized trial. *Acta Obstetricia et Gynecologica Scandinavica*, 1987, 66(6):531-536.

11. Berget A, Andreasson B, Bock JE. Laser and cryo surgery for cervical intraepithelial neoplasia. A randomized trial with longterm follow-up. *Acta Obstetricia et Gynecologica Scandinavica,* 1991, 70(3):231-235.

12. Bhatla N, et al. Evaluation of cervical screening in rural North India. *International Journal of Gynaecology & Obstetrics,* 2009, 105(2):145-149.

    a. Boelter WC, Newman RL. Cryosurgery therapy of cervical dysplasia. *Rocky Mountain Medical Journal,*1978, 75(5):258-260.

13. Brun JL, Youbi A, Hocké C. [Complications, sequellae and outcome of cervical conizations: evaluation of three surgical technics]. *Journal de gynécologie, obstétrique et biologie de la reproduction (Paris)*. 2002, 31(6):558-564.

14. Bryson SC, Lenehan P, Lickrish GM. The treatment of grade 3 cervical intraepithelial neoplasia with cryotherapy: an 11-year experience. *American Journal of Obstetrics & Gynecology*, 1985, 151(2):201-206.

15. Charles EH, et al. Cryosurgical treatment of cervical intraepithelial neoplasia. *Gynecologic Oncology*, 1981, 12(1):83-88.

16. Chirenje ZM, et al. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. *Journal of Obstetrics & Gynaecology*, 21(6):617-621.

    a. Chirenje ZM, et al. Effect of HIV disease in treatment outcome of cervical squamous intraepithelial lesions among Zimbabwean women. *Journal of Lower Genital Tract Disease,* 2003, 7(1):16-21.

17. Chumworathayi B, et al. Cryotherapy for HPV clearance in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions. *International Journal of Gynaecology & Obstetrics*, 2010, 108(2):119-122.

18. Coney P, et al. Cryosurgical treatment of early cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1983, 62(4):463-466.

19. Creasman WT et al. Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1973, 41(4):501-506.

20. Creasman WT, Hinshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. *Obstetrics & Gynecology*, 1984, 63(2):145-149.

21. Crisp WE, et al. Cryosurgical treatment of premalignant disease of the uterine cervix. *American Journal of Obstetrics & Gynecology*, 1970, 107(5):737-742.

22. Crisp WE. Cryosurgical treatment of neoplasia of the uterine cervix. *Obstetrics & Gynecology,* 1972, 39(4):495-449.

23. Dey, P, et al. Loop diathermy excision compared with cervical laser vaporisation for the treatment of intraepithelial neoplasia: a randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology*, 2002, 109:381-385.

24. Doh AS, Kouam L. The management of pre-invasive cervical lesions using cryotherapy in Yaounde, Cameroon. *Journal of Obstetrics & Gynaecology*, 1999, 19(6):640-642.

25. Einerth Y. Cryosurgical treatment of CIN I-III. A long-term study. *Acta Obstetricia et Gynecologica Scandinavica,* 1988, 67(7):627-630.

26. El-Bastawissi AY, Becker TM, Daling JR. Effect of cervical carcinoma in situ and its management on pregnancy outcome. *Obstetrics & Gynecology,* 1999, 93(2):207-212.

27. Elmfors B, Stormby N. A study of cryosurgery for dysplasia and carcinoma in situ of the uterine cervix. *British Journal of Obstetrics & Gynaecology,* 1979, 86(12):917-921.

28. Ferenczy A. Comparison of cryo- and carbon dioxide laser therapy for cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1985, 66(6):793-798.

29. Fray RE, Sims CD. Cryosurgical treatment of cervical intra-epithelial neoplasia. *South African Medical Journal,* 1982, 25 (14):469-470.

30. Frega A, et al. Clinical management and follow-up of squamous intraepithelial cervical lesions during pregnancy and postpartum. *Anticancer Research,* 2007, 27(4C):2743-2746.

31. Gök M, et al. HPV16 and increased risk of recurrence after treatment for CIN. *Gynecologic Oncology* 2007, 104(2):273-275.

    a. Hogewoning CJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *International Journal of Cancer*, 2003, 107(5):811-816.

    b. Nobbenhuis MA, et al. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *British Journal of Cancer*, 2001, 84(6):796-801.

    c. Kafali H. HPV16 and increased risk of recurrence after treatment for CIN. *Gynecologic Oncology,* 2008, 109(2):309-310.

32. Guijon F, Paraskevas M, McNicol P. Human papillomavirus infection and the size and grade of cervical intraepithelial neoplastic lesions associated with failure of therapy. *International Journal of Gynaecology & Obstetrics,* 1993, 42(2):137-142.

33. Hatch KD, et al. Cryosurgery of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1981, 57(6):692-698.

34. Hellberg D, Nilsson S. 20-year experience of follow-up of the abnormal smear with colposcopy and histology and treatment by conization or cryosurgery. *Gynecologic Oncology,* 1990, 38(2):166-169.

35. Hemmingsson E, Stendahl U, Stenson S. Cryosurgical treatment of cervical intraepithelial neoplasia with follow-up of five to eight years. American Journal of *Obstetrics & Gynecology,* 1981, 139(2):144-147.

36. Hemmingsson E, Stenson S. The results of cryosurgical treatment in young women with cervical intra-epithelial neoplasia. *Acta Obstetricia et Gynecologica Scandinavica,* 1983, 62(1):39-42.

37. Javaheri G, Balin M, Meltzer RM. Role of cryosurgery in the treatment of intraepithelial neoplasia of the uterine cervix. *Obstetrics & Gynecology,* 1981, 58(1):83-87.

38. Jones DE, et al. Cervical intraepithelial neoplasia in adolescents. *Journal of Adolescent Health Care,* 1984, 5(4):243-247.

39. Kalliala I, et al. Cancer free survival after CIN treatment: comparisons of treatment methods and histology. *Gynecologic Oncology,* 2007, 105(1):228-233.

40. Kaufman RH, et al. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1973, 42(6):881-886.

41. Kaufman RH, Irwin JF. The cryosurgical therapy of cervical intraepithelial neoplasia. III. Continuing follow-up. *American Journal of Obstetrics & Gynecology,* 1978, 131(4):381-388.

42. Kirwan P, Smith I, Naftalin N. A study of cryosurgery and CO2 laser in treatment of carcinoma in situ (CINIII) of the uterine cervix. *Gynecologic Oncology,* 1985, 22:195–200.

43. Krebs HB, Wheelock JB. Endocervical curettage after cryotherapy for cervical intraepithelial neoplasia. *Journal of Reproductive Medicine,* 1985, 30(5):379-382.

44. Kwikkel HJ, et al. Laser or cryotherapy for cervical intraepithelial neoplasia: a randomized study to compare efficacy and side effects. *Gynecologic Oncology,* 1985, 22(1):23-31.

45. Kyrgiou M, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet,* 2006, 367(9509):489-498.

46. Leiman G, Andronikou AD. Cryotherapy of the uterine cervix: an inadequate treatment modality in a newly screened population. *South African Medical Journal,* 1980, 12 (2):39-43.

47. Levine RU, Carillo EJ, Crum CP. Outpatient management of cervical intraepithelial neoplasia. A summary of 279 cases. *Journal of Reproductive Medicine,* 1985, 30(4):351-354.

48. Li ZG,et al. Three-step versus “see-and-treat” approach in women with high-grade squamous intraepithelial lesions in a low-resource country. *International Journal of Gynecology and Obstetrics,* 2009, 106(3):202-205.

49. Lickrish GM, Fortier M. Conservative management of intraepithelial cervical neoplasia. *Canadian Medical Association Journal,* 1977, 116(6):641-643.

50. Loizzi P, et al. Rational use of cryosurgery and cold knife conization for treatment of cervical intraepithelial neoplasia. *European Journal of Gynaecologic Oncology,* 1992, 13(6):507-513.

51. Luciani S, et al. Effectiveness of cryotherapy treatment for cervical intraepithelial neoplasia. *International Journal of Gynaecology & Obstetrics,* 2008, 101(2):172-177.

52. Martirosian TE, et al. Depot medroxyprogesterone acetate: a risk factor for cervical stenosis after loop electrosurgical excisional procedure management of cervical intraepithelial neoplasia? *Journal of Lower Genital Tract Disease*, 2010, 14(1):37-42.

53. Melnikow J, et al Management of the low-grade abnormal Pap smear: what are women’s preferences? *Journal of Family Practice*, 2002, 51(10):849-855.

54. Melnikow J, et al. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *Journal of the National Cancer Institute,* 2009, 101(10):721-728.

55. Mitchell MF, et al. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstetrics & Gynecology,* 1998, 92(5):737-744.

56. Mitsuhashi A, Sekiya S. Loop electrosurgical excision procedure (LEEP) during first trimester of pregnancy. *International Journal of Gynecology and Obstetrics,* 2000, 71(3):237-239.

57. Monaghan JM, Kirkup W, Davis JA, Edington PT. Treatment of cervical intraepithelial neoplasia by colposcopically directed cryosurgery and subsequent pregnancy experience. *British Journal of Obstetrics & Gynaecology,* 1982, 89(5):387-392.

58. Moncada E, López Canales JR, Romero Rovelo A. Crioterapia en el tratamiento de las neoplasias intraepiteliales cervicales (NIEC). *Rev méd hondur,* 1992, 60(2):58-63.

59. Morradell MA, Murillo F. Criocirugía en el tratamiento de la neoplasia intraepitelial cervical NIC. *Rev méd hondur,* 1988, 56(1):4-11.

60. Nealon NA, Christopherson WM. Cervix cancer precursors in young offspring of low-income families. *Obstetrics & Gynaecology,* 1979, 54(2):135-139.

61. Nene BM, et al. Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. *International Journal of Gynaecology & Obstetrics,* 2008, 103(3):232-236.

62. Olatunbosun OA, Okonofua FE, Ayangade SO. Outcome of cryosurgery for cervical intraepithelial neoplasia in a developing country. *International Journal of Gynecology and Obstetrics,* 1992, 38(4):305-310.

63. Ostergard DR. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1980, 56(2):231-233.

64. Palle C, Bangsbøll S, Andreasson B. Cervical intraepithelial neoplasia in pregnancy. *Acta Obstetricia et Gynecologica Scandinavica,* 2000, 79(4):306-310.

65. Persad VL, Pierotic MA, Guijon FB. Management of cervical neoplasia: a 13-year experience with cryotherapy and laser. *Journal of Lower Genital Tract Disease,* 2001, 5(4):199-203.

66. Poomtavorn Y, et al. Cervical cytologic abnormalities of cervical intraepithelial neoplasia 1 treated with cryotherapy and expectant management during the first year follow-up period. *Asian Pacific Journal of Cancer Prevention,* 2009, 10(4):665-668.

67. Popkin DR, Scali V, Ahmed MN. Cryosurgery for the treatment of cervical intraepithelial neoplasia. *American Journal of Obstetrics & Gynecology,* 1978, 130(5):551-554.

68. Robinson WR, et al. Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. *Gynecologic Oncology,* 1997, 64(1):153-155.

69. Rojas T, et al. Evaluación histológica de la criocirugía en neoplasia intraepitelial de alto grado (NIE III) del cuello uterino. *Rev chil obstet ginecol,* 1993, 58(3):200-205.

70. Saidi MH, White AJ, Weinberg PC. The hazard of cryosurgery for treatment of cervical dysplasia. *Journal of Reproductive Medicine,* 1977, 19(2):70-74.

71. Sankaranarayanan R, et al. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *British Journal of Cancer*, 2007, 96(5):738-743.

72. Sanu O, Pal A, George S. A pilot study comparing efficacy of a cervical intraepithelial neoplasia Excisor with loop electrosurgical excision procedure. *European Journal of Obstetrics, Gynecology and Reproductive Biology,* 2010, 151(1):91-95.

73. Savage EW, Matlock DL, Salem FA, Charles EH. The effect of endocervical gland involvement on the cure rates of patients with cervical intraepithelial neoplasia undergoing cryosurgery. *Gynecologic Oncology,* 1982, 14(2):194-198.

74. Schantz A, Thormann L. Cryosurgery for dysplasia of the uterine ectocervix. A randomized study of the efficacy of the single- and double-freeze techniques. *Acta Obstetricia et Gynecologica Scandinavica,* 1984, 63(5):417-420.

75. Sedlis A, Castadot MJ, Glatt B. Cryotherapy in cervical disease. *New York State Journal of Medicine, 1981,* 81(12):1757-1760.

76. Selim MA, Razi A. Cryosurgery for intraepithelial neoplasia of the cervix. *Cancer,* 1980, 46(10):2315-2318.

77. Stuart GCE, Anderson RJ, Corlett BMA, Maruncic MA. Assessment of failures of cryosurgical treatment in cervical intraepithelial neoplasia. *American Journal of Obstetrics and Gynecology*, 1982, 142(6-I):658-663.

78. Tate DR, Anderson RJ. Recrudescence of cervical dysplasia among women who are infected with the human immunodeficiency virus:a case-control analysis. *American Journal of Obstetrics & Gynecology,* 2002, 186(5):880-882.

79. Townsend DE, Richart RM. Cryotherapy and carbon dioxide laser management of cervical intraepithelial neoplasia: a controlled comparison. *Obstetrics & Gynecology,* 1983, 61(1):75-78.

80. Tredway DR, Townsend DE, Hovland DN, Upton RT. Colposcopy and cryosurgery in cervical intraepithelial neoplasia. *American Journal of Obstetrics & Gynecology,* 1972, 114(8):1020-1024.

81. Van Lent M, Trimbos JB, Heintz AP, Van Hall EV. Cryosurgical treatment of cervical intraepithelial neoplasia (CIN III) in 102 patients. *Gynecologic Oncology,* 1983, 16(2):240-245.

82. Varawalla N, Patton P, Hodder R, Usherwood M. A comparison of cryocauterisation, laser vaporisation and large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. *Journal of Obstetrics and Gynecology,* 1996, 16(6):529-534.

    a. Soutter WP. A comparison of cryocauterisation, laser vaporisation and large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. *Journal of Obstetrics & Gynecology,* 1997, 17(4):419.

83. Walton LA et al. Cryosurgery for the treatment of cervical intraepithelial neoplasia during the reproductive years. *Obstetrics & Gynecology,* 1980, 55(3):353-357.

84. Weed JC, Jr et al. Fertility after cryosurgery of the cervix. *Obstetrics & Gynecology,* 1978, 52(2):245-246.

85. Woodrow N, et al. Abnormal cervical cytology in pregnancy: experience of 811 cases. *Australia and New Zealand Journal of Obstetrics and Gynaecology,* 1998, 38(2):161-165.

86. Yost NP, et al. Postpartum regression rates of antepartum cervical intraepithelial neoplasia II and III lesions. *Obstetrics & Gynecology,* 1999, 93(3):359-362.

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