WHO/RHR/12.11

Use of cryotherapy for cervical intraepithelial neoplasia

Evidence base

World Health Organization

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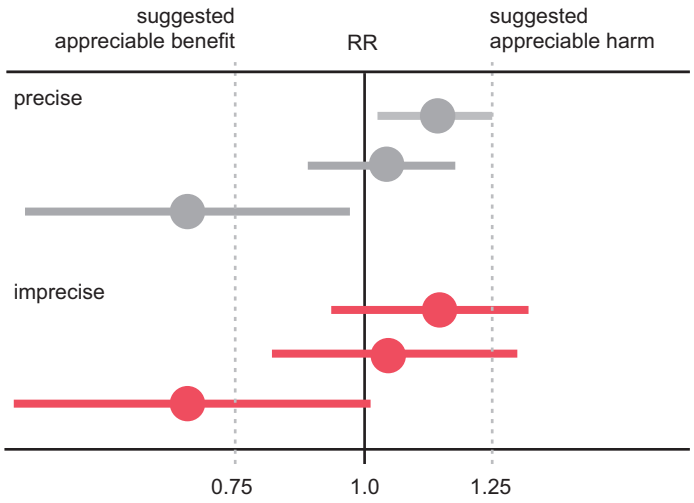
PART 1. STANDARD GRADE CRITERIA FOR GRADING OF EVIDENCE

Table 1. Standard GRADE criteria for grading of evidence[1]

Domain	Grade	Characteristic
STUDY DESIGN	0	All randomized controlled trials
	–1	All observational studies
STUDY DESIGN LIMITATIONS	0	Most of the pooled effect provided by studies, with low risk of bias ("A")
	–1	Most of the pooled effect provided by studies with moderate (“B”) or high (“C”) risk of bias. Studies with high risk of bias weighs <40%
	–2	Most of the pooled effect provided by studies with moderate (“B”) or high (“C”) risk of bias. Studies with high risk of bias weighs ≥40%
	Note:	Low risk of bias (no limitations or minor limitations) –“A” Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) –“B” High risk of bias (Limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) –“C”
INCONSISTENCY	0	No severe heterogeneity (I^2<60% or χ^2≥0.05)
	–1	Severe, non-explained, heterogeneity (I^2≥ 60% or χ^2<0.05) If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice)
INDIRECTNESS	0	No indirectness
	–1	Presence of indirect comparison, population, intervention, comparator, or outcome.

1 Adapted from: Schünemann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available at: <http://ims.cochrane.org/revman/gradepro>. (This document is contained within the "Help" section of the GRADE profiler software version v.3.2.2.)

Domain	Grade	Characteristic
IMPRECISION	0	The confidence interval is precise according to the figure below. The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30. 
	–1	One of the above-mentioned conditions is not fulfilled.
	–2	The two above-mentioned are not fulfilled.
	Note: If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence). If there are no events in both intervention and control groups, the quality of evidence in the specific outcome should be regarded as very low.	
PUBLICATION BIAS	0	No evident asymmetry in the funnel plot or less than five studies to be plotted.
	–1	Evident asymmetry in funnel plot with at least five studies.

PART 2. GRADE TABLES

Note about the GRADE tables

Each GRADE table relates to one specific comparison. The evidence summarized in the tables is derived from a larger body of data extracted primarily from Cochrane reviews, which in many cases contained multiple comparisons. Additional background data can be made available upon request.

LEGEND:

⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕○ Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕○○ Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕○○○ Very low quality: We are very uncertain about the estimate.

Recommendation 1.a. Should cryotherapy versus no treatment be used in women with histologically confirmed CIN?

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	No treatment	Relative (95% CI)	Absolute at 1 year (95% CI)	Quality	Importance
Recurrence CIN II–III (follow-up 12 months randomized trials; 6 to 16 months observational studies)[1]												
1	randomized trials	no serious limitations	no serious inconsistency	serious[2]	very serious[3]	none	1/29 (3.4%)	2/31 (6.5%)	OR 0.52 (0.04 to 6.04)	30 fewer per 1000 (from 62 fewer to 230 more)	⊕○○○	CRITICAL
3	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	10/82 (12.2%)	43/320 (13.4%) 6.5%[4]	OR 1.52 (0.72 to 3.23)	- 31 more per 1000 (from 17 fewer to 118 more)	⊕○○○	CRITICAL
Cervical Cancer (follow up mean 6 months to 16 months)												
3	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	3/222 (1.4%)	9/285 (3.2%)	-	20 more per 1000 (from 40 fewer to 70 more)	⊕○○○	CRITICAL
29	observational studies	serious limitations[5]	no serious inconsistency	no serious indirectness	serious[6]	none		1%[6]	0.61[6]	6 fewer per 1000[6]	⊕○○○	CRITICAL
Treatment unacceptable to women (follow-up 2 weeks; acceptability questionnaire)												
1	observational studies	serious limitations[5]	no serious inconsistency	no serious indirectness	serious[3]	none	15/170 (8.8%)	-	-	90 per 1000	⊕○○○	CRITICAL
HIV transmission (HIV acquisition, HIV shedding) (assessed in women who were HIV-positive at 4 weeks)[7]												
1	observational studies	serious limitations[5]	no serious inconsistency	serious [5]	serious[3]	none	21/50 (42%)	-	OR 1.29 (0.71 to 2.33)	-	⊕○○○	CRITICAL
All severe adverse events (major bleeding, major infections, etc.)												
19	observational studies	serious limitations[5]	no serious inconsistency	serious[5]	no serious imprecision	none	22/6125 (0.36%)	-	-	0 per 1000	⊕○○○	CRITICAL
Major infection (requiring hospital admission and antibiotics)												
16	observational studies	serious limitations[5]	no serious inconsistency	serious[5]	no serious imprecision	none	10/5451 (0.18%)	-	-	0 per 1000	⊕○○○	CRITICAL
Major bleeding (requiring hospital admission or blood transmission)												
13	observational studies	serious limitations[5]	no serious inconsistency	serious[5]	no serious imprecision	none	2/3697 (0.05%)	-	-	0 per 1000	⊕○○○	CRITICAL

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	No treatment	Relative (95% CI)	Absolute at 1 year (95% CI)	Quality	Importance
Mortality (follow-up 11 181 patient years)												
1	observational studies	serious limitations[5]	no serious inconsistency	serious[5]	no serious imprecision	none	32/11181 pt years	–	–	3 per 1000 pt years	⊕○○○	CRITICAL
Fertility (e.g. numbers of pregnant women with desire for child bearing unknown) (follow-up 6 months to 10 years)												
7	observational studies	serious limitations[5]	no serious inconsistency	serious [5]	no serious imprecision	none	180/1029 (17%)	–	–	Range 20 to 420 pregnant women per 1000	⊕○○○	IMPORTANT
Recurrence all CIN (follow-up 12 months randomized trials; 6 to 16 months observational studies)												
1	randomized trials	no serious limitations	no serious inconsistency	serious[2]	very serious[3]	none	1/29 (3.4%)	3/31 (9.7%)	OR 0.33 (0.03 to 3.4)	63 fewer per 1000 (from 94 fewer to 170 more)	⊕○○○	IMPORTANT
4	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	41/260 (16%)	132/334 (40%)	OR 0.93 (0.53 to 1.64)	–	⊕○○○	IMPORTANT
								9.7%[4]		6 fewer per 1000 (from 42 fewer to 50 more)		
Spontaneous abortion per pregnancy (follow-up 6 months to 10 years)												
7	observational studies	serious limitations[5]	no serious inconsistency	no serious indirectness	serious[3]	none	7/46 pregnancies (15%)	–	–	Range 0 to 15 spontaneous abortions per 100 pregnancies	⊕○○○	IMPORTANT
Pain (requiring local treatment)												
8	observational studies	serious limitations[5]	no serious inconsistency	no serious indirectness	serious[3]	none	167/2449 (6.8%)	–	–	90 per 1000 (from 50 to 130)	⊕○○○	IMPORTANT
Minor infection (requiring outpatient treatment only)												
11	observational studies	serious limitations[5]	no serious inconsistency	no serious indirectness	serious[3]	none	157/3937 (4%)	–	–	20 per 1000 (from 10 to 20)	⊕○○○	IMPORTANT
Recurrence CIN I (follow-up 12 months randomized trials; 6 to 16 months observational studies)												
1	randomized trials	no serious limitations	no serious inconsistency	serious[2]	very serious[3]	none	0/29 (0%)	1/31 (3.2%)	OR 0.34 (0.01 to 8.8)	21 fewer per 1000 (from 32 fewer to 195 more)	⊕○○○	IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	No treatment	Relative (95% CI)	Absolute at 1 year (95% CI)	Quality	Importance
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	11/69 (15.9%)	31/212 (14.6%)	OR 1.42 (0.65 to 3.13)	–	⊕○○○	IMPORTANT
								3.2%[4]		13 more per 1000 (from 11 fewer to 62 more)		
Maternal morbidity - not measured												
Referrals after treatment for complications - not measured												
Treatment unacceptable to women assessed by providers - not measured												
Resource use - not measured												

[1] Recurrence rates from pooled analysis of observational studies providing cryotherapy with no controls (with 30 000, 7200, and 21 000 women respectively) show: 6% recurrence all CIN, 2% recurrence CIN I, 4% recurrence CIN II–III after cryotherapy. Heterogeneity among studies was high. [2] All women CIN I diagnosis. [3] Few events with wide confidence intervals including appreciable harm with cryotherapy. [4] Rate with no treatment from randomized controlled trial at 12 months. [5] Based on studies with no control. [6] In observational studies with no independent control the relative risk reduction with cryotherapy is 86%; considering spontaneous regression of 28% the relative risk reduction with cryotherapy is approximately 61% [86% – (28% × 86%)]. Using 1% baseline risk without cryotherapy (McCredie et al. 2010), the absolute risk reduction with cryotherapy is 0.61% over 1 year. [7] Unpublished data provided by Chung et al. 2010.

Subgroup analyses:

For recurrence rates of all CIN, there was significant interaction between women with different histological diagnosis (CIN I versus CIN II+). Rates of recurrence below.

Recurrence rates of all CIN in women diagnosed with CIN II+ or CIN I

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
In women diagnosed with CIN II+										
Recurrence of all CIN										
29	observational studies	serious limitations[1]	no serious inconsistency	serious[2]	No serious imprecision	none	2677/16688 (16%)	14 per 100 (from 13 to 14)	⊕○○○	CRITICAL
In women diagnosed with CIN I										
Recurrence of all CIN										
25	observational studies	serious limitations[1]	no serious inconsistency	serious[2]	No serious imprecision	none	533/7081 (7.5%)	6 per 100 (from 5 to 6)	⊕○○○	CRITICAL

[1] Studies did not have independent control group. [2] High inconsistency among studies.

Recommendation 1.b. Should cryotherapy versus LEEP be used in women with histologically confirmed CIN?

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	LEEP	Relative (95% CI)	Absolute effect at 1 year (95% CI)	Quality	Importance
Recurrence CIN2–3 (follow-up 12 months randomized trials; 3–85 months observational studies)												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a,b]	none	12/161 (7.5%)	4/168 (2.4%)	OR 3.3 (1.04 to 10.46)	51 more per 1000 (from 1 to 179 more)	⊕⊕⊕○	CRITICAL
3	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2227/14 387 (15.5%)	319/7454 (4.3%) 2.4%[c]	OR 2.66 (1.89 to 3.75)	— 37 more per 1000 (from 20 to 60 more)	⊕⊕○○	CRITICAL
Cervical cancer (follow-up 12 months randomized trials; 3–85 months to 26 years observational studies)												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	0/200 (0%)	0/200 (0%)	—	0 fewer per 1000[d]	⊕⊕○○	CRITICAL
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/679 (0.3%)	3/3350 (0.1%)	—	0 fewer per 1000[e]	⊕⊕○○	CRITICAL
Treatment unacceptable to women (follow-up 2 weeks; acceptability question)												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[f]	none	15/170 (8.8%)	8/186 (4.3%)	OR 2.15 (0.89 to 5.22)	45 more per 1000 (from 5 fewer to 147 more)	⊕⊕○○	CRITICAL
All severe adverse events (follow-up mean 12–16 months; stenosis and PID)												
2	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[f]	none	3/300 (1%)	2/298[f] (0.67%)	—	0.4 more per 1000 (from 8 fewer to 9 more)	⊕⊕○○	CRITICAL
All severe adverse events (follow-up 33 months; PID, plug syndrome, stenosis, blood transfusion)												
5	randomized trials	no serious limitations	no serious inconsistency	serious[h]	serious[h]	none	136	480 4%[i]	OR 0.53 (0.1 to 2.88)	— 18 fewer per 1000 (from 36 fewer to 67 more)	⊕⊕○○	CRITICAL
All severe adverse events (follow-up 12 months; PID, stenosis, major bleeding)												
9	observational studies	serious limitations[j]	no serious inconsistency	serious[i]	serious[f]	none	1/2233 (0%)	38/960 (4%)[a]	—	10 fewer per 1000 (from 20 fewer to 0)	⊕○○○	CRITICAL
Mortality (follow-up up to 26 years)												
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	32/11 181 pt years	52/17 072 patient-years 3/1000 patient-years[i]	OR 4.18 (2.66 to 6.56)	— 9 more per 1000 patient-years (from 5 to 16 more)	⊕⊕○○	IMPORTANT
Fertility (e.g. conception, number of pregnancies with or without intention, time to conceive)												
9	observational studies	serious limitations[k]	no serious inconsistency	no serious indirectness	no serious imprecision	none	—	—	not pooled[l]	not pooled[l]	⊕○○○	IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	LEEP	Relative (95% CI)	Absolute effect at 1 year (95% CI)	Quality	Importance
Recurrence all CIN (follow-up mean 12–16 months randomized controlled trials; 3–85 months observational studies)												
2	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[a,b]	none	51/300 (17%)	27/298 (9.1%)	OR 2.14 (1.05 to 4.33)	85 more per 1000 (from 4 fewer to 211 more)	⊕⊕⊕○	IMPORTANT
								4%[i]		42 more per 1000 (from 2 to 113 more)		
5	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2296/14604 (15.7%)	356/7689 (4.6%)	OR 2.62 (2.32 to 2.97)	—	⊕⊕○○	IMPORTANT
								4%[i]		58 more per 1000 (from 48 to 70 more)		
Spontaneous abortion (inferred from severe preterm delivery <32/34 weeks)[m]												
6	observational studies	no serious limitations	no serious inconsistency	very serious[h,j]	serious[g]	none	680	3997	RR 0.56 (0.23 to 1.36)	—	⊕○○○	IMPORTANT
								7%[j]		33 fewer per 1000 (from 58 fewer to 27 more)		
Pain or minor infections (requiring local treatment; follow-up mean 12–16 months)												
2	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	0/309 (0%)	0/316 (0%)	—	0 fewer per 1000[f]	⊕⊕○○	IMPORTANT
CIN1 (follow-up 12 months)												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	6/300 (2%)	2/298 (0.7%)	OR 2.74 (0.62 to 12.07)	12 more per 1000 (from 3 fewer to 71 more)	⊕⊕○○	IMPORTANT
Resource use – not measured												
Maternal morbidity – not measured												
Referrals after treatment for complications – not measured												
Treatment unacceptable to women assessed by providers – not measured												
HIV transmission (HIV acquisition, HIV shedding) – not measured												

[1] Few events and participants. [2] Observational studies show similar results therefore only downgraded once for imprecision. [3] Recurrence rate at 12 months from randomized controlled trials. [4] Confidence intervals not calculated. [5] Large cohort study showed risk of cervical cancer greater (OR 2.98, 2.09 to 4.26) with cryotherapy compared to other modalities (which included LEEP). [6] Few participants with confidence intervals including more or fewer women. 7 1 study reports a major infection requiring antibiotics but did not indicate if with cryotherapy or LEEP, assumed major in both. [8] Comparison is between studies of cryotherapy to another treatment versus another treatment to LEEP. [9] Rate of events from observational studies of LEEP at 12 months. [10]Comparison is between observational studies evaluating only one intervention . [11] Systematic review of observational studies with controls showed no significant differences in total number of pregnancies and time to conceive with LEEP compared to no treatment. With cryotherapy no control, 7 studies found 180 women out of 1029 pregnant (2 to 42% over 1 year). 12 Surrogate outcome used as preterm delivery. Systematic review and 2 new observational studies included in analysis; not all women CIN histologically confirmed. Also from observational studies with no control of cryotherapy – 7 studies report 0 to 15% of pregnancies resulted in spontaneous abortion (over 1 year) – average baseline risk of 7% used to calculate effects.

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

Note: 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%).

Small lesion

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
Recurrence all CIN (follow-up 4–84 months)										
7	observational studies	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	231/1705 (14%)	60 per 1000 (from 50 to 70)	⊕○○○	IMPORTANT

[1] There was high heterogeneity/inconsistency in results across these studies (I^2=72%).

Moderate lesion

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
Recurrence all CIN (follow-up 4–84 months)										
11	observational studies	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	225/2211 (10%)	70 per 1000 (from 60 to 80)	⊕○○○	IMPORTANT

[1] There was high heterogeneity/inconsistency in results across these studies (I^2=76%).

Large lesion

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
Recurrence all CIN (follow-up 4–84 months)										
5	observational studies	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	52/246 (21%)	18 per 1000 (from 130 to 230)	⊕○○○	IMPORTANT

[1] There was high heterogeneity/inconsistency in results across these studies (I^2=64%).

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

Note: Positive ECC indicated a lesion that extended 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.

Cryotherapy in women with a lesion that extends into the endocervical canal (positive ECC)

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
Recurrence all CIN (follow-up 4–84 months)										
9	observational studies	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	63/302 (21%)	160 per 1000 (from 130 to 200)	⊕○○○	IMPORTANT

[1] There was high heterogeneity/inconsistency in results across these studies (I^2= 80%).

Cryotherapy in women with a lesion that DOES NOT extend into the endocervical canal (negative ECC)

Quality assessment							No. of patients (raw data)	Absolute effect at 1 year (95% CI)	Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other				
Recurrence all CIN (follow-up 4–84 months)										
33	observational studies	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	1086/10901 (10%)	60 per 1000 (from 50 to 60)	⊕○○○	IMPORTANT

[1] There was high heterogeneity/inconsistency in results across these studies (I^2=90%).

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Double freeze	Single freeze	Relative (95% CI)	Absolute effect at 1 year(95% CI)	Quality	Importance
Resource use – not measured												
Recurrence CIN II–III (follow-up 3–12 months)												
3	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/429 (8.2%)	27/91 (30%)	OR 0.40 (0.22 to 0.75)	152 fewer per 1000 (from 56 to 212 fewer)	⊕⊕⊕○	CRITICAL
Cervical Cancer (follow-up 3–42 months)												
3	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/510 (0%)	0/152 (0%)	–	0 per 1000[3]	⊕⊕○○	CRITICAL
All severe adverse events (including major bleeding, major infections, etc.)												
5	randomized trials	no serious limitations	no serious inconsistency	serious[4]	serious[2]	none	5/190 (2.6%)	2/135(1.5%)	–	20 fewer per 1000 (73 fewer to 33 more)[5]	⊕⊕○○	CRITICAL
Fertility (number of pregnancies with or without intention)												
5	observational studies	serious limitations[6]	no serious inconsistency	serious[6]	serious[7]	none	77/590[7] (13%)	47/123[7] (38%)	not pooled	–	⊕○○○	CRITICAL
Recurrence all CIN (follow-up 12–110 months)												
4	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/510 (9%)	43/152 (28%)	OR 0.37 (0.21 to 0.63)	156 fewer per 1000 (from 84 to 206 fewer)	⊕⊕⊕○	CRITICAL
Spontaneous abortions per pregnancies												
5	observational studies	no serious limitations	no serious inconsistency	serious[6]	serious[2]	none	4/145 (3%)	1/8 (13%)	not pooled	–	⊕○○○	IMPORTANT
Pain (requiring local treatment)												
2	randomized trials	no serious limitations	no serious inconsistency	serious[4]	serious[2]	none	0/100 (0%)	5/100 (5%)	–	40 fewer per 1000 (from 112 fewer to 320 more)	⊕⊕○○	IMPORTANT
8	Observational studies	serious[6] limitations	no serious inconsistency	Serious[6]	serious[2]	none	167/2311 (7%)	0/138 (0%)	–	110 more per 1000 (from 64 to 156 more)	⊕○○○	IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Double freeze	Single freeze	Relative (95% CI)	Absolute effect at 1 year(95% CI)	Quality	Importance
Minor infection (requiring outpatient treatment only)												
7	observational studies	serious limitations[6]	no serious inconsistency	serious[6]	serious[2]	none	153/3486 (4.4%)	4/243 (1.6%)	–	20 per 1000 more (from 4 to 36 more)	⊕○○○	IMPORTANT
CIN I												
1	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	8/48 (17%)	6/27 (22%)	OR 0.70 (0.21 to 2.28)	56 more per 1000 (from 166 fewer to 172 more)	⊕⊕○○	IMPORTANT
Treatment unacceptable to women (acceptability question) – not measured												
Referrals after treatment for complications – not measured												
Treatment unacceptable to women assessed by providers – not measured												
HIV transmission (HIV acquisition, HIV shedding) – not measured												
Maternal morbidity – not measured												

[1] The methodological quality of the included study is low. The method of randomization, allocation concealment, blinding, dealing with incomplete outcome data is inadequate. [2] Few participants with confidence intervals including more or fewer women. [3] Confidence intervals not calculated. [4] Indirect estimation from two randomized trials comparing single freeze cryotherapy versus laser ablation and double freeze cryotherapy versus laser ablation. [5] Data from observational uncontrolled studies yield similar estimates. [6] Indirect estimation from observational studies with no independent control. [7] This is data from uncontrolled observational studies the number of pregnancies in the double freeze cryotherapy group ranged from 2 to 16 while it was 38 in the single freeze cryotherapy study

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Nitrous oxide	Carbon dioxide	Relative (95% CI)	Absolute effect at 1 year (95% CI)	Quality	Importance
Recurrence CIN II-III (follow-up 12 months)												
17	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	219/4815 (4.5%)	70/912 (7.7%)	OR 0.67 ! (0.38 to 1.18)	–	⊕○○○	CRITICAL
								3%[4]		10 fewer per 1000 (from 19 fewer to 6 more)		
Cervical Cancer (follow-up to 10 years)												
15	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	11/5578 (0.2%)	2/853 (0.23%)	not pooled	not pooled	⊕○○○	CRITICAL
All severe adverse events (follow-up 12 months; major infections and bleeding, pelvic inflammatory disease, stenosis, etc.)												
13	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	21/5080 (0.41%)	2/1434 (0.14%)	–	0 fewer per 1000	⊕○○○	CRITICAL
Major infection (follow-up 12 months; (requiring hospitalization or blood transfusion))												
13	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	8/4634 (0.17%)	2/1434 0.14%)	–	0 fewer per 1000	⊕○○○	CRITICAL
Major bleeding (follow-up 12 months; (requiring hospitalization or blood transfusion))												
11	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	2/2877 (0.07%)	0/1332 (0%)	–	0 fewer per 1000	⊕○○0	CRITICAL
Recurrence all CIN (follow-up 12 months)												
32	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	1156/10848 (10.7%)	91/1090 (8.3%)	OR 1.2 (0.96 to 1.50)	–	⊕○○○	IMPORTANT
								5%[4]		10 more per 1000 (from 2 fewer to 25 more)		
Minor infections (follow-up 12 months)												
10	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	58/2500 (0.48%)	95/1332 (7.1%)	–	20 fewer per 1000 (from 30 to 10 fewer)	⊕○○○	IMPORTANT

CIN I (follow-up 12 months)												
14	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	368/4909 (7.5%)	44/912 (4.8%)	OR 1 (0.58 to 1.73)	0 fewer per 1000 (from 8 fewer to 15 more)	⊕○○○	IMPORTANT
Mortality – not measured[5]												
Fertility (e.g. conception) – not measured[5]												
Spontaneous abortion – not measured[5]												
Resource use – not measured												
Treatment unacceptable to women – not measured[5]												
Referrals after treatment for complications or follow-up treatment – not measured												
Treatment unacceptable to women assessed by providers – not measured												
HIV transmission (HIV acquisition, HIV shedding) – not measured												
Pain (requiring only local treatment) – not measured[5]												
Maternal morbidity – not measured												

[1] Observational studies with no independent controls. [2] High heterogeneity among studies with nitrous oxide or with carbon dioxide. [3] Indirect evidence from observational studies with no control pooled and compared. [4] Baseline risk from observational studies with no control providing carbon dioxide. [5] There were no studies using carbon dioxide that measured these outcomes for comparison.

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy using cough technique	Cryotherapy	Relative (95% CI)	Absolute effect at 1 year (95% CI)	Quality	Importance
CIN II, III (follow-up 4–72 months)												
24	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	20/472 (4.2%)	2546/20806 (12.2%)	OR 1.00 (0.58 to 1.73)	–	⊕○○○	IMPORTANT
								4%[3]		0 fewer per 1000 (from 16 fewer to 27 more)		
Cervical carcinoma (follow-up to 10 years)												
25	observational studies	serious limitations[1]	no serious inconsistency	very serious[1]	serious imprecision[4]	none	2/472 (0.42%)	19/8306 (0.23%)	Not pooled[4]	Not pooled	⊕○○○	IMPORTANT
All severe adverse events (follow-up 12 months; assessed with: includes major bleeding, major infections, etc.)												
19	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	1/472 (0.21%)	22/5653 (0.39%)	–	0 per 1000	⊕○○○	CRITICAL
HIV transmission (HIV acquisition, HIV shedding) – not measured												
Major infection (follow-up 12 months; assessed with: requiring hospital admission and antibiotics)												
16	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	0/472 (0%)	10/4979 (0.2%)	–	50 more per 1000 (from 30 to 70 more)	⊕○○○	IMPORTANT
Major bleeding												
13	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	0/472 (0%)	2/3225 (0.06%)	–	0 per 1000	⊕○○○	IMPORTANT
Recurrence all CIN (follow-up 4–84 months)												
54	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	53/472 (11.2%)	3799/29544 (12.9%)	OR 2.75 (1.89 to 4.00)	–	⊕○○○	IMPORTANT
								4%[3]		63 more per 1000 (from 33 to 103 more)		

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy using cough technique	Cryotherapy	Relative (95% CI)	Absolute effect at 1 year (95% CI)	Quality	Importance
Pain (follow-up 12 months; requiring local treatment only)												
7	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	20/222 (9%)	147/2227 (6.6%)	OR 3.00 (1.79 to 5.04)	–	⊕○○○	IMPORTANT
								3%[3]		55 more per 1000 (from 22 to 105 more)		
CIN I												
20	observational studies	serious limitations[1]	serious[2]	very serious[1]	serious[2]	none	33/472 (7%)	411/6978 (5.9%)	OR 3.5 (2.22 to 5.51)	–	⊕○○○	IMPORTANT
								2%[3]		47 more per 1000 (from 23 to 81 more)		
Minor infection (follow-up 12 months; assessed with: requiring outpatient treatment only)												
11	observational studies	serious limitations[1]	serious[2]	very serious[1]	no serious imprecision	none	95/1194 (8%)	62/2743 (2.3%)	–	0 per 1000 (from 7 fewer to 7 more)	⊕○○○	IMPORTANT
Resource use – not measured												
Spontaneous abortion – not measured[4]												
Maternal morbidity – not measured												
Mortality – not measured												
Fertility – not measured												
Treatment unacceptable to women – not measured												
Referrals for complications – not measured												
Treatment unacceptable to women assessed by providers – not measured												

[1] Observational studies with no independent controls compared in network meta-analysis. [2] Studies that did not indicate type of technique used were assumed as no cough technique used. These studies had high heterogeneity for most outcomes (except severe adverse effects and bleeding). [3] Baseline risks from all observational studies with no control. [4] Not pooled over widely varying lengths of follow-up.

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy with antibiotics	No antibiotics	Relative (95% CI)	Absolute	Quality	Importance
Major infection (follow-up 12 months; requiring hospitalization or blood transfusion)												
16	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1600 (0%)	10/4573 (0.22%)	–	0 per 1000[3]	⊕○○○	IMPORTANT
All severe adverse events (follow-up 12 months; (major infections and bleeding, pelvic inflammatory disease, stenosis, etc)												
17	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1705 (0%)	22/5142 (0.43%)	–	0 per 1000[3]	⊕○○○	IMPORTANT
Minor infections (follow-up 12 months)												
10	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	50/1600 (3.1%)	107/2337 (4.6%)	–	30 fewer per 1000 (from 40 to 20 fewer)	⊕○○○	IMPORTANT
Treatment acceptable to women (acceptability question) – not measured[4]												
Abnormal discharge (follow-up 12 months)												
9	observational studies	serious limitations[1]	serious[5]	very serious[2]	no serious imprecision	none	24/1600 (1.5%)	247/2210 (12.3%)	–	50 fewer per 1000 (from 40 to 60 fewer)	⊕○○○	IMPORTANT
All minor adverse events – events per woman (follow-up 12 months; minor infections, bleeding, discharge, pain, etc.)												
17	observational studies	serious limitations[1]	serious[5]	very serious[2]	no serious imprecision	none	119/1770 (6.7%)	1771/3260 (54.3%)	–	1.26 fewer events per woman (from 1.32 to 1.20 fewer)	⊕○○○	IMPORTANT
Major bleeding (follow-up 12 months; (requiring hospitalization or blood transfusion)												
13	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1705 (0%)	2/1992 (0.07%)	–	0 per 1000[3]	⊕○○○	IMPORTANT

Resource use – not measured
Treatment unacceptable to women assessed by providers – not measured
Referrals after cryotherapy for complications – not measured
HIV transmission (shedding, acquisition) – not measured
Mortality – not measured[5]

[1] Observational studies with no independent control. [2] Indirect analysis between observational studies with no control. Studies considered not to provide antibiotics were those that did not report antibiotic use or reported no antibiotic use. [3] Confidence intervals not calculated. [4]1 study without antibiotics found 15/170 women assessed cryotherapy as unacceptable. [5] High heterogeneity among studies with and without antibiotics. [6] 1 study without antibiotics measured long-term mortality 32/488.

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy provided by nurse	Cryotherapy provided by physician	Relative (95% CI)	Absolute	Quality	Importance
CIN II, III (follow-up 6–72 months)												
5	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	35/1600 (2.2%) 7%[4]	54/793 (6.8%)	OR 0.14 (0.05 to 0.38) 60 fewer per 1000 (from 42 to 66 fewer)	–	⊕○○○	CRITICAL
All severe adverse events (follow-up 12 months; assessed with: includes major bleeding, major infections, etc.)												
4	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	0/1600 (0.06%)	0/633 (0%)	–	0 per 1000[5]	⊕○○○	CRITICAL
Cervical carcinoma (follow-up 4 to 72 months)												
7	observational studies	serious limitations[1]	no serious inconsistency	very serious[3]	no serious imprecision	none	0/1600 (0%)	0/1127 (0%)	–	0 per 1000[5]	⊕○○○	CRITICAL
Recurrence all CIN (follow-up 4–72 months)												
13	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	232/1600 (14.5%)	368/3270 (11.3%)	OR 0.63 (0.49 to 0.73)	–	⊕○○○	IMPORTANT
CIN I (follow-up 6 to 72 months)												
6	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision none		197/1600 (12.3%) 8%[4]	121/1563 (7.7%) OR 0.5 (0.32 to 0.78)[6] 28 fewer per 1000 (from 19 to 70 more)		–	⊕○○○	IMPORTANT
Minor infection (follow-up 12 months; assessed with: requiring outpatient treatment only)												
4	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	50/1600 (3.1%)	95/1364 (7%)	–	5 fewer per 1000 (from 3 to 7 fewer)	⊕○○○	IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy provided by nurse	Cryotherapy provided by physician	Relative (95% CI)	Absolute	Quality	Importance
Pain (follow-up 12 months; assessed with: requiring local treatment only)												
3	observational studies	serious limitations[1]	serious[2]	very serious[3]	no serious imprecision	none	36/1600 (2.3%)	94/392 (24%)	OR 0.22 (0.10 to 0.46) 29 fewer per 1000 (from 13 to 40 fewer)	–	⊕○○○	IMPORTANT
							6%[4]					
Treatment unacceptable to women assessed by providers – not measured												
Treatment unacceptable to women – not measured												
Resource use – not measured												
Referrals for complications – not measured												
HIV transmission (HIV acquisition, HIV shedding) – not measured												
Mortality – not measured												
Fertility – not measured												
Spontaneous abortion – not measured												
Maternal morbidity – not measured												

[1] Observational studies with no independent controls. [2] High heterogeneity among studies provide by physicians and/or by nurses. [3] Indirect analysis between observational studies with no control. Studies were included if the provider was explicitly reported. [4]Baseline risks from observational studies with no control in which cryotherapy provided by physician. [5] Confidence intervals not calculated. [6] When analysing all studies which did not report provider but it was assumed physician, the result favour physicians instead, OR 1.5 (0.91 to 2.5).

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy (or laser vaporization)	No surgical procedure	Relative (95% CI)	Absolute	Quality	Importance
Obstetric outcomes (Preterm birth <37 weeks)												
1	Observational study	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	0/5 (0%)	10/98 (10%)	OR 0.77 (0.04 to 14.86)	19 fewer per 1000 (from 86 fewer to 505 more)	⊕○○○	IMPORTANT

[1] Women were diagnosed with carcinoma in situ. Analysis includes women who received cryotherapy or laser vaporization. Data could not be separated for each procedure (El-Bastawissi et al. 1999). [2] Absolute effect includes both fewer preterm births with cryotherapy and more preterm births.

Should cryotherapy versus LEEP be used in women with histologically confirmed cervical intraepithelial neoplasia who are pregnant?

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy (or laser vaporization)	LEEP (or laser or cold knife)	Relative (95% CI)	Absolute	Quality	Importance
Obstetric outcomes (Preterm birth <37 weeks)												
1	Observational study	No serious limitations	no serious inconsistency	serious[1]	serious[2]	none	0/5 (0%)	11/122 (9%)	OR 0.88 (0.05 to 16.98)	10 fewer per 1000 (from 85 less to 537 more)	⊕○○○	IMPORTANT

[1] Women were diagnosed with carcinoma in situ. Analysis includes women who received cryotherapy or laser vaporization; and women who received LEEP, laser or cold knife. Data could not be separated for each procedure (El-Bastawissi et al. 1999). [2] Absolute effect includes both fewer preterm births with cryotherapy and more preterm births.

Summary of observational studies with no control CRYOTHERAPY

Four studies reported outcomes for 7 women who were pregnant (CIN I,II,III histologically confirmed) and received cryotherapy. Of the studies that reported recurrence/residual disease, 1/5 had invasive carcinoma at follow-up. Of the studies that reported pregnancy outcomes, 0/4 had preterm deliveries or complications (⊕○○○ quality of evidence)

Summary of observational studies with no control LEEP

Three studies reported outcomes in histologically confirmed pregnant women (⊕○○○ quality of evidence).

- Frega et al. 2007 reports 5 women with CIN III who had LEEP at 16 weeks. LEEP did not modify duration of pregnancy, its outcome or delivery. There was no recurrence postpartum.
- Robinson et al. 1997 reports 20 women with CIN III (with suspicion of invasion) who had LEEP at 8 to 34 weeks. There were 3 preterm deliveries (28 to 35 weeks), 2 major bleeding (1 leading to 'fetal demise'), 9/19 residual/recurrence of CIN II,III.
- Mitsuhashi et al. 2000 reports 14 women with CIN III (CIS mainly) who had LEEP at 14 weeks. No women had premature delivery, spontaneous abortion or major bleeding, but 1 woman had cervical incompetence which was treated with no future difficulties. 2/9 women had recurrent CIN II,III.

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

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	Conization	Relative (95% CI)	Absolute	Quality	Importance
Recurrence all CIN												
12	observational studies	no serious limitations	no serious inconsistency	serious[1]	Serious[2]	none	26/99 (26.3%)	6/76 (7.9%)	OR 2.35 (0.82 to 6.7)	–	⊕○○○	CRITICAL
								30%[3]		202 more per 1000 (from 40 fewer to 442 more)		

[1] Follow-up interval after first cryotherapy treatment and diagnosis of CIN/retreatment often not reported in studies. [2] Few participants and events with confidence intervals including no difference or lower recurrence rates with cryotherapy versus conization. [3] Recurrence rate with conization ranged from 0 to 50%.

For more information, please contact:

Department of Reproductive Health and Research
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27, Switzerland
Fax: +41 22 791 4171
E-mail: reproductivehealth@who.int
www.who.int/reproductivehealth

World Health Organization