

Question

Should **cryotherapy** vs. **LEEP** be used for **women with confirmed CIN II**?

Population:	Women with confirmed CIN II	Background: Cervical intraepithelial neoplasia (CIN) is a pre-malignant lesion for cervical cancer which can be confirmed histologically from a biopsy in multiple stages, CIN 1, 2, 3. It can be estimated that in 70% of women CIN 2-3 may persist or progress to cervical cancer after 10 to 20 years [ref]. For this reason, treatment is typically provided to women with histologically confirmed CIN 2-3. There are three principle treatment options available in low- and middle-income countries: cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), and cold knife conisation (CKC).
Intervention:	Cryotherapy	
Comparison:	LEEP	
Main outcomes:	Recurrence CIN II-III, severe adverse events, pain or minor infections, severe preterm delivery in pregnancies, mortality	
Setting:	Canada (rural and urban settings)	
Perspective:	Population	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	<p>Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.</p> <p>There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths.</p>	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	<p>Limited qualitative evidence suggests high anxiety related to colposcopy/treatment but patients generally satisfied with cryotherapy; and fear of effects on pregnancy outcomes.</p>	

DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Summary of findings table of critical outcomes</p> <table border="1" data-bbox="667 164 1690 760"> <thead> <tr> <th>Outcomes (after 1 year)</th> <th>Cryotherapy (per 1000)</th> <th>LEEP (per 1000)</th> <th>Difference (per 1000) (95% CI)</th> <th>Risk ratio (95% CI)</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td><i>Recurrence CIN 2-3</i></td> <td>75</td> <td>24</td> <td>51 more (from 1 to 179 more)</td> <td>OR 3.3 (1.04 to 10.46)</td> <td>⊕⊕⊕○ Moderate</td> </tr> <tr> <td><i>All severe adverse events</i></td> <td>22</td> <td>40</td> <td>18 fewer (from 36 fewer to 67 more)</td> <td>OR 0.53 (0.1 to 2.88)</td> <td>⊕⊕○○ Low</td> </tr> <tr> <td><i>Pain or minor infections</i></td> <td>0</td> <td>0</td> <td>0 more or less</td> <td>1.52 (1.46 to 1.58)</td> <td>⊕⊕○○ Low</td> </tr> <tr> <td><i>Severe preterm delivery</i></td> <td>37</td> <td>70</td> <td>33 fewer (from 58 fewer to 27 more)</td> <td>RR 0.56 (0.23 to 1.36)</td> <td>⊕○○○ Very Low</td> </tr> <tr> <td><i>Mortality</i></td> <td>12</td> <td>3</td> <td>9 more (from 5 to 16 more)</td> <td>OR 4.18 (2.66 to 6.56)</td> <td>⊕⊕○○ Low</td> </tr> </tbody> </table>					Outcomes (after 1 year)	Cryotherapy (per 1000)	LEEP (per 1000)	Difference (per 1000) (95% CI)	Risk ratio (95% CI)	Certainty of the evidence (GRADE)	<i>Recurrence CIN 2-3</i>	75	24	51 more (from 1 to 179 more)	OR 3.3 (1.04 to 10.46)	⊕⊕⊕○ Moderate	<i>All severe adverse events</i>	22	40	18 fewer (from 36 fewer to 67 more)	OR 0.53 (0.1 to 2.88)	⊕⊕○○ Low	<i>Pain or minor infections</i>	0	0	0 more or less	1.52 (1.46 to 1.58)	⊕⊕○○ Low	<i>Severe preterm delivery</i>	37	70	33 fewer (from 58 fewer to 27 more)	RR 0.56 (0.23 to 1.36)	⊕○○○ Very Low	<i>Mortality</i>	12	3	9 more (from 5 to 16 more)	OR 4.18 (2.66 to 6.56)	⊕⊕○○ Low	
Outcomes (after 1 year)	Cryotherapy (per 1000)	LEEP (per 1000)	Difference (per 1000) (95% CI)	Risk ratio (95% CI)	Certainty of the evidence (GRADE)																																						
<i>Recurrence CIN 2-3</i>	75	24	51 more (from 1 to 179 more)	OR 3.3 (1.04 to 10.46)	⊕⊕⊕○ Moderate																																						
<i>All severe adverse events</i>	22	40	18 fewer (from 36 fewer to 67 more)	OR 0.53 (0.1 to 2.88)	⊕⊕○○ Low																																						
<i>Pain or minor infections</i>	0	0	0 more or less	1.52 (1.46 to 1.58)	⊕⊕○○ Low																																						
<i>Severe preterm delivery</i>	37	70	33 fewer (from 58 fewer to 27 more)	RR 0.56 (0.23 to 1.36)	⊕○○○ Very Low																																						
<i>Mortality</i>	12	3	9 more (from 5 to 16 more)	OR 4.18 (2.66 to 6.56)	⊕⊕○○ Low																																						
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 																																										
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ No included studies 																																										
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 																																										

RESOURCES REQUIRED	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>Cryotherapy is an outpatient procedure that can be provided in primary care settings; takes about 15 minutes; no anaesthesia required; CO2 or N2O used (no electricity); can be performed by trained providers (e.g. physicians, nurses, midwives). Cryotherapy is lower in cost to provide.</p> <p>LEEP is an outpatient procedure provided in facilities with back up hospital support; takes about 5-10 minutes; local anaesthesia required; can be performed by well-trained clinicians who can manage complications; requires electricity.</p> <p>More sophisticated equipment necessary for LEEP versus cryotherapy</p>	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ No included studies 		
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	<p>Most women would have access to either treatment.</p>	
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	<p>Evidence from one RCT showed no difference in acceptability between cryotherapy and LEEP in women.</p>	

FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	<p>LEEP or cryotherapy may be performed in doctor's office, at a colposcopy clinic or at a hospital.</p> <p>Cryotherapy is currently provided in most facilities even in rural settings.</p>	
--------------------	---	--	--

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should cryotherapy vs. LEEP be used for women with confirmed CIN II?					
TYPE OF RECOMMENDATION	<p>Strong recommendation against the intervention</p> <p>○</p>	<p>Conditional recommendation against the intervention</p> <p>○</p>	<p>Conditional recommendation for either the intervention or the comparison</p> <p>○</p>	<p>Conditional recommendation for the intervention</p> <p>○</p>	<p>Strong recommendation for the intervention</p> <p>○</p>
RECOMMENDATION					
JUSTIFICATION					
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					