WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ

Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation

World Health Organization

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Contents

Introduction

This document includes the judgements and evidence for each recommendation as presented and used by the Guideline Development Group to make recommendations for the *WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ*.[1]

For each recommendation, we provide:

- recommendation and remarks, which include the strength of the recommendation and the quality of the evidence;
- an evidence-to-recommendation table, describing the judgements made by the Guideline Development Group;
- evidence for each recommendation in a GRADE evidence profile;
- references.

Acronyms and abbreviations

AIS	adenocarcinoma in situ
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
LEEP	loop electrosurgical excision procedure (also LLETZ, large loop excision of the transformation zone)
OR	odds ratio
PID	pelvic inflammatory disease
RCT	randomized controlled trial
RR	risk ratio

1 Available at: www.who.int/reproductivehealth/publications/cancers/treatment_CIN_2-3/en/index.html

Recommendation 1

The expert panel recommends cryotherapy over no treatment for women who have histologically confirmed CIN2+ disease
(strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: This recommendation is strong, although the available evidence was very low quality. The expected benefit of cervical cancer prevention is very high and outweighs harms and any use of resources, but there is uncertainty related to preterm delivery in future pregnancies. However, the panel felt that women would prefer to be treated despite the uncertainty of these risks. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	There is low- to very-low-quality evidence from non-randomized studies with no independent control. There was also imprecision as a result of few events or participants in the studies, inconsistency, and/or risk of bias as a result of selective reporting of complications.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☒ / No ☐	Residual/recurrence rates of CIN2+ are probably lower with cryotherapy resulting in lower risk of cervical cancer and related mortality compared to no treatment. These benefits outweigh the low risk of major bleeding and infection with cryotherapy, and the unclear risk of premature delivery or spontaneous abortion.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the risk of cervical cancer and mortality with no treatment. The panel felt that women would prefer to be treated despite the uncertainty of the risks related to reproductive outcomes.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources for cryotherapy when no other treatments are available are worth the net benefits.

Evidence profile 1: Should cryotherapy or no treatment be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with cryotherapy** (95% CI)
CIN2+ residual/recurrence at 12 months											
121 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW[1]** due to imprecision	42/108 (38.9%)	7/13 (53.8%)	**OR 1.83** (0.58 to 5.83)	**700 recurrences per 1000**	**581 more recurrences per 1000** (from 294 fewer to 3381 more)
CIN2+ residual/recurrence average over 12 months											
13 907 (12 non-randomized studies)	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW[2]** due to inconsistency	–	562/13 907 (4%)	–	**Moderate baseline risk[3]**	
										700 recurrences per 1000	**647 fewer recurrences per 1000** (from 632 to 661 fewer)
Damage to other organs/surgery required											
4974 (7 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	3/4974 (0%)	–	**Moderate**	
										0 per 1000	**0 per 1000** (from 0 to 1)
Major bleeding (requiring hospital admission or blood transfusion)											
11 570 (17 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	39/11 570 (0.3%)	–	**0 per 1000**	**0 per 1000** (from 0 to 0)
Major infection or pelvic inflammatory disease (requiring hospital admission and antibiotics)											
11 938 (18 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	7/11 938 (0.1%)	–	**0 major infections per 1000**	**0 major infections per 1000** (from 0 to 1)
Premature delivery <37 weeks											
117 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness4	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW[1,4]** due to imprecision	1/81 (1.2%)	1/36 (2.8%)	**RR 2.25** (0.14 to 34.98)[4]	**44 preterm deliveries per 1000**	**55 more preterm deliveries per 1000** (from 38 fewer to 1000 more)

Evidence profile 1 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with cryotherapy** (95% CI)
Spontaneous abortions											
46 (7 non-randomized studies) Follow-up 6 months to 10 years	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[5] due to risk of bias	–	7/46 pregnancies (15.2%)[6]	–	**–**	**0 abortions per 1000 pregnancies** (from 0 to 15)[7]
Infertility											
439 (4 non-randomized studies)	serious[5]	no serious inconsistency	no serious indirectness[6]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[5] due to risk of bias	–	65/439 (14.8%)[6]	–	**0 per 1000**	**130 per 1000** (from 40 to 210)
Minor bleeding											
8757 (17 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	12/8757 (1%)	–	**0 per 1000**	**0 per 1000** (from –1 to 1)
Maternal mortality – not measured											
HPV (after 6, 12, 24 months) – not measured											

Footnotes:

1 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.

2 High heterogeneity across studies that could not be explained according to a priori hypothesis.

3 Natural history data from McCredie et al. (2008) and Castle et al. (2009): 70% CIN persistence with no treatment.

4 Data are from CIN1, 2, 3 from Bruinsma & Quinn (2011) systematic review.

5 Selective reporting of this outcome likely and, therefore, the confidence in the estimate is lowered.

6 Data are from CIN1, 2, 3.

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Natural history data

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McCredie MR et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncology*, 2008, 9(5):425–434.

Recommendation 2

The expert panel recommends LEEP over no treatment for women who have histologically confirmed CIN2+ disease
(strong recommendation, ⊕⊕⊖⊖ evidence)

Remarks: This recommendation is strong despite low-quality evidence. The benefits outweigh any uncertainty about harms and the use of resources. This recommendation places a high value on women's preference for treatment. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	There is low- to very-low-quality evidence from non-randomized studies with no independent control. There was also imprecision as a result of few events or participants in the studies, inconsistency, and/or risk of bias as a result of selective reporting of complications.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☒ / No ☐	Residual/recurrence rates of CIN2+ are probably lower with LEEP resulting in lower risk of cervical cancer and related mortality compared to no treatment. These benefits outweigh the low risk of major bleeding and infection with LEEP, and the unclear risk of premature delivery or spontaneous abortion.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the risk of cervical cancer and mortality with no treatment. The panel felt that women would prefer to be treated despite the uncertainty of any risks.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources for LEEP when no other treatments are available are worth the net benefits.

Evidence profile 2: Should LEEP or no treatment be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With LEEP**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with LEEP** (95% CI)
CIN2+ residual/recurrence average over 12 months											
8269 (19 non-randomized studies)	no serious risk of bias	serious[1]	no serious indirectness[2]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW[1,2]** due to inconsistency	–	391/8269 (4.7%)	–	**Moderate baseline risk[2]**	
										700 recurrences per 1000	**647 fewer recurrences per 1000** (from 631 to 663 fewer)
Major bleeding (requiring hospital admission or blood transfusion)											
16 423 (40 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	121/16 423 (0.7%)	–	**0 per 1000**	**2 per 1000** (from 1 to 3)
HPV clearance at 6 months											
119 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW[3]** due to imprecision	–	106/119 (89.1%)	–		**890 per 1000** (from 830 to 950)
HPV clearance at 12 months											
119 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW[3]** due to imprecision	–	77/119 (64.7%)	–		**650 per 1000** (from 560 to 730)
Major infection or pelvic inflammatory disease (requiring hospital admission and antibiotics)											
7796 (19 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	37/7796 (5%)	–	**0 major infections per 1000**	**1 major infections per 1000** (from 0 to 2)
Premature delivery											
656 581 (8 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness[4]	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW[4]**	26 070/645 905 (4%)	782/10 676 (7.3%)	**RR 1.85** (1.59 to 2.15)[4]	**44 preterm deliveries per 1000**	**37 more preterm deliveries per 1000** (from 26 to 51 more)

Evidence profile 2 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With LEEP**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with LEEP** (95% CI)
Spontaneous abortion											
207 (3 non-randomized studies)	no serious risk of bias	serious[6]	serious[7]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7] due to inconsistency, indirectness	–	0/207 (0%)	**not pooled**[7]		See footnote[5]
Infertility											
134 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness[8]	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,8] due to imprecision	–	0/134 (0%)	**not pooled**[8]		See footnote[8]
Minor bleeding											
19 861 (52 non-randomized studies)	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to inconsistency	–	308/19 861 (1.6%)	–	**0 per 1000**	**200 per 1000** (from 10 to 380)
Damage to other organs/surgery required											
5727 (12 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	21/5727 (0%)	–	**0 per 1000**	**2 per 1000** (from 0 to 4)
Maternal mortality – not measured											

Footnotes:

1 High heterogeneity across studies that could not be explained according to a priori hypothesis.

2 Natural history data from McCredie et al. (2008) and Castle et al. (2009): 70% CIN persistence with no treatment.

3 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.

4 From Bruinsma & Quinn (2011) systematic review evaluating LEEP versus no treatment in women with CIN1+. Ortoft et al. (2010), in 955 women with CIN2+, also showed RR 2.46 (95% CI: 1.41 to 4.28).

5 In 3 studies evaluating LEEP, 1/169 (0.59%) (combined data from Michelin et al., 2009 and Zeng et al., 2009) and 11/38 (29%) (Girardi et al., 1994) had spontaneous abortion. Data are from CIN1, 2, 3.

6 Baseline proportions of spontaneous abortions ranged from 0.5% to 30%.

7 Only data for LEEP, no comparison to no treatment.

8 No difference in time to conceive in 134 women at 3 years and more (Bigrigg et al., 1994). Data are from CIN1, 2, 3.

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Systematic review of non-randomized studies with two groups (premature delivery <37 weeks)

Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2011, 118(9):1031–1041.

Natural history data

Castle PE et al. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstetrics & Gynecology*, 2009, 113(1):18–25.

McCredie MR et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncology*, 2008, 9(5):425–434.

Recommendation 3

The expert panel recommends cold knife conization (CKC) over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: This recommendation considers that no other treatments may be available. In such situations, CKC is recommended over no treatment as the benefits outweigh the harms, and patient preference for treatment was likely to be greater than the preference for no treatment. More data are needed to determine the risk of preterm births, the safety of CKC in settings with differing availability of resources, and whether CKC should be recommended for both CIN2 and CIN3. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes: ☐ No: ☒	There is low- to very-low-quality evidence from non-randomized studies with no independent control (leading to risk of bias) and studies that include women with CIN1 (inconsistency).
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes: ☒ No: ☐	Residual/recurrence rates of CIN2+ are probably lower with CKC resulting in lower risk of cervical cancer and related mortality compared to no treatment. These benefits outweigh the risk of major bleeding and infections with CKC, and the unclear risk of premature delivery or spontaneous abortions.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes: ☒ No: ☐	A high value was placed on the risk of cervical cancer and mortality with no treatment and low value on risk of complications with CKC.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	The resources for CKC when no other treatments are available are worth the net benefits.

Evidence profile 3: Should CKC or no treatment be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With CKC**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with CKC** (95% CI)
CIN2+ residual/recurrence average events at 12 months											
17 616 (11 non-randomized studies)	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW[1]** due to inconsistency	–	413/17 616 (5.4%)	–	**Moderate baseline risk[2]**	
										700 recurrences per 1000	**677 fewer recurrences per 1000** (from 668 to 683 fewer)
Major bleeding (requiring hospital admission or blood transfusion)											
9311 (25 non-randomized studies)	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW[1]** due to inconsistency	–	216/9311 (2.3%)	–	**Moderate**	
										0 per 1000	**9 per 1000** (from 7 to 11)
HPV clearance at 24 months											
119 (1 non-randomized study[4])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW[3]** due to imprecision	–	86/119 (72.3%)	–	–	**720 per 1000** (from 640 to 800)
Major infection or PID (requiring hospital admission and antibiotics)											
3443 (11 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW[3]** due to imprecision	–	12/3443 (0.3%)	–	**Moderate**	
										0 major infections per 1000	**9 major infections per 1000** (from 0 to 3)
Premature delivery <37 weeks[5]											
30 216 (3 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness[6]	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW[6]**	1976/30 012 (6.6%)	33/204 (16.2%)	**RR 3.41** (2.38 to 4.88)	**44 preterm deliveries per 1000**	**106 more preterm deliveries per 1000** (from 61 to 171 more)

Evidence profile 3 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With CKC**	**Relative effect** (95% CI)	**Risk with no treatment**	**Risk difference with CKC** (95% CI)
Spontaneous abortion											
1090 (3 non-randomized studies)	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[7] due to risk of bias	–	10/1090 (0.92%)	–	–	**12 abortions per 1000** (from 7 to 32)
Infertility[8]											
202 (2 non-randomized studies)	serious7	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[7] due to risk of bias	–	0/202 (0%)	**not pooled**[8]		See footnote[8]
Minor bleeding											
7638 (27 non-randomized studies)	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to inconsistency	–	324/7638 (4.2%)	–	**0 per 1000**	**24 per 1000** (from 21 to 28)
Maternal mortality – not measured											
Damage to other organs/surgery required											
3180 (8 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	–	17/3180 (0.5%)	–	**0 per 1000**	**3 per 1000** (from 0 to 5)

Footnotes:

1 High heterogeneity across studies that could not be explained according to a priori hypothesis.

2 Natural history data from McCredie et al. (2008) and Castle et al. (2009): 70% CIN persistence with no treatment.

3 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.

4 He et al. (2011).

5 CKC compared to no treatment data from Bruinsma & Quinn (2011) systematic review of women with all CIN.

6 Population in trials included women with CIN1+.

7 Selective reporting of this outcome likely and, therefore, the confidence in the estimate is lowered.

8 For CKC: Weber & Obel (1979) found no difference in time to conceive in 36 women up to 24 months, and Mazouni et al. (2005) found no infertility up to 12 months in 166 women.

References 3

Non-randomized studies with two groups

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Systematic review of non-randomized studies with two groups (premature delivery <37 weeks)

Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2011, 118(9):1031–1041.

Natural history data

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Recommendation 4

The expert panel suggests cryotherapy or LEEP for women who have histologically confirmed CIN2+ disease (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: This recommendation is distinct from recommendations made for women who have screened positive without histology or for women with histologically confirmed CIN1. For women who have histologically confirmed CIN2+, the overall benefits may be greater with LEEP, and adverse events are similar with LEEP or cryotherapy. The availability and implementation of LEEP or cryotherapy will depend on resources. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	There is low- to very-low-quality evidence from non-randomized studies with no independent control (leading to high risk of bias). There were also imprecise results from the available randomized controlled trials.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☐ / No ☒	Residual/recurrence rates of CIN2+ are probably greater with cryotherapy resulting in higher risk of cervical cancer and related mortality compared to LEEP. However, there may be little or no difference in complications with cryotherapy or LEEP. Overall the benefits of LEEP likely outweigh those of cryotherapy.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the risk of recurrence, cervical cancer, and related mortality. The panel felt that the patient values are similar between the treatment modalities and that there is no difference in patient satisfaction between cryotherapy and LEEP.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources are worth the expected benefits from using cryotherapy or LEEP.

Evidence profile 4: Should cryotherapy or LEEP be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With LEEP**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with LEEP** (based on non-randomized studies)	**Risk difference with cryotherapy** (95% CI)
CIN2+ residual/recurrence at 12 months											
400 (1 RCT)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	4/200 (2%)	12/200 (6%)	**RR 3.00** (0.99 to 8.38)	**53 recurrences per 1000**	**106 more recurrences per 1000** (from 1 fewer to 391 more)
247 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	34/238 (14.3%)	1/9 (11.1%)	**RR 0.78** (0.1 to 3.55)	**53 recurrences per 1000**	**12 fewer recurrences per 1000** (from 48 fewer to 135 more)
Major bleeding (requiring hospital admission or blood transfusion)											
400 (1 RCT)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	0/200 (0%)	0/200 (0%)	–	**Moderate**	
										9 per 1000	**0 more per 1000**
1272 (6 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊖⊖ **LOW**	0/353 (0%)	3/919 (0.3%)	–	**9 per 1000**	**0 more per 1000** (from 0 to 1 more)
Damage to other organs/surgery required											
10 701 (15 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[2] due to indirectness	21/5727 (0%)	3/4974 (0%)	**RR 0.16** (0.05 to 0.55)	**2 per 1000**	**2 fewer per 1000** (from 1 to 2 fewer)
HPV clearance (after 6, 12 months)											
119 (1 non-randomized study4)	no serious risk of bias	no serious inconsistency	serious[4]	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4] due to indirectness, imprecision	–	0/119 (0%)	**not pooled**		See footnote[4]

Evidence profile 4 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With LEEP**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with LEEP** (based on non-randomized studies)	**Risk difference with cryotherapy** (95% CI)
Major infection or pelvic inflammatory disease (requiring hospital admission and antibiotics)											
19 734 (37 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[5]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW[5]** due to indirectness	37/7796 (5%)	7/11 938 (0.1%)	**RR 0.12** (0.06 to 0.28)[5]	**1 major infections per 1000**	**1 fewer major infection per 1000** (from 1 to 1 fewer)
Premature delivery											
10 712 (10 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[7]	serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW[7,8]** due to indirectness, imprecision	782/10 676 (7.3%)9	1/36 (2.8%)	**RR 1.22** (0.08 to 19.3)	**81 premature deliveries per 1000**	**18 more premature deliveries per 1000** (from 74 fewer to 672 more)
Spontaneous abortion											
253 (10 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[5]	serious[10]	undetected	⊕⊖⊖⊖ **VERY LOW[5,10]** due to indirectness, imprecision	207	46	**not pooled**		See footnote[10]
Infertility											
573 (5 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[5]	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW[1,5]** due to indirectness, imprecision	134	439	**not pooled**		See footnote[11]
Minor bleeding											
400 (1 RCT)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊕⊕⊖ **MODERATE[1]** due to imprecision	151/200 (75.5%)	69/200 (34.5%)	**RR 0.46** (0.34 to 0.59)	**200 per 1000**	**108 fewer per 1000** (from 132 to 82 fewer)
Maternal mortality – not measured											

Footnotes:

1 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.

2 RR could not be calculated.

3 This outcome was not measured in studies evaluating LEEP.

4 No studies evaluating cryotherapy measured this outcome. In 1 study evaluating LEEP, 106/119 (89.1%) women were clear of HPV at 6 months and 77/119 (64.7%) women were clear of HPV at 12 months (Kucera et al., 2001).

5 Results from indirect comparison of non-randomized studies with no independent control.

6 Data are from CIN1, 2, 3.

7 Data from an indirect analysis of preterm delivery in women with CIN1+ from Bruinsma & Quinn (2011) systematic review.

8 Very wide confidence intervals, including fewer or more preterm deliveries with cryotherapy.

9 In 1 study evaluating LEEP for CIN2+ diagnosis, premature delivery (<37 weeks) occurred in 55/572 (9.6%) (Ortoft et al., 2010).

10 In 7 studies evaluating cryotherapy, 7/46 (15%) pregnancies ended in spontaneous abortion (range: 0 to 15 spontaneous abortions per 100 pregnancies), with follow-up of 6 months to 10 years. In 3 studies evaluating LEEP, 1/169 (0.59%) (combined data from Michelin et al., 2009, and Zeng et al., 2009) and 11/38 (29%) (Girardi et al., 1994) had spontaneous abortion. Data are from CIN1, 2, 3.

11 In 4 studies evaluating cryotherapy, 65/439 (14.8%) had infertility. In 1 study evaluating LEEP, there was no difference in time to conceive in 134 women after 3 years (Bigrigg et al., 1994). Data are from CIN1, 2, 3.

Subgroup analysis by HIV status

Outcome: recurrence CIN2+ at 12 months

No subgroup interaction between HIV-negative and HIV-positive status (very low quality evidence due to imprecision, high loss to follow-up at 12 months) (Chirenje et al, 2001 and 2003).

References 4

Randomized controlled trials

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Non-randomized studies with one group – LEEP

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Systematic review of non-randomized studies with two groups (premature delivery <37 weeks)

Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2011, 118(9):1031–1041.

Crane JMG, Delaney T, Hutchens D. Transvaginal ultrasonography in the prediction of preterm birth after treatment for cervical intraepithelial neoplasia. *Obstetrics & Gynecology*, 2006, 107(1):37–44.

Recommendation 5

The expert panel recommends cryotherapy over CKC for women who have histologically confirmed CIN2+ disease and for whom cryotherapy or CKC could be appropriate (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: There is low-quality to very-low-quality evidence for the benefits and harms of cryotherapy and CKC. Although there may be fewer recurrences of CIN2+ with CKC than with cryotherapy, the harms may be greater. The resources required are also greater for CKC, including the need for operating rooms, anaesthesia, and highly trained providers or specialists. The limited data on values and preferences of women for either treatment were considered similar. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	There is low- to very-low-quality evidence from non-randomized studies with no independent control (leading to high risk of bias). There was also inconsistency among studies and likely selective reporting of complications.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☐ / No ☒	Residual/recurrence rates of CIN2+ are probably greater with cryotherapy resulting in higher risk of cervical cancer and related mortality compared to CKC. However, there may be fewer complications with cryotherapy. Benefits and harms may be affected by the skills of the provider. It is unclear that the benefits outweigh the harms of providing cyrotherapy over CKC when a woman is eligible for cryotherapy or CKC.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the risk of complications with CKC. The panel felt that there might not be a lot of choice provided to the patient as CKC is used now only with severe cases. Moreover, professionals tend to prefer cryotherapy, which is communicated to patients. CKC is also considered major surgery compared to cryotherapy, requiring inpatient care, so it is likely patients would prefer cryotherapy.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources are greater for CKC than cryotherapy, and include the need for operating rooms, anaesthesia, and skilled providers.

Evidence profile 5: Should cryotherapy or CKC be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with CKC** (based on non-randomized studies)	**Risk difference with cryotherapy** (95% CI)
CIN2+ residual/recurrence average effect at 12 months											
20 776 (6 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	123/10 262 (1.2%)	383/10 514 (3.6%)	**RR 3.29** (2.67 to 4.02)	**23 recurrences per 1000**	**53 more recurrences per 1000** (from 39 to 74 more)
Major bleeding (requiring hospital admission or blood transfusion)											
20 881 (42 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to indirectness	216/9311 (2.3%)	39/11 570 (0.3%)	**RR 0.15** (0.10 to 0.20)[1]	**Moderate** **9 per 1000**	**8 fewer per 1000** (from 7 to 9 fewer)
Maternal mortality											
438 (1 non-randomized study)	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision	0/396 (0%)	0/42 (0%)	–	–	–
HPV (after 6 months)[5]											
119 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[4] due to imprecision	–	119	–	See footnote[5]	–
Major infection or pelvic inflammatory disease (requiring hospital admission and antibiotics)											
15 371 (29 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to indirectness	12/3443 (0.3%)	7/11 938 (0.1%)	**RR 0.17** (0.07 to 0.43)[1]	**Moderate** **9 major infections per 1000**	**7 fewer per 1000** (from 5 to 8 fewer)

Evidence profile 5 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With no treatment**	**With cryotherapy**	**Relative effect** (95% CI)	**Risk with CKC** (based on non-randomized studies)	**Risk difference with cryotherapy** (95% CI)
Premature delivery <37 weeks[6]											
240 (2 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[4] due to indirectness, imprecision	33/204 (16.2%)	1/36 (2.8%)	**RR 0.**7 (0.05 to 4.16)6	**150 preterm deliveries per 1000**	**45 fewer preterm deliveries per 1000** (from 143 fewer to 158 more)
Spontaneous abortion											
1139 (10 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4] due to indirectness, imprecision	1090	49	–	See footnote[7]	–
Infertility											
641 (5 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4] due to indirectness, imprecision	202	439	–	See footnote[8]	–
Minor bleeding											
16 395 (44 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to indirectness	324/7638 (4.2%)	12/8757 (1%)	**RR 0.03** (0.02 to 0.06)[1]	**24 per 1000**	**23 fewer per 1000** (from 23 to 24 fewer)
Damage to other organs/surgery required											
8154 (15 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to indirectness	17/3180 (0.5%)	3/4974 (0%)	**RR 0.11** (0.03 to 0.38)1	**3 per 1000**	**3 fewer per 1000** (from 2 to 3 fewer)

Footnotes:

1 Non-randomized studies with no independent control in CKC were compared to studies in LEEP (indirect comparison).
2 RR was not calculated; instead a risk difference between interventions was calculated.
3 Only 1 study reported this outcome.
4 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.
5 For CKC we found a non-randomized study that reported that 86/119 (72.3%) had HPV clearance. We did not find clearance data for the cryotherapy group.
6 This is an indirect comparison between cryotherapy to no treatment and CKC to no treatment in women with CIN1+ (Bruinsma & Quinn, 2011). Two recent studies of CKC in women with CIN2+ found 4% (1% to 8%) had premature delivery (Michelin et al., 2009, and Ortoft et al., 2010).
7 There are no pooled data. There were 3 studies in women who were pregnant and had CKC: 10/1090 had spontaneous abortions (1.2%; 95% CI: 0.7% to 3.2%). There were 7 studies in women who were pregnant and had cryotherapy: 7/49 had spontaneous abortions (14%; 95% CI: 4% to 24%).
8 There are no pooled data. For CKC, Weber & Obel (1979) found no difference in the time to conceive in 36 women up to 24 months, and Mazouni et al. (2005) found no infertility up to 12 months in 166 women. For cryotherapy, 4 studies found 63/439 women had infertility (Crisp, 1972; Einerth, 1978; Weed et al., 1978; Elmfors & Stormby, 1979).

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Recommendation 6

The expert panel recommends LEEP over CKC for women who have histologically confirmed CIN2+ disease and for whom LEEP or CKC could be appropriate (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The quality of evidence was low for some outcomes and very low for critical outcomes, often with inconsistent results. Therefore, the overall benefits and harms of LEEP over CKC were unclear. Typically, CKC is provided over LEEP for clinical reasons and in specific situations. However, in situations in which there is a choice, the panel agreed that most women would prefer LEEP, as CKC is considered major surgery compared to LEEP. The resources required are also greater with CKC, including anaesthesia, operating rooms, and skilled providers. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	The quality of evidence was low for some of the outcomes but very low for other critical outcomes, and with often inconsistent results.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☐ / No ☒	Residual/recurrence rates of CIN2+ are probably greater with LEEP resulting in higher risk of cervical cancer and related mortality compared to CKC. However, there may be fewer complications with LEEP. Benefits and harms may be affected by the skills of the provider. It is unclear that the benefits outweigh the harms of providing LEEP over CKC when a woman is eligible for LEEP or CKC.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the risk of complications with CKC. The panel felt that there might not be a lot of choice provided to the patient as CKC is used now only with severe cases. Moreover, professionals tend to prefer LEEP, which is communicated to patients. CKC is also considered major surgery compared to LEEP, requiring inpatient care, so it is likely patients would prefer LEEP.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources are greater for CKC than cryotherapy, and include the need for operating rooms, anaesthesia, and skilled providers.

Evidence profile 6: Should CKC or LEEP be used in women with histologically confirmed CIN2+?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With LEEP**	**With CKC**	**Relative effect** (95% CI)	**Risk with LEEP** (based on non-randomized studies)	**Risk difference with CKC** (95% CI)
CIN2+ residual/recurrence (average events at 12 months)											
253 (2 RCTs)	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	12/127 (9.4%)	6/126 (4.8%)	**RR 0.52** (0.13 to 1.81)	**Moderate**[3] **53 recurrences per 1000**	**25 fewer recurrences per 1000** (from 46 fewer to 42 more)
14 610 (7 non-randomized Studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	195/4119 (4.7%)	326/10491 (3.1%)	**RR 0.64** (0.34 to 1.2)	**53 recurrences per 1000**	**19 fewer recurrences per 1000** (from 35 fewer to 11 more)
Major bleeding (requiring hospital admission or blood transmission)											
336 (3 RCTs)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	5/155 (3.2%)	5/181 (2.8%)	**RR 0.79** (0.23 to 2.58)	**9 per 1000**	**2 fewer per 1000** (from 7 fewer to 14 more)
861 (2 non-randomized studies)	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,4] due to imprecision	2/226 (0.88%)	31/635 (4.9%)	**RR 3.42** (0.14 to 50.49)	**9 per 1000**	**21 more per 1000** (from 8 fewer to 438 more)
HPV clearance at 6, 12, 24 months											
236 (2 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious6	serious	undetected	⊕⊖⊖⊖ **VERY LOW**[6] due to indirectness, imprecision	119	117	not pooled[5]		See footnote[5]

Evidence profile 6 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With LEEP**	**With CKC**	**Relative effect** (95% CI)	**Risk with LEEP** (based on non-randomized studies)	**Risk difference with CKC** (95% CI)
Major infection or pelvic inflammatory disease (PID) (requiring hospital admission and antibiotics) – only PID reported											
745 (1 non-randomized study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2] due to imprecision	0/153 (0%)	4/592 (0.68%)	**RR 2.35** (0.13 to 43.84)	**Moderate** **1 major infections per 1000**	**1 more major infections per 1000** (from 0 fewer to 43 more)
Premature delivery <37 weeks											
836 (2 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2] due to imprecision	56/667 (8.4%)	11/169 (6.5%)	**RR 1.29** (0.56 to 2.74)	**81 preterm deliveries per 1000**	**23 more preterm deliveries per 1000** (from 36 fewer to 141 more)
Spontaneous abortion											
90 (1 RCT)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊕⊖⊖ **LOW**[2] due to imprecision	11/38 (28.9%)	11/52 (21.2%)	**RR 0.73** (0.32 to 1.43)	**Moderate**[7] **6 abortions per 1000**	**2 fewer abortions per 1000** (from 4 fewer to 3 more)
1140 (2 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2] due to imprecision	1/169 (0.59%)	9/971 (0.93%)	**RR 2.36** (0.26 to 19.57)	**6 abortions per 1000**	**8 more abortions per 1000** (from 4 fewer to 110 more)
Infertility											
300 (3 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[6]	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,6] due to indirectness, imprecision	134	166	**not pooled**[8]		See footnote[8]

Evidence profile 6 *(continued)*

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With LEEP**	**With CKC**	**Relative effect** (95% CI)	**Risk with LEEP** (based on non-randomized studies)	**Risk difference with CKC** (95% CI)
Minor bleeding											
253 (2 RCTs)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	11/125 (8.8%)	10/128 (7.8%)	**RR 0.89** (0.38 to 1.95)	**Moderate**[7] **200 per 1000**	**22 fewer per 1000** (from 124 fewer to 190 more)
1890 (3 non-randomized studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	2/329 (0.61%)	14/1561 (0.9%)	**RR 3.99** (1 to 15.03)	**Moderate**[7] **200 per 1000**	**598 more per 1000** (from 0 to 1000 more)
Damage to other organs/surgery required											
8907 (20 non-randomized studies)	no serious risk of bias	no serious inconsistency	serious[9]	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW** due to indirectness	21/5727 (0%)	17/3180 (0.5%)	**RR 1.46** (0.77 to 2.76)	**2 per 1000**	**1 more per 1000** (from 0 to 4 more)
Maternal mortality – not measured											

Footnotes:

1 Direction of effect was inconsistent with data from non-randomized studies.

2 Wide confidence intervals were due to few events and participants, possibly leading to different decisions.

3 Based on the results of non-randomized studies.

4 Moderate heterogeneity across studies was considered with imprecision that could not be explained according to a priori hypothesis.

5 For LEEP, Kucera et al. (2001, non-randomized study) found HPV clearance events at 6 months were 106/119 (89%) and at 12 months were 77/119 (65%). For CKC, He et al. (2011, non-randomized study) found HPV clearance events at 24 months were 86/117 (74%).

6 Results from indirect comparison of non-randomized studies with no independent control.

7 Baseline from non-randomized studies with one group.

8 For LEEP, Bigrigg et al. (1994) found no difference in time to conceive in 134 women at 3 years and greater. For CKC, Weber & Obel (1979) found no difference in the time to conceive in 36 women up to 24 months, and Mazouni et al. (2005) found no infertility up to 12 months in 166 women

9 Indirect comparison of non-randomized studies with no independent controls.

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Recommendation 7

The expert panel suggests CKC over LEEP for women who have histologically confirmed AIS disease (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: This recommendation is based on very low quality evidence, which resulted in imprecise data for the differences in benefits and harms between CKC and LEEP. CKC may result in fewer recurrences and the panel felt these benefits outweighed the additional resources required for CKC. The preferences of women were also felt to be variable as women in higher income countries may not have as much aversion to CKC (e.g. anaesthesia), while women in lower income countries may prefer LEEP due to the additional risks associated with invasive surgery. This recommendation applies to women regardless of HIV status.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ / No ☒	The quality of evidence was very low due to imprecise data.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☐ / No ☒	Recurrence of AIS is probably lower with CKC than with LEEP. It was unclear whether harms, such as preterm delivery or spontaneous abortions, were greater with CKC or LEEP.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☐ / No ☒	A high value was placed on the risk of recurrence. The panel felt the preferences of women may be variable as women in higher income countries may not have as much aversion to CKC (e.g. anaesthesia), while women in lower income countries – where there may be other risks from invasive surgery – may prefer LEEP.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	The resources are greater for CKC than LEEP; however, the panel agreed that the benefits from CKC were worth the resources.

Evidence profile 7: Should LEEP or CKC be used in women with histologically confirmed AIS?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects *Time frame is 12 months*	
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence by outcome** (confidence in the estimate)	**With CKC**	**With LEEP**	**Relative effect** (95% CI)	**Risk with CKC**	**Risk difference with LEEP** (95% CI)
Recurrence/residual AIS											
394 (7 non-randomized studies) 30–82 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	14/257 (5.4%)	9/137 (6.6%)	**RR 1.56** (0.64 to 3.52)	**54 recurrences per 1000**	**31 more recurrences per 1000** (from 20 fewer to 137 more)
Invasive adenocarcinoma											
264 (3 non-randomized studies) 30–82 months	no serious risk of bias2	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to imprecision	6/174 (3.4%)	2/90 (2.2%)	**RR 2.43** (0.52 to 9.18)	**34 cancers per 1000**	**49 more cancers per 1000** (from 17 fewer to 282 more)
Preterm delivery											
49 (1 non-randomized study) 51 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	2/39 (5.1%)	0/10 (0%)	**OR 0.71** (0.03 to 16.06)	**51 preterm deliveries per 1000**	**14 fewer preterm deliveries per 1000** (from 50 fewer to 413 more)
Spontaneous abortions per pregnancy											
49 (1 non-randomized study) 51 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	6/39 (15.4%)	2/10 (20%)	**OR 1.38** (0.23 to 8.13)	**154 abortions per 1000 pregnancies**	**47 more abortions per 1000 pregnancies** (from 114 fewer to 443 more)

Footnotes:

1 Very few events and participants, resulting in wide confidence intervals including both reduction or increase in events with LEEP.

2 Not all studies reported whether invasive cancer had occurred or not.

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