

Question 7

For women who are HPV positive with AIS or possible high-grade glandular lesion cytology or biopsy confirmed AIS what is the safety and effectiveness of LLETZ, Fischer Cone, Laser Cone, SWETZ or NETZ compared with cold knife cone biopsy?

Search words: AIS, adenocarcinoma in situ, ACIS, HGGA, HGGL, glandular dysplasia/abnormality/lesion, AGUS, atypical endocervi*, atypical gland*, excision, cone biopsy, conisation, CKC, loop electro-excisional procedure, LLETZ, SWETZ, laser con*, Fischer cone, electro-surg*. HPV was not added as a search term to keep the search as wide as possible.

1. Summary table of studies comparing CKC with other excisional modalities

Author	Country	Study type	Subjects	Findings
Munro et al, 2015	Australia	Retrospective population based cohort	338 women diagnosed on LEEP or CKC between 2001 and 2012 with ACIS identified from the Cervical Screening Register of WA. Mean age was 33.2y (range 18- 76y) Median follow-up = 3.6y (<1 year- 11.8y) CKC N = 231 LEEP N = 107	<p>Positive margins were found in 34 LEEP biopsies (32%) and 59 CKC specimens (25.5%). LEEP was associated with a greater likelihood of more than one surgical specimen being excised compared to CKC.</p> <p>Overall, 27 (8.0%) patients had ACIS persistence/recurrence and a further 9 (2.7%) patients were diagnosed with adenocarcinoma during the follow-up. No patient died of cervical cancer. Positive margin status was associated with disease persistence/ occurrence Risk = 3.4 (95%CI = 1.5 – 7.8) After adjusting for margin status there were no significant differences in the incidence of persistent and/or recurrent neoplasia according to the type of procedure.</p> <p>The authors concluded that LEEP and CKC appeared equally effective in the treating ACIS but patients should be closely monitored, particularly if biopsy margins are positive in initial excision specimens because these patients were 3.4 times more likely to have disease persistence or recurrence.</p>
Baalbergen et al, 2015	Netherlands	Retrospective cohort	132 cases of AIS diagnosed between 1989-2012 of which 124 were treated with LEEP, CKC or LC and 8 with hysterectomy. Mean age at diagnosis = 37y	For CKC 65/69 had known margin status of which 12 (18%) were positive. For LEEP 45/52 had known margin status of which 40% were positive. The 3 patients who had LC had negative margins. 53/124 patients initially treated, had further therapy 9m after initial diagnosis; 1 had LEEP, 14 had CKC, 1 had CKC and hysterectomy and

			CKC N = 69 LEEP N = 52 LC N = 3	37 had hysterectomies. Of the 86 women who continued with conservative treatment 2 (1 negative margin other could not be evaluated) had recurrences after CKC and 1 (negative margins) after LEEP, within 24m after therapy. Overall FU was 62m (2-217m) and recurrence after conservative therapy by CKC, LEEP or laser was not significantly different than after hysterectomy (p=0.56).
Latif et al, 2015	US	Retrospective cohort	115 conization procedures in patients with a pre-op or post-op diagnosis of ACIS of the cervix from 1997-2011. Treatment choice determined by treating physician; generally a LEEP was undertaken when the entire lesion judged the entire lesion visible on colposcopy could be removed in one pass Mean age = 34y (range 20-65y). Conization with therapeutic intent CKC N = 48 Median follow-up = 24m LEEP N = 30 Median follow-up = 72m	For 78 patients who underwent conization with therapeutic intent, there were no significant differences in rates of positive margins (20% vs 17%), recurrence of ACIS (6.7% vs 8.3%), or subsequent development of invasive adenocarcinoma (0 vs 2%) between LEEP and CKC, respectively. There was no significant difference in the rate of repeat procedures after primary conization between LEEP and CKC (23.3% vs 18.7%) or hysterectomy after LEEP/CKC (10% vs 6%). There were 4 recurrences of ACIS (all had negative margins at first procedure) in the CKC group and 2 (one had negative margins in first procedure in the LEEP group). The authors concluded that LEEP is as good as CKC in the treatment of a preoperative diagnosis of ACIS of the cervix in all age groups.
Taylor et al, 2014	US	Retrospective cohort	52 patients with histologically confirmed AIS from 1998-2011, treated with either LEEP or CKC. Treatment choice was determined by the standard practice of the treating physician. Mean age = 33y (range 17-51y) CKC N = 37 LEEP N = 15	There was no significant difference in rate of positive margins between LEEP and CKC (40% vs. 54%, respectively. p = 0.55), nor volumes of tissue excised, nor rate of recurrence . A positive surgical margin was associated with residual disease in 47% of patients with AIS treated with conization. No patient with negative cone margins had recurrent or progressive disease after 32m. The authors concluded that CKC and LEEP were equally efficacious treatments although they stated that comparison of CKC to LEEP was a secondary objective, and because number were small the statistical power to address this question was limited.

Baalbergen et al, 2014	Multiple (mainly US)	Systematic review	16 studies were identified comparing LLETZ to CKC (and in 6 of these comparison with laser conisation was also included) in the literature from 1996-2013	<p>Pooling of data found higher rates of incomplete excision with LLETZ (mean 51%) vs CKC (mean 30%) [laser conisation rate was 28%]. Recurrence rate after LLETZ ranged from 9%- 29% compared to 6% - 11% after CKC – data not shown (based on 2 cohort studies and 2 case series).</p> <p>The authors concluded that, the safety of LLETZ is comparable to CKC when negative margins are achieved and that large loop excision of the transformation zone as treatment will lead to better obstetric outcomes.</p>
Kietpeerakool et al, 2012 (Included in Baalbergen 2014 systematic review)	Thailand	Retrospective cohort	60 women with ACIS or mixed ACIS (with HSIL or LSIL) who had conisation between 1998-2010 in Chiang Mai Hospital. Mean age = 45y (27-66y) CKC N = 23 LEEP N = 37	<p>When adjusted for age and completeness of visualization of the cervical squamocolumnar junction during colposcopy, women who had LEEP were 4 times more likely to have positive cone margins than those who had CKC (95% CI, 1.13–16.43). 54/60 had a second procedure (51 underwent hysterectomy) Residual disease was not found among 26 women who had negative cone margins (12 for LEEP and 14 for CKC), but was observed in 17 (65.4%)/26 women with positive cone margins (P<0.001)</p> <p>(12/20 LEEP and 5/6 CKC biopsies with positive margins).</p>
Van Hanegem et al, 2012 (Included in Baalbergen 2014 systematic review)	US	Retrospective cohort	112 patients with ACIS, age ≤30y, treated with CKC or LEEP between 1998-2010 identified from databases Treatment choice based on the size of colposcopic lesions (smaller for LEEP, larger for CKC). CKC N = 58 LEEP N = 53	<p>The odds ratio for CKC to achieve negative cone margins compared with LEEP was 1.4 (95%CI 0.6-3.5). 25 patients had positive cone margins (11 from CKC group and 14 from LEEP group). There was no difference in residual or recurrent ACIS between patients treated with LEEP vs CKC (3 patients in each group).</p> <p>The authors conclude that although treatments were equally effective, LEEP should be considered the treatment of choice for these patients because of more favourable obstetric outcomes based on 2 meta-analyses of studies (Kyrgiou et al, 2006; Arbyn et al, 2008).</p>
Darymple et al, 2008 (Included in Baalbergen 2014 systematic review)	Australia	Retrospective cohort	82 patients with AIS on their referral smear or confirmed histology at treatment, identified from Royal Prince Alfred Hospital records. Treatment choice based on specialists' preferences and abilities	<p>The margins of all LC specimens could be assessed. 8/38 of the CKC biopsies and 6/44 from the laser biopsies had positive margins. These were managed either conservatively (3 cases), with repeat conisation (3 cases) or hysterectomy (8 cases). During FU there were no recurrences of glandular neoplasia in either group. 4 women in the CKC group and 4 in the LC group</p>

			<p>CKC N = 38 Mean age = 34y (range 22-62y) Follow-up = 1-9y Laser cone (LC) N = 44 Mean age = 38y (range 23-65y) Follow up = 1-10y</p>	<p>subsequently developed abnormal smears (1HGSIL in each group). There were no complications in the CKC group and 1 patient with heavy bleeding in the LC group.</p> <p>The authors concluded LC biopsy is as effective as CKC but in the absence of clear evidence for either approach in the literature, management must be individualized by discussion with a fully informed patient.</p>
<p>Young et al, 2007 (Included in Baalbergen 2014 systematic review)</p>	US	Retrospective chart review	<p>74 patients with a diagnosis of AIS on cervical conisation treated between 1988-2006. Median age = 31y (range 18-73y). CKC N = 52 LEEP, laser or Fisher excision N = 20</p>	<p>There was no significant difference in the depth of specimen between CKC and the other groups. 15 (29%) in the CKC group had positive margins vs 6 (30%) in the alternative procedures and 1 (2%) in the CKC group had indeterminate margins vs 4 (20%) in the alternative procedures thus overall patients undergoing CKC were more likely to have negative margins (69% for CKC vs 50% for other, p=0.013). 55% of patients with positive margins and 13% of those with negative margins were diagnosed with residual or recurrent disease.</p>

Abbreviations: AIS: adenocarcinoma in situ, CKC: cold knife cone; FU: follow-up; LEEP: loop electrosurgical excision procedure; m: months; y: years;

2. Summary tables of excision modality studies for the treatment of CIN2 or CIN3

Author	Country	Study type	Subjects	Findings
Camargo et al,	Brazil and	randomised	103 women with indication to treat	52 women allocated to LLETZ-cone group and 51 to SWETZ. 10

2015	Ireland	controlled trial	CIN located at cervical canal, randomised to receive LLETZ cone or SWETZ recruited between 1999-2004. Mean ages 45.6y in LLETZ group and 43.7y in SWETZ group.	women were lost for main outcome because of damaged specimens. 42 women in the LLETZ group had free endocervical margin versus 43 women in the SWETZ group (RR 1.04, 95% CI 0.87–1.25; P = 0.64). For secondary outcomes related to margins, RR of 1.15 (95% CI 0.95–1.39; P = 0.15) for ectocervical free margin. For free stromal margin, the RR was 1.07 (95% CI 0.89–1.29; P = 0.47). No death was observed 1y after. The study was inconclusive; SWETZ and LLETZ were equally effective to treat endocervical disease, with no difference in protecting against margin involvement. Fragmentation of sample during excision in 14% of LLETZ cases vs 4% of SETZ cases. Higher, but not severe, blood loss and longer surgical time were observed in the SWETZ group.
Khalid et al, 2012	Ireland	Retrospective observational study	321 women who had LLETZ treatment for CIN between 1999-2002 and then had a pregnancy and eligible for study inclusion. All women were under 42y old.	Of 321 women, 245 (76.3%) delivered at term, 9.1% delivered at <37 weeks of gestation and 14.6% miscarried at <24 weeks of gestation. There was a three-fold increase in the risk of pre-term labour (PTL) if the excision volume exceeded 6 cm ³ (RR = 3.00; 95% CI 1.45–5.92), or when the thickness of the excised tissue was greater than 12 mm (RR 2.98; 95% CI 1.27–7.01) but no difference in risk related to the length of the tissue. All were single piece excisions; no top hat excisions were performed. The time interval between LLETZ and pregnancy did not have an effect on PTL rates (mean 25.7m). There was no association between the grade of CIN and risk of PTL
Carcopino et al, 2013	France and Ireland	Retrospective multicentre observational study	436 women who had a LLETZ excision for CIN identified from participants included in 2 cohort studies, one conducted in France (2005-2009) and one in Ireland (2007-2010). Women grouped into those having LLETZ guided by previous colposcopy, those having LLETZ immediately after colposcopy and those having LLETZ under direct colposcopic vision (DCV)	Compared to LLETZ guided by previous colposcopy report only and to LLETZ preformed immediately after colposcopy, colposcopy with DCV resulted in significantly higher rate of clear margins: 33 (52.4 %), 104 (68.0 %) and 142 (84.5 %), respectively (p<0.001). In multivariate analysis, when compared with the use of previous report or with colposcopy immediately before the LLETZ, DCV resulted in significantly higher probability of negative margins (Adjusted odds ratio (AOR): 4.61; 95 % CI: 2.37–8.99 and AOR: 2.55; 95 % CI: 1.47–4.41), combined negative margins and depth <75th percentile (AOR: 3.67; 95 % CI: 1.97–6.86 and AOR: 3.05; 95 % CI: 1.91–4.87) and combined negative margins and volume <75th percentile (AOR: 12.96; 95 %CI: 5.99–28.05 and AOR: 6.16; 95 % CI: 3.75–10.14), respectively. The authors recommended LLETZ for the treatment of CIN should routinely be performed under DCV. Confounding bias due

				to physicians' expertise could not be eliminated and large randomised trials were recommended to validate the findings.
Allam et al, 2005	UK	Retrospective review	666 women treated with large loop excision and cold coagulation (LLECC) with the Semm Cold Coagulator from 1992-2000. Mean age 33y	At initial presentation 576/666 women had CIN2 or CIN3 and 90 had CIN1. Of 524 women who had high grade CIN initially and 6m follow-up information, 22 (4.2%) had an abnormal smear 6m after LLECC and had further treatment. Of the remaining 502, 3 had abnormal cytology at 12m. Of the 79 who had low grade CIN, 3 had an abnormal smear at 6m and none of 66 who attended the 12m visit had abnormal cytology at 12m. Out of 577 cases noted by the pathologist, excision of CIN was complete in 417 and incomplete in 91. Of the latter, 16 had an abnormal cytology at 6m and 2 women at 12m. Short term bleeding complications (within 24h) occurred in 3 of 275 cases for which there was information. 1 woman needed sutures. The authors concluded that this method was a new and effective approach for the treatment of CIN.

Possible useful information

Polterauer et al (2013) stated in a recent review that There are several potential arguments for CKC to be the preferred method in the treatment of AIS. Surgical margins show less thermal artifacts after CKC and typically more tissue is removed by CKC compared with laser and electrosurgical conization. In addition, LEEP and laser cone biopsies often are fragmented making evaluation of margins difficult. This occurs typically with larger lesions, in which several loop passes have to be performed to excise the lesion completely. The authors recommend performing CKC or large loop excision of the transformation zone (LLETZ) when AIS is diagnosed by colposcopically guided biopsies or endocervical curettage, for large AIS lesions, and especially when conization is performed as a definitive treatment in patients desiring to preserve fertility.

The 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors by the American Society for Colposcopy and Cervical Pathology (Massad et al, 2013) stated that:

- Diagnostic excision for AIS using any modality is allowed but care must be taken to keep the specimen intact and margins interpretable, avoiding fragmentation of the specimen, including "top-hat" serial endocervical excisions. This may require use of larger loops than those employed to excise visible squamous lesions.

- If the margins of the specimen are involved or endocervical sampling obtained at the time of excision contains CIN or AIS, re-excision to increase the likelihood of complete excision is preferred.
- Re-evaluation at 6 months using a combination of HPV DNA testing and cytology co-testing and colposcopy with endocervical sampling is acceptable in this circumstance.
- Long-term follow-up is recommended for women who do not undergo hysterectomy.

In a study by Costa et al (2012) in which 119 women who were treated conservatively for AIS and followed-up (mean 40.9 m) using colposcopy, PAP-smear, biopsy and HPV-testing with Hybrid Capture 2, testing HR-HPV positive at any time point during FU was the most significant independent predictor of progressive disease, while showing free margins in cone had a significant protective effect against progression to Adenocarcinoma. Furthermore, because 4.3% women with persistent, recurrent or progressive disease experienced a late (5th and 6th FU) diagnosis of HG-CGIN or microinvasive AC, the authors recommended that close surveillance should be scheduled for at least three years in conservatively treated AIS patients.

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