Question 4 Literature review

PICO Question 4: For HPV positive women currently not in treatment follow-up who have undergone colposcopy (without treatment) with colposcopy LSIL (low-grade intraepithelial lesion) and CIN 1 or less on biopsy, what is the safety and effectiveness of:

1. repeat HPV test at 12 months if referral cytology was negative or possible/definite low-grade squamous intraepithelial lesion (p/d LSIL)
2. excisional treatment if referral cytology was possible/definite high-grade intraepithelial lesion (p/d HSIL)

compared with repeat cytology and HPV testing in 12 months?

Population	Study design	Intervention	Control	Outcome
HPV positive women, who have undergone colposcopy and colposcopy LSIL, confirmed by biopsy CIN1 or less, and referral cytology was: i. negative or p/d LSIL or ii. p/dHSIL	Randomized or pseudo randomized controlled trial	Excisional treatment or Repeat HPV test at 12 months	**i. Negative cytology or p/dLSIL:** Repeat cytology and HPV testing at 12 months: Colposcopy if HPV positive test or if cytology pHSIL or worse; If HPV negative and cytology negative or p/dLSIL: repeat HPV and cytology test at 24 months **ii. p/dHSIL**: repeat cytology and colposcopy in 6 months	Cervical cancer mortality Cervical cancer diagnosis Precancerous high grade lesion detection

CIN1: cervical intraepithelial neoplasia grade one; dLSIL = definite LSIL; LSIL = low-grade squamous intraepithelial lesion; pLSIL = possible LSIL; HSIL: high-grade intraepithelial lesion

Abbreviations: LBC: liquid based cytology; ECC: endocervical curettage; NILM: negative for intraepithelial lesion or malignancy; ASCUS/ASC-US: atypical squamous cells of undetermined significance; AGUS: atypical glandular cells of undetermined significance; AGC: atypical glandular cells; LSIL/LGSIL: low-grade intraepithelial lesion; ASC-H: atypical squamous cells, possible high-grade lesion; HSIL: high-grade intraepithelial lesion; CIN: cervical intraepithelial neoplasia; TZ: transition zone; RR: relative risk; CI: confidence interval

1. Existing guidelines

Table 1: Existing guidelines on the management of women CIN1 or less on biopsy

Guideline	Author/ Organisation Country	Year	Evidence base	Recommendation
2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors Massad et al., for the 2012 ASCCP Consensus guidelines conference (2013). 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Lower Genital Tract Disease 17(5): S1 – S27	**American Society for Colposcopy and Cervical Pathology**.	2012	Consensus based on literature searches and Kaiser Permanente Northern California data	**Management of Women with CIN 1 or No Lesion Preceded by ''Lesser Abnormalities''** (ASCUS, LSIL, HPV 16/18+, persistent HPV) Co-testing at 1 year is recommended (BII). **Management of Women with CIN 1 or No Lesion Preceded by ASC-H or HSIL** When CIN 2+ is not identified histologically, either a diagnostic excisional procedure or observation with co-testing at 12 months and 24 months is recommended, provided in the latter case that the colposcopic examination is adequate and the endocervical sampling is negative. (BIII).
Colposcopic management of abnormal cytology and histology 2012 Bentley et al., (2012) Colposcopic management of abnormal Cervical Cytology and histology J Obstet Gynaecol Can 34 (12) 1188-1202	Society of Obstetricians and Gynaecologists of Canada	2102	Unclear if evidence based	The preferred option for biopsy-proven CIN 1 is observation with repeat assessment at 12 months with cytology testing. (Colposcopy at 12 months is an acceptable option.) Management should be according to the cytology result. (II-1B) In the case of a patient with biopsy-proven CIN 1 after HSIL or AGC, cytology and histology should be reviewed, where available. If a discrepancy remains, then an excisional biopsy may be considered. (III-B)
European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, Part 2 2009 Jordan et al., (2009) Cytopathology 20:5-16	Jordan et al	2009	Unclear if evidence based	**CIN1 management** Two options can be recommended: follow-up or treatment. Follow-up consists of repeat cytology at 12 and 24 months or hrHPV DNA testing at 12 months, with referral for colposcopy when cytology reports atypical squamous cells of undetermined significance (ASC-US) or a more serious lesion or when the HPV test is positive.

2. Table 2: Study characteristics

Study	Study Design	Population	Prognostic factors	Follow-up	Outcome	Comment/Results
Pacchiarotti 2014 Italy	Prospective cohort	Women in a screening program recruited from 2008 and 2010 with negative (n=248) or CIN1 (n=113) histology on colposcopy-guided biopsy and at least one follow-up N=361 Aged 24-64 years	**Baseline** Cytology	Cytology and HPV triage?	CIN3 CIN2+ Follow-up 1.86 years (mean)	Criteria for colposcopy referral and follow-up not explicitly stated HPV triage was usually performed on ASC-US cytology at any age and women over 35 years with LSIL During follow-up, colposcopy guided biopsies were only performed if a lesion was visible; ECC was performed if the TZ was not visible
Katki 2013 (KPNC) USA	Prospective cohort	Women screened from 2003 to 2010 with HPV-positive/ASC-US, LSIL or worse cytology with CIN1/negative colposcopy (a biopsy result of CIN1 or normal/metaplasia, normal colposcopy without biopsy or presumed normal colposcopy exam) With at least 1 follow-up test N=20,319 Aged ≥ 25 years	**Follow-up** Cytology Hr-HPV **Baseline** Cytology	Predominantly cytology and HPV testing but unclear as to whether all HPV positive women referred for colposcopy during follow-up	CIN2+ CIN3+ Follow-up 7 years (maximum)	Criteria for colposcopy referral and follow-up not explicitly stated; predominantly co-testing at 6 or 12 months For screening women with HPV-positive ASC-US or LSIL or worse referred for colposcopy At least one biopsy was taken at the majority of colposcopies Cumulative 5-year CIN2+ risk associated with baseline cytology calculated starting from the date of first follow-up test 5-year CIN2+ risks calculated from date of last negative follow–up test Only raw data present for CIN3+

Litjens 2013 The Netherlands	Retrospective	CIN3 cervical biopsy specimens – only patients that did not have a therapeutic biopsy (i.e. LLETZ or conisation) between CIN1 and CIN3 diagnosis (44/1474, 3%)
		Paired CIN3 and CIN1 lesions – tested for hrHPV
		
		Study reviewed patients with a CIN3 and previous CIN1 diagnosis and reviewed HPV genotyping to determine progression rate and if change in HPV genotype
			HPV status
			• hrHPV
			• HPV genotype
					CIN3	• hrHPV positive:
						  ○ CIN1: 57%
						  ○ CIN3: 90%
						• Most frequent HPV genotype(s):
						  ○ CIN1: HPV16 and HPV31
						  ○ CIN3: HPV16
						• HPV genotype differed between paired CIN1 and CIN3 lesion in 63%
						• Time interval between CIN1 and CIN3 lesion was on average 28 months (range: 1 month to 14 years)
						• Cytological diagnosis leading to CIN1 biopsy was HSIL in 58% with a change in HPV genotype and in 64% of those with the same HPV genotype

Matsumato 2012	Prospective cohort	554 women with LSIL cytology and histologic diagnosis of CIN1 or less on baseline colposcopy(biopsy-negative n=64; CIN1 histology n=491) Secondary analysis of data from cohort study conducted by Japan HPV and Cervical Cancer (JHACC) Study Group identifying determinants of LSIL/CIN regression and progression	Histology hrHPV status	Cytology and colposcopy testing every 3-4 months for 2 years; colposcopy-guided biopsy if cytology HSIL	CIN3+ Follow-up 2 years	Regression: defined as normal colposcopy result and at least two consecutive normal smears Biopsy-negative LSIL group versus LSIL/CIN1: • %hrHPV positive: 62.1% vs78.4%, p=0.01 • cumulative risk of CIN3+ in 2 years: 0% vs 5.5%, p=0.07 • cumulative probability of regression:

		Aged 18-54 years				○ within 12 months: 71.2% vs 48.6%, p=0.0001 ○ within 2 years: 75.1% vs 64.0%, p=0.003 • median time to regression: 6.3 months vs 12.4 months hrHPV status and probability of regression at 12 months: • biopsy-negative LSIL: similar between hrHPV positive and hrHPV negative (67.3% vs 74.4%, p=0.74) • LSIL/CIN1: significantly influenced by hrHPV detection (hrHPV positive 45.2% vs hrHPV negative 62.6%, p=0.006)
Lanneau 2007 USA	Retrospective cohort	Women with HSIL referral cytology and either normal or CIN1 histology and as a result underwent loop electrocautery excision procedure (LEEP) of transformation zone (TZ) N=59 Age range 19-58 years (median 26.8)	**Baseline** Histology	Not applicable	CIN3 Cross-sectional	Only included women with satisfactory colposcopic examination **Additional results** 27/59 women underwent a LEEP cone surgery – no new CIN3 found on second pass
Pretorius 2006 USA	Retrospective cohort	Women with ASCUS or LSIL cytology with colposcopic diagnosis of CIN1 or less (1998 – 2005) and a follow-up visit (N=2490) • 2250 (90%) women had baseline biopsy • 1288 women had colposcopic impression of HPV or CIN1 • 1239 women had biopsy or ECC of HPV or CIN1 • 1251 women had negative biopsy and ECC Aged 13-87 years (median = 26.8 years)	**Baseline** Colposcopic impression Histology Cervical Hr-HPV status Age	Not described	CIN3+ Follow-up 26.3 months (median)	**Additional results** The rate of subsequent CIN3+ was not affected by the colposcopic impression (normal vs HPV or CIN1, p=0.24) nor result of the initial biopsy result (normal vs HPV or CIN1, p=0.66) Increasing risk of subsequent CIN3+when initial hrHPV was positive (p=0.0002) and with increasing age (p=0.045) ASCUS includes some ASC-H
ALTS Walker 2006 USA	Prospective cohort	Participants in ALTS, a randomised controlled trial comparing 3 management strategies in women referred for ASCUS (n=3488) or LSIL (n=1572) cytology, recruited 1999-2000. With an initial colposcopy/biopsy of <CIN2 (29% no biopsy deemed necessary, 34% negative biopsy, 36% CIN1 on biopsy) Who underwent a second colposcopy and had cytology specimen collected at least 6 months later. N = 1976 Aged ≥ 18 years	**Follow-up** hr-HPV Cytology	Cytology every 6 months for 2 years and sent to colposcopy if cytology was HSIL	CIN3+ CIN2+ Follow-up 24 months (median)	ASCUS includes ASC-H Exit colposcopy at 2 years scheduled for all women Follow-up cytology specimens analysed for hr-HPV **Additional results** Hr-HPV follow-up test • Sensitivity for CIN3 = 84% • PPV for CIN3 = 12% cytology (≥ HSIL) follow-up • Sensitivity for CIN3 = 23% • PPV for CIN3 = 42% cytology (≥ HSIL) and hr-HPV follow-up • Sensitivity for CIN3 = 84% • PPV for CIN3 = 12%

ALTS Castle 2011 USA		Participants in ALTS who underwent colposcopy at baseline: 1. regardless of HPV status OR 2. if HPV-positive ASCUS or HPV-positive LSIL With a colposcopy result of ≤CIN1 who underwent exit visit at 2 years or were treated: • 594 women with CIN1 • 289 women with negative histology • 281 women referred to colposcopy but no biopsy Aged ≥ 18 years	**Baseline** Colposcopy result Cytology Hr-HPV	Cytology every 6 months for 2 years and sent to colposcopy if cytology was HSIL	CIN3+ Follow-up 2 years	Exit colposcopy at 2 years was scheduled for all women ASCUS includes ASC-H HPV triage arm for management of LSIL was closed early as more than 80% LSIL were HPV positive **Additional results** Taking HPV genotype into account, having CIN1 (compared with no CIN1) was not a risk factor for developing CIN3 (OR 0.99, 95%CI 0.54-1.8)
			Predictive factors			
Bekker 2008 (Australia)	Retrospective cohort; predictive accuracy	Satisfactory colposcopies undertaken between 1999- 2004 at the Royal Women's Hospital, Carlton, Victoria, Australia. N = 18,421 Punch biopsies N = 6,020 HSIL on colposcopy N = 1,710 LSIL on colposcopy N = 4,310 Referral smear results available N = 3,510	Impact of referral cytology on positive predictive value of colposcopic impression		LSIL on biopsy HSIL on biopsy	**For detection of HSIL on biopsy** *If high grade abnormality on cytology* Colpsocopic assessment of HSIL had a sensitivity of 76% and a positive predictive value of 73% *If low grade abnormality on cytology* Colpsocopic assessment of HSIL had a sensitivity of 26% and a positive predictive value of 48% **For detection of LSIL on biopsy** *If high grade abnormality on cytology* Colpsocopic assessment of LSIL had sensitivity of 46% and positive predictive value of 34%

3. Study results - This review focuses on CIN3+ outcomes which is considered a surrogate outcome for cervical cancer

3.1 REFERRAL CYTOLOGY NEGATIVE OR p/d LSIL

3.1.1: Studies in HPV-positive women with **negative or p/d LSIL referral cytology** comparing follow-up with HPV testing to follow-up with cytology and HPV testing: no studies found

3.1.2: Prognostic value of **follow-up cytology and/or HPV status** for women with negative or p/dLSIL referral cytology – 2 studies

Study	Study design	Population	Follow-up	Follow-up cytology	Follow-up hr-HPV	N	Length of follow-up	CIN3+ n	CIN3+ risk
Walker 2006 (ALTS)	Prospective cohort Aged ≥ 18 years	Women with **ASCUS** (includes ASC-H) **OR LSIL** referral cytology and **< CIN2** Hr-HPV status not reported	6 monthly cytology with colposcopy if HSIL cytology or exit colposcopy at 2 years scheduled for all women	All	negative	962	24 months (median)	19	2.0%
					positive	874		103	11.8%
				Normal	negative or positive	1157		36	3.1%
					negative	726		9	1.2%
					positive	344		25	7.3%
				ASCUS (includes ASC-H)	negative or positive	466		37	7.9%
					negative	199		10	5.0%
					positive	240		26	10.8%
				LSIL	negative or positive	273		25	9.2%
					negative	25		0	-
					positive	225		24	10.7%
				HSIL	negative or positive	69		29	42.0%
					negative	4		0	-
					positive	62		28	45.2%
Katki 2013 (KPNC)	Prospective cohort Aged ≥ 25 years	Women with **HPV- positive ASC-US OR LSIL** referral cytology and **< CIN2**	Predominantly cytology and HPV testing but unclear as to whether all HPV positive women referred for colposcopy during follow-up	one negative smear		11389	7 years (maximum)	81	0.7%
				two negative smears		5019		24	0.5%
					one negative test	6970		17	0.2%
					two negative tests	2649		7	0.3%
				one negative cotest		5939		6	0.1%
				two negative cotests		1963		3	0.2%

3.1.3: Prognostic value of **baseline** **colposcopic impression, histology, cytology and/or HPV status** for women with negative or p/dLSIL referral cytology – longitudinal studies – 5 studies

Study	Study design	Baseline histology/colposcopic impression	Baseline cytology	Baseline Hr-HPV status	N	Length of follow-up	CIN3+ n	CIN3+ risk (95%CI)
Baseline HPV								
Pretorious 2006	Retrospective cohort Aged 13 - 87 years	Colposcopic diagnosis of ≤ CIN1	ASCUS or LSIL	negative	530	26.3 months (median)	2	0.4%
				positive	1960		45	2.3%
Baseline cytology								
Pacchiarotti 2014	Prospective cohort Aged 24 - 64 years	< CIN2 diagnosis	ASC-US	NR	89	1.86 years (mean)	0	0%
			LSIL	NR	264		2	0.8%
Baseline HPV and cytology								
Katki 2013 (KPNC)	Prospective cohort Aged ≥ 25 years	< CIN2 diagnosis	ASC-US	positive	9936	7 years (maximum)	219	2.2%
			LSIL	positive or negative	7161		132	1.8%
Baseline histology, HPV and cytology								
Castle 2011 (ALTS)	Prospective cohort Aged ≥ 18 years	CIN1 histology	ASCUS	positive	300	2 years	24	8.0% (5.2-11.7)
			LSIL	negative or positive	294		37	12.6% (9.0-16.9)
		negative histology	ASCUS	positive	186		16	8.6% (5.0-13.6)
			LSIL	negative or positive	103		5	4.9% (1.5-10.7)
		colposcopy no biopsy	ASCUS	positive	188		10	5.3% (2.6-9.6)
			LSIL	negative or positive	93		8	8.6% (3.8-16.2)
Baseline histology and cytology								
Castle 2011 (ALTS)	Prospective cohort Aged ≥ 18 years	CIN1 histology	ASCUS	negative or positive	244	2 years	18	7.4% (4.4-11.4)
			LSIL	negative or positive	238		32	13.4% (9.4-18.4)

		negative histology	ASCUS	negative or positive	259		12	4.6% (2.4-8.0)
			LSIL	negative or positive	81		4	4.9% (1.4-12.2)
		colposcopy no biopsy	ASCUS	negative or positive	268		11	4.1% (2.0-7.2)
			LSIL	negative or positive	64		5	7.8% (2.6-17.3)
Baseline histology								
Pretorious 2006	Retrospective cohort Aged 13 - 87 years	negative histology	ASCUS or LSIL	negative or positive	1251	26.3 months (median)	22	1.8%
		HPV or CIN1 histology			1239		25	2.0%
Castle 2011 (ALTS)	Prospective cohort Aged ≥ 18 years	colposcopy no biopsy	ASCUS or LSIL	negative or positive	332	2 years	16	4.8%
		negative histology			340		16	4.7%
		CIN1 histology			482		50	10.4%
Matsumato 2012	Prospective cohort Aged 18 - 54 years	negative biopsy	LSIL	negative or positive	64	2 years	0	0.0%
		CIN1 histology			479		NR	5.5%
Baseline colposcopic impression								
Pretorious 2006	Retrospective cohort Aged 13 - 87 years	normal colposcopic impression	ASCUS or LSIL	negative or positive	1202	26.3 months (median)	26	2.2%
		HPV or CIN1 colposcopic impression			1288		21	1.6%

3.2. REFERRAL CYTOLOGY p/dHSIL

3.2.1. Studies in HPV-positive women with p/dHSIL referral cytology **comparing excisional treatment to follow-up with cytology and HPV testing**: no studies found

3.2.2. Prognostic value of **follow-up cytology and/or HPV status** for women with p/dHSIL referral cytology – 1 study

Study	Study design	Population	Follow-up	Follow-up cytology	Follow-up hrHPV	N	Length of follow-up	CIN3+ n	CIN3+ risk
Katki 2013 (KPNC)	Prospective cohort Aged ≥ 25 years	**ASC-H** referral cytology and < CIN2	Predominantly cytology and HPV testing but unclear as to whether all HPV positive women referred for colposcopy during follow-up	one negative smear		798	7 years (maximum)	11	1.4%
					one negative test	550		4	0.7%
				one negative cotest		456		1	0.2%
		≥ HSIL referral cytology and < CIN2		one negative smear		286		4	1.4%
					one negative test	185		3	1.6%
				one negative cotest		144		0	0.0

3.2.3: Prognostic value of **baseline cytology and/or HPV status** for women with p/dHSIL referral cytology – 2 longitudinal studies

Study	Study design	Baseline histology	Baseline cytology	Baseline hrHPV status	N	Length of follow-up	CIN3+ n	CIN3+ risk
Baseline cytology								
Pacchiarotti 2014	Prospective cohort Aged 24 - 64 years	< CIN2 diagnosis	ASC-H	NR	7	1.86 years (mean)	0	0%
			HSIL	NR	4		1	25%
Katki 2013 (KPNC)	Prospective cohort Aged ≥ 25 years	< CIN2 diagnosis	ASC-H	positive or negative	1189	7 years (maximum)	59	5.0%
			≥ HSIL	positive or negative	549		57	10.4%

3.2.4 Predictive value of **baseline histology** for women with p/dHSIL referral cytology – cross-sectional study

Study	Study design	Baseline histology	Baseline cytology	hrHPV status	N	CIN3 n	CIN3 risk on LEEP
Lanneau 2007	Retrospective cohort Aged 19-58 years	**normal** histology	HSIL	NR	34	14	41%
		CIN1 histology	HSIL	NR	25	16	64%

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