

General review for Questions 2c

PICO question 2c

For women who are HPV positive with p/dHSIL referral cytology and p/dHSIL after cytologic review and colposcopy is negative, what is the safety and effectiveness of cytologic and colposcopic follow-up at 3-6 months compared with excision of the transformation zone?

Population	Study design	Intervention	Control	Outcome
HPV positive women who have undergone colposcopy and the colposcopy was negative and referral and review cytology was p/d HSIL	Randomized or pseudo randomized controlled trial	Conservative management; cytologic and colposcopic follow-up at 3-6 months	Excision of the transformation zone	Cervical cancer mortality Cervical cancer diagnosis Precancerous high grade lesion detection

dHSIL = definite HSIL; HSIL = high-grade squamous intraepithelial lesion; pHSIL = possible HSIL

Definitions

A negative colposcopy is a colposcopy in which no abnormalities are seen: it does not include the subsequent reports on any biopsy taken.

Background to this general review

A systematic search of the literature found no studies that directly addressed this question (Please see Question 2c systematic review report). As a result it was decided to undertake a general review of the literature on the management of women with p/dHSIL cytology and a negative colposcopy to inform the drafting of relevant consensus-based recommendations.

GENERAL REVIEW OF THE LITERATURE

Existing guidelines

1. Current (2005) Australian guidelines

Women with possible high-grade squamous lesions - If the cervical TZ is fully visible and is found to be normal, then an option is to closely observe the patient (Figure 7.1 – Pap and colposcopy repeated at 3-6 months) – (Comment - not an actual recommendation)

2. Other existing potentially relevant guidelines

Guideline	Organisation	Evidence-based?	Recommendation
2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors	American Society for Colposcopy and Cervical Pathology	Consensus based on literature searches and Kaiser Permanente Northern California data	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).
2012 Colposcopic management of abnormal cervical cytology and histology	Society of Obstetricians and Gynaecologists of Canada	Unclear as to evidence base	Managing HSIL on referral for colposcopy In the absence of an identifiable lesion at colposcopy, whether satisfactory or unsatisfactory, an endocervical curettage and directed biopsies should be performed. (III-B) With an ASC- H Pap smear, the finding of negative colposcopy does not automatically warrant a diagnostic excisional procedure. (III-E)
2009 European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, Parts 1 and 2	European Cancer Screening Network and European Cancer Network	Unclear if evidence based	If colposcopy is satisfactory and colposcopy and biopsy rule out the presence of high-grade CIN, a review of cytology and histology is recommended. Management should be decided according to the reviewed diagnosis. If the cytological interpretation of HSIL is upheld, excision of the TZ is recommended provided the woman is not pregnant. Cyto-colposcopic discrepancies – high grade abnormal cytology confirmed on review A second colposcopy is required. If the SCJ is visible and no colposcopic abnormality is apparent, the investigation should be completed by a detailed examination of the vagina. If again there is no obvious lesion, the endocervical canal should be assessed as thoroughly as possible. If no abnormality can be seen, then the TZ should be excised in its entirety; this should be combined with an endocervical curettage. Where the presence of HSIL is suspected (ASC-H), and the colposcopy is negative, and when a diagnosis of ASC-US is agreed after review of cytology, colposcopy and histology, a repeat smear at 6 and 12 months or hrHPV DNA test at 12 months is recommended. (Wright 2002 consensus guidelines)

Search Strategy

This review **focused on negative colposcopies** and drew on the articles collected as a result of systematic searches of Medline, Premedline and Embase databases from 2004 onwards that were designed to identify all studies reporting negative or normal colposcopies. We examined these studies for any data for women with an HSIL diagnosis on initial cytology.

Results

Studies following-up women with p/dHSIL initial cytology following a negative colposcopy and **review cytology either LSIL or HSIL – None found**

Studies **following-up** women with p/dHSIL initial cytology following a negative colposcopy – **None found**

Studies **of** women with p/dHSIL initial cytology and a **negative colposcopy – 1 study found (Table 1)**

Table 1: Characteristics and results of studies of women with **p/dHSIL** initial cytology and a subsequent **negative colposcopy – 1 study**

Study	Study design	Population	Results
Lerma Puertas 2011 (Spain)	Prospective cohort? Cross-sectional	Women with no history of abnormal smears who underwent cytology screening between 2000 and 2007 and were diagnosed with HSIL and underwent colposcopy (N = 340) and the colposcopy was normal N = 17 <i>No information as to whether LSIL or HSIL on review cytology</i> Age not reported N = 9 underwent biopsy (endocervical curettage for at least 4) despite normal colposcopy	Women with normal colposcopy n = 17 11.8% (n = 2) diagnosed with cervical adenocarcinoma 11.8% (n = 2) diagnosed with cervical adenocarcinoma in situ Results for the other 13 women not reported HPV status not reported Women with HSIL who underwent biopsy n = 331 4 were diagnosed with cervical adenocarcinoma or cervical adenocarcinoma in situ – all 4 had negative colposcopies

HSIL = high-grade squamous cell lesion (Bethesda); LSIL= low-grade squamous cell lesions

Less relevant or irrelevant studies

Studies of women with p/dHSIL initial cytology and a **negative biopsy** – 1 study found (**Table 2**)

Studies of women with p/dHSIL initial cytology and **CIN2+ disease** examining the contribution of endocervical curettage and random biopsies of normal cervical quadrants to the diagnosis of CIN2+ disease – 1 study found (**Table 3**)

Table 2: Characteristics and results of studies of women with p/dHSIL initial cytology and a subsequent **negative biopsy**

Study	Study design	Population	Results
Lanneau 2007 (USA)	Retrospective cohort Cross-sectional	Women who had undergone LEEP (N = 32) or LEEP cone (N = 27) as a result of HSIL cytology and a normal biopsy (n = 34) or CIN1 (n = 25) histology (2-step discrepancy) N = 59 Mean age = 26.8 years <i>No information as to whether HSIL on review or initial cytology</i>	Normal cervical biopsy: 14/34 (41%) CIN3 on excisional biopsy CIN1 on cervical biopsy: 16/25 (64%) CIN3 on excisional biopsy OR (95% CI) 4.05 (1.1 – 14.6) of CIN3 on LEEP for CIN1 biopsy vs normal histology on biopsy HPV status not reported

CIN1 = cervical intraepithelial neoplasia grade 1; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HSIL = high-grade squamous cell lesion (Bethesda); LEEP = loop electrocautery excision procedure; LSIL = low-grade squamous cell lesions; OR = odds ratio

Table 3: Characteristics and results of studies of women with p/dHSIL initial cytology and **CIN2+ disease** examining the contribution of endocervical curettage and random biopsies of normal cervical quadrants to the diagnosis of CIN2+ disease

Study	Study design	Population	Results
Pretorius 2004 (China)	Cases only Cross-sectional	Women with CIN2+ diagnosis between 2000 and 2002 as a result of a satisfactory colposcopy in which normal quadrants were randomly biopsied and which included endocervical curettage HSIL or cancer smears N = 196 Maximum age range 32-50 years Did not report how many women with HSIL had normal colposcopies	Women with CIN2+ disease and HSIL or cancer smear 290/689 (42.1%) of targeted biopsies were CIN2+ 97/551 (17.6%) of random biopsies of normal cervical quadrants were CIN2+ 75/196 (38.3%) were CIN2+ on endocervical curettage For women with HSIL do not report what % CIN2+ diagnosed by random biopsy or endocervical curettage

CIN = cervical intraepithelial neoplasia; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HSIL = high-grade squamous cell lesion (Bethesda)

References

1. Lanneau GS, Skaggs V, Moore K et al. A LEEP cervical conization is rarely indicated for a two-step discrepancy. *Journal of Lower Genital Tract Disease*. 2007;11:134-137.
2. Lerma PE, Ota SC, Rios Martin JJ et al. Human papillomavirus detection by PCR assay in a large series of high-grade squamous intraepithelial lesions with cytohistological correlation and follow-up. *Acta Cytologica*. 2011;55:426-432.
3. Pretorius RG, Zhang WH, Belinson JL et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. *Am J Obstet Gynecol*. 2004;191:430-43

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