General review for Questions 5b

Question 5b: For women who are HPV positive with atypical glandular cells of undetermined significance (AGUS) or possible high grade glandular lesion (confirmed on review) and negative colposcopy what is the safety and effectiveness of repeating HPV and cytology testing when compared with treatment with excisional cone biopsy?

Population	Study design	Intervention	Control	Outcomes
Women who are HPV positive with AGUS or possible HGGA (confirmed on review) and colposcopy negative	Randomized or pseudo randomized controlled trial	Repeat HPV and liquid based cytology testing at 6 months	Excisional cone biopsy	Cervical cancer mortality Other gynaecologic cancer diagnosis (endometrial, ovarian) Cervical cancer diagnosis Precancerous high grade lesion (including AIS) detection

AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; HGGA = high grade glandular lesion

Definitions

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

Possible high-grade glandular lesion corresponds to the category of atypical glandular cells, possibly neoplastic (AGC-FN) in the 2001 Bethesda System which corresponds to possible high grade glandular lesion.

Background to this general review

A systematic search of the literature found no studies that directly addressed these questions. To assist with the drafting of consensus-based recommendations a general review (this review) was undertaken of the literature reporting outcomes for women with atypical endocervical or glandular cells on cytology and a subsequent negative colposcopy.

GENERAL REVIEW OF THE LITERATURE

Existing guidelines

1. Current (2005) Australian guidelines

Possible high-grade glandular lesion

The flow chart in figure 8.3 indicates the options of cone biopsy or repeat Pap test and colposcopy at 3 months if the cervical TZ is normal. ***(In management flow chart - not an actual recommendation)***

Atypical glandular or endocervical cells of undetermined significance

In the presence of a normal colposcopy and a normal cervical TZ, close observation with a repeat Pap test and colposcopy at six months is an option. ***(Comment - not an actual recommendation)***

2. Other existing potentially relevant guidelines

Title	Organisation	Evidence-based?	Recommendation
2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors Massad et al., (2013) J Lower Genital Tract Disease 17(5): S1 – S27	American Society for Colposcopy and Cervical Pathology.	Consensus based on literature searches and Kaiser Permanente Northern California data	**Management of Women With AGC** For women with AGC not otherwise specified cytology in whom CIN2+ is not identified, co-testing at 12 months and 24 months is recommended. If both co-tests are negative, return for repeat co-testing in 3 years is recommended. If any test is abnormal, colposcopy is recommended. For women with AGC ''favor neoplasia'' or endocervical AIS cytology, if invasive disease is not identified during the initial colposcopic workup, a diagnostic excisional procedure is recommended (AII). It is recommended that the type of diagnostic excisional procedure used in this setting provide an intact specimen with interpretable margins (BII).
2012 Colposcopic management of abnormal cervical cytology and histology Bentley et al., (2012) J Obstet Gynaecol Can 34 (12):1188-1202	Society of Obstetricians and Gynaecologists of Canada	Consensus-based	**Managing atypical glandular cytology** With AGC-NOS cytology and the absence of an identified lesion, women are still at risk of developing a lesion. In this situation, follow-up assessment every 6 months for 2 years includes repeat cytology testing, colposcopy, and ECC.
2008 European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, Part 1 Jordan et al., (2008) Cytopathology 19:342-354	European Cancer Screening Network and European Cancer Network	Unclear if evidence based	When the indication for referral is AGC not otherwise specified and colposcopy reveals no neoplasia, repeat cytology every 6 months for 2 years using additional endocervical brush sampling is recommended. If a woman with AGC suggestive either of neoplasia or endocervical AIS has negative colposcopy, diagnostic conization should be carried out. Cold knife excision is recommended in order to avoid destruction of the margins.

AGC = atypical glandular lesion; AGC-NOS = atypical glandular lesion not otherwise specified; AIS = adenocarcinoma in situ; ASCCP = American Society for Colposcopy and Cervical Pathology; ECC = endocervical curettage

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 glandular abnormalities on initial cytology.

Results:

Studies **following-up** women with **abnormal glandular cytology** and a subsequent negative colposcopy – **1 study found**

Table 1: Characteristics and results of studies following-up women with **borderline glandular*** cytology and a subsequent **negative colposcopy**

Study	Study design	Population	Results
Jadoon 2009 (UK)	Retrospective cohort	Women diagnosed initially or for the second time with borderline glandular cytology* between 2001 and 2005 who were referred for and underwent colposcopy (N = 56) and the **colposcopy was normal** N = 19 Of these, women with follow-up cytology at 6,12, and 24 months N = 18 Age not reported 52/56 underwent some form of biopsy Punch biopsy n = 33 LLETZ n = 12 Punch followed by LLETZ n = 5 Punch/LLETZ and pipelle sampling n = 2	Women with **borderline glandular cytology*** and **normal colposcopy** who underwent **biopsy (unspecified) n = 15** 0/15 diagnosed with CIN2+ at colposcopy Women with **normal colposcopy who had 24 month cytology follow-up n = 18** 0/18 had abnormal smears on follow-up cytology by 24 months **All** women with **borderline glandular cytology*** who underwent colposcopy and histology available **n = 52** 75.0% <CIN2 (n = 39) 9.6% CGIN or high grade CGIN (n = 5) 13.5% CIN2+ (n = 7) 1.9% invasive cancer (n = 1 SCC) *HPV status not reported*

AGC-FN = Atypical glandular cells favour neoplastic (Bethesda 2001); AGC-NOS = Atypical glandular cells not otherwise specified; CGIN = cervical glandular intraepithelial neoplasia; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; LLETZ = Large loop excision of the transformation zone
** Authors states borderline glandular cytology = changes "beyond those encountered in a benign reactive process but insufficient for a diagnosis of invasive/preinvasive disease*

Note studies examining outcomes for women with ?glandular neoplasia were not included as this included women with ≥ AIS cytology

Studies examining risk of cervical disease with AGC cytology and a subsequent negative colposcopy – cross-sectional - **2 studies found**

Table 2: Characteristics and results of studies of women with **AGC** initial cytology and a subsequent **negative colposcopy –** cross-sectional

Study	Study design	Population	Results
Chummun 2012 (Ireland)	Retrospective cohort Cross-sectional	Women (19.2% symptomatic, 21.8% history of previous treatment) diagnosed with **AGC** (endometrial or endocervical, **not otherwise specified or favour neoplastic**) in 2009 and underwent colposcopy (N = 156) Mean age = 41 years and the **colposcopy was normal** N = 27 And underwent treatment or biopsy N = 23 Unclear as to reason for and method of biopsy 146/156 underwent some form of biopsy Punch and or endometrial biopsy n = 89 LLETZ or cone biopsy n = 57	**Women with normal colposcopy n = 27** 23 underwent treatment or biopsy - remaining 4 who were not biopsied had normal smears 6 months later 2/27 (7.4%) AIS histology (unclear as to how biopsied) 2/27 (7.4%) CIN2 or CIN3 histology (unclear as to how biopsied) **Women with AGC** with available histology regardless of colposcopic impression **n = 146** 68.5% normal histology 2.7% invasive cancer (3 SCC and 1 adenocarcinoma) – only 16 patients underwent endometrial sampling 3.4% AIS (n = 5) 14.4% CIN2 or CIN3 (n = 21)
Ullal 2008 (UK)	Retrospective cohort Cross-sectional	Women diagnosed with endocervical dyskaryosis (in this study considered equivalent **to AGC** endocervical - **favour neoplastic**) in 1993-1998 and underwent colposcopy and the **colposcopy was normal** N = 31 smears followed by normal colposcopy N = 27 smears followed by normal colposcopy and biopsy Unclear as to reason for and method of biopsy Biopsy either LLETZ, cervical punch biopsy or laser cone biopsy	**Endocervical dyskaryosis smears followed by normal colposcopy and biopsy n = 27** 4/27 (14.8%) normal biopsy (unclear as to how biopsied, "normal" not defined) 23/27 (85.2%) cervical lesion on biopsy (unclear as to how biopsied, "cervical lesion" not defined – described as "significant lesion" in abstract) **All endocervical dyskaryosis smears** with available histology **n = 101** (colposcopy biopsy n = 95) 69.3% glandular or CIN2+ cervical lesion (n = 70) – 29/70 suggested on colposcopy 71.3% significant glandular or squamous lesion of the genital tract (n = 72) 49.5% endocervical lesion (n = 50) – 5/50 suggested on colposcopy 31.7% CIN2+ lesion (n = 32) 61.4% cervical squamous lesion of any grade (n = 62)

AGC = atypical glandular cells (Bethesda 2001); AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; CIN2 = CIN grade 2; CIN3 = CIN grade 3; SCC = squamous cell carcinoma

References

1. Chummun K, Fitzpatrick M, Lenehan P et al. Diagnostic and therapeutic dilemma associated with atypical glandular cells on liquid-based cervical cytology. *Cytopathology*. 2012;23:378-382.
2. Jadoon BA, Kehoe S, Romain K et al. Analysis of outcome in women with borderline glandular change on cervical cytology. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*. 2009;147:83-85.
3. Ullal A, Roberts M, Bulmer JN et al. The role of cervical cytology and colposcopy in detecting cervical glandular neoplasia. *Cytopathology*. 2009;20:359-366.