General review for Questions 5a

**Question 5a:** For women who are HPV positive with atypical endocervical cells of undetermined significance (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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Study design</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women who are HPV positive with atypical endocervical cells of undetermined significance (confirmed on review) and colposcopy negative *</td>
<td>Randomized or pseudo randomized controlled trial</td>
<td>Repeat HPV and liquid based cytology testing at 6 months</td>
<td>Excisional cone biopsy</td>
<td>Cervical cancer mortality</td>
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<td>Other gynaecologic cancer diagnosis (endometrial, ovarian)</td>
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<td>Cervical cancer diagnosis</td>
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<td>Precancerous high grade lesion (including AIS) detection</td>
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*AIS = adenocarcinoma in situ

*Sub group analysis of women under 30 where possible

**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.

A **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 this question. 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


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

<table>
<thead>
<tr>
<th>Title</th>
<th>Organisation</th>
<th>Evidence-based?</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>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</td>
<td>American Society for Colposcopy and Cervical Pathology.</td>
<td>Consensus based on literature searches and Kaiser Permanente Northern California data</td>
<td>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).</td>
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<tr>
<td>2012 Colposcopic management of abnormal cervical cytology and histology Bentley et al., (2012) J Obstet Gynaecol Can 34 (12):1168-1202</td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
<td>Consensus-based</td>
<td>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.</td>
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<tr>
<td>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</td>
<td>European Cancer Screening Network and European Cancer Network</td>
<td>Unclear if evidence based</td>
<td>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.</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>Jadoon 2009 (UK)</td>
<td>Retrospective cohort</td>
<td>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</td>
<td>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% &lt;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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
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<th>Population</th>
<th>Results</th>
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</table>
| Chummun 2012  | Retrospective cohort    | 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  
Punch and or endometrial 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) |
| (Ireland)      | Cross-sectional         |                                                                                                                                                                                                     |                                                                                                                                                                                                     |
| Ullal 2008     | Retrospective cohort    | 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) |
| (UK)           | Cross-sectional         |                                                                                                                                                                                                     |                                                                                                                                                                                                     |

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