Management of Women with High-Grade Squamous Intraepithelial Lesion and Atypical Glandular Cell Cervical Cytology

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The management of women with high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells (AGC) cytological results is less controversial than the management of women with lower grade cytological abnormalities. In large part, this stems from the fact that women with both of these cytological results have a considerable risk of harboring a high-grade cervical intraepithelial neoplasia (CIN2,3) or even an invasive cancer. This chapter outlines the recommendations made by the 2001 Consensus Conference which was sponsored by the American Society of Colposcopy and Cervical Pathology together with 28 other organizations, federal and international agencies, and professional organizations [1].

High-Grade Squamous Intraepithelial Lesions

The 2001 Bethesda System continued the two-tiered classification of squamous cervical neoplasia initially introduced by the 1988 Bethesda System [2, 3]. In this classification, cytological changes corresponding to CIN1 are referred to as low-grade squamous intraepithelial lesions (LSIL), and cytological changes corresponding to CIN2 and CIN3 are combined into a single cytological category referred to as high-grade squamous intraepithelial lesions (HSIL). Women with a cytological result of HSIL have a 70–75% risk of having a high-grade cervical intraepithelial neoplasia (CIN2,3) lesion and a 1–2% chance of having an invasive cervical cancer [4, 5]. HSIL cytology results are
relatively uncommon and according to 2003 data from the College of American Pathologists (CAP) the median HSIL rate of laboratories in the US is only 0.5% [6]. Because HSIL results are relatively uncommon and there is a considerable risk that women with a HSIL result have a high-grade cervical neoplasia, women with HSIL should be referred for colposcopic evaluation with endocervical assessment (if not pregnant). In most instances, high-grade neoplasia is identified on either the cervix (CIN2,3 or AIS) or the vagina (VAIN2,3). If not, the woman must still be considered to be a significant risk for having an unrecognized CIN2,3 lesion since it is now recognized that a single colposcopic examination can miss approximately one-third of CIN2,3 lesions [7, 8]. Therefore women with a referral cytology of HSIL but in whom high-grade neoplasia is not identified require additional evaluation. The type of evaluation that is appropriate depends on whether or not the colposcopic examination is satisfactory, whether the patient is pregnant, and whether or not immediate excisional treatment is considered an option.

Synopsis of 2001 Consensus Guidelines for HSIL Cytology

Initial Evaluation

Colposcopy with endocervical sampling is recommended for women with HSIL. Subsequent management depends on whether a lesion is identified, whether the colposcopic examination is satisfactory, whether the patient is pregnant, whether immediate excision is considered acceptable, and the age of the patient. Omission of endocervical sampling is acceptable if a diagnostic excisional procedure is planned.

Subsequent Evaluation

For women with satisfactory colposcopic examinations it is recommended that when either no lesion or only CIN1 is identified that all cytologic, histologic, and colposcopic results be reviewed. If the diagnosis is not revised or a review is not possible, then a diagnostic excisional procedure is recommended in non-pregnant patients. In young women of reproductive age it is acceptable to follow-up at 4- to 6-month intervals for 1 year using cytology and colposcopy, provided the colposcopic examination is satisfactory. For women with an unsatisfactory colposcopic examination in whom no lesion is identified at colposcopy, it is recommended that all the material be reviewed. If the review does not result in a changed diagnosis, a diagnostic excisional procedure is recommended in all nonpregnant women. Ablative methods should not be utilized in this situation.
Pregnant Patients

The 2001 Consensus Guidelines recommend that colposcopy for HSIL in pregnant patients be conducted by clinicians who are experienced in the colposcopic changes induced by pregnancy. The biopsy of lesions colposcopically considered to be high-grade or suspicious for cancer is preferred and the biopsy of other lesions is considered acceptable. Endocervical curettage is unacceptable in pregnant women. It should be noted that unsatisfactory colposcopic examinations frequently become satisfactory as the pregnancy progresses. Therefore, pregnant patients with unsatisfactory colposcopic examinations should undergo repeat colposcopy in 6–12 weeks. Pregnant patients with HSIL who do not have invasive disease identified at the initial colposcopic evaluation should have additional colposcopic and cytologic examinations with biopsy only if the appearance of the lesion worsens or there is a cytological suggestion of invasive cancer. Reevaluation using colposcopy and cytology is recommended no sooner than 6 weeks postpartum [1].

Atypical Glandular Cells

According to data from the College of American Pathologists (CAP), in 2003 the average atypical glandular cell (AGC) rate for laboratories in the US was 0.2% or 2 cases per 1,000 Pap tests [6]. This is considerably lower than the average ASC-US rate which was 3.9%. The 2001 Bethesda System classifies atypical glandular cells (AGC) into three categories: atypical glandular cells, either endocervical, endometrial, or ‘glandular cells’ not otherwise specified (AGC-NOS); atypical endocervical cells or ‘glandular cells’, favor neoplasia (AGC, favor neoplasia); and endocervical adenocarcinoma in situ (AIS). Women with a cytological result of AGC have a somewhat lower risk for having a CIN2,3 lesion than do women with HSIL, but have a considerably increased risk of having invasive cancer. These risks appear to vary as a function of the type of AGC which is diagnosed and the age of the patient. Various studies have documented rates of biopsy-confirmed CIN (of all grades) of 9–54% in women with AGC. The rate of biopsy-confirmed adenocarcinoma in situ ranges from 0 to 8% and the rate of cancer from 1 to 9% in the various studies. The separation of AGC into AGC-NOS and AGC, favor neoplasia was included in the 2001 Bethesda System since these categories appear to be at different risk for having high-grade cervical neoplasia or cancer (table 1) [4, 9–12].

Women with an AGC-NOS result have a 9–41% risk of having a high-grade neoplasia (either glandular or squamous) and a 0–15% risk of having a high-grade glandular lesion (either adenocarcinoma in situ or invasive adenocarcinoma) [4, 9–15]. In contrast, women with an AGC, favor neoplasia result have a 27–96% risk
of having high-grade neoplasia and a 10–93% risk of having a high-grade glandular lesion. A cytological result of AIS is associated with a 48–69% risk of biopsy-confirmed AIS and a 38% risk of invasive adenocarcinoma. Because of this differing risk, women with AGC-NOS are managed less aggressively than are women with an AGC, favor neoplasia result or a cytological diagnosis of AIS.

As table 1 demonstrates, there is a wide variability between different reports in the prevalence of high-grade neoplasia in women with AGC cytology. This reflects differences in the patient populations that have been studied. For example, reports from centers with busy gynecological oncology services typically report much higher rates of glandular neoplasia and invasive adenocarcinomas than do series produced from more routine screening populations [9, 16]. One of the most representative series is a study in which 46,009 women undergoing routine screening were enrolled from the Kaiser healthcare system (table 2) [9]. Of the 46,009 women a total of 137 (0.3%) had AGC cytology results. When these women were evaluated it was found that 9% had biopsy-confirmed CIN2,3 lesions, 4% had AIS, and one (1%) had an invasive endometrial adenocarcinoma.

Almost all series of women with AGC results have reported, somewhat paradoxically, that the single most frequent histopathological abnormality

<table>
<thead>
<tr>
<th>Table 1. Rates of biopsy-confirmed neoplasia in women with AGC</th>
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<tr>
<td>Cytology</td>
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<td>---------</td>
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<tr>
<td>AGC-NOS (%)</td>
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<tr>
<td>AGC, favor neoplasia (%)</td>
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From [4, 9–15].

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<th>Table 2. Findings at work-up of women with AGC</th>
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<tr>
<td>Histological findings</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>No lesion identified</td>
</tr>
<tr>
<td>CIN1</td>
</tr>
<tr>
<td>CIN2,3</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
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<tr>
<td>Invasive adenocarcinoma</td>
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Ronnett et al. [9].
identified in these women is CIN2,3 [9, 16]. Based on the high prevalence of
CIN2,3 in women with AGC and the fact that repeat cytological testing is less
sensitive for identifying CIN2,3 or AIS in women with AGC, the 2001
Consensus Guidelines recommend that all women with an AGC cytological
result be referred for a colposcopic evaluation [1]. Moreover, since it can be
quite difficult to identify AIS based on colposcopic appearance alone and AIS
lesions can be confined to the endocervical canal, the 2001 Consensus
Guidelines recommend that the colposcopic evaluation of women with AGC be
accompanied by endocervical sampling. Age is another key indicator for deter-
mining both the type and frequency of neoplasia identified in women with
AGC. Table 3 provides the impact of menopausal status in women with AGC
[12, 15, 17, 18]. Premenopausal patients with AGC are much more likely to
have a CIN2,3 lesion or AIS than to have endometrial disease. In contrast, post-
menopausal patients are more likely to have endometrial disease including
endometrial adenocarcinoma than CIN2,3 or AIS. Based on the relationship
between patient’s age or menopausal status and risk for endometrial neoplasia,
the 2001 Consensus Guidelines recommend that initial evaluation for all non-
pregnant women with ACG be colposcopy with endocervical sampling and that
this be accompanied by sampling of the endometrium in women greater than 35
years of age and in all women with AGC with abnormal uterine bleeding. The
one exception is postmenopausal women with a cytological result of abnormal
endometrial cells who do not require colposcopy. The 2001 Consensus
Conference concluded that there was insufficient data to allow an assessment of
the role of HPV DNA testing in the management of AGC and AIS [1].

Table 3. Impact of age on rates of neoplasia in women with AGC

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<th>CIN2,3 or AIS</th>
<th>Endometrial hyperplasia or neoplasia</th>
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<tr>
<td>Premenopausal (%)</td>
<td>22–30</td>
<td>3</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>6–7</td>
<td>19</td>
</tr>
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</table>

From [12, 15, 17, 18].

**Synopsis of 2001 Consensus Guidelines for AGC Cytology**

**Initial Evaluation**

Colposcopy with endocervical sampling is recommended for women
with all subcategories of AGC (including AIS) with exception that women with

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atypical endometrial cells should initially be evaluated with endometrial sampling. Endometrial sampling should also be performed if a woman is older than 35 years or has unexplained vaginal bleeding. The presence of a co-existing squamous abnormality does not change management. It should also be noted that the 2001 Consensus Guidelines consider initial management of a woman with an AGC or AIS using a program of repeat cytological examination to be unacceptable.

Subsequent Evaluation

If CIN or AIS is identified at colposcopy in a woman with a cytological result of AGC-NOS, then the patient should be treated according to the appropriate guideline. If no lesion is identified the patient should be followed up with repeat cytological examinations at 6 monthly intervals for 2 years. Patients referred for evaluation of AGC, favor neoplasia or an AIS cytology result who are not found to have an invasive lesion identified at colposcopy should undergo a diagnostic excisional procedure. In these instances a cold-knife conization procedure is preferred because it is more likely to provide diagnostic information on the state of the margins of excision.

References

8 Cox JT, Schiffman M, Solomon D: Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. Am J Obstet Gynecol 2003;188: 1406–1412.

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