Management Recommendations in Abnormal Cytology

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Organized screening with Papanicolaou smear has reduced the prevalence of invasive cervix cancer in developed world, and in the recent screening guidelines, HPV as a co-test after 30 years of age has been added to Pap smear. The goal of screening is to find persistent HPV infection, detect and treat high-grade CIN, i.e. CIN 2 and 3 (with no margin of error), and not to miss invasive cancer.

In this chapter, cytology requiring further evaluation will be discussed in three categories:

1. Epithelial cell abnormalities as per revised Bethesda system
2. Unsatisfactory Pap smear as defined by Bethesda system
3. Negative cytology with positive HPV

5.1 Epithelial Cell Abnormalities as per Revised Bethesda System

Epithelial cell abnormalities are listed in Table 5.1 [1]. American Society for Colposcopy and Cervical Pathology (ASCCP) has laid down comprehensive, evidence-based consensus guidelines to aid clinicians in managing women with abnormal cervical cytology, cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS) and can be downloaded from www.asccp.org [2]. These are based on risk analysis. The risk of having CIN 3 based on cytology alone and cytology plus HPV test is given in Tables 5.2 and 5.3 [3–5].

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Table 5.1 Epithelial cell abnormality as per Bethesda system

Epithelial cell abnormalities
Squamous cell
Atypical squamous cells (ASC)
Of undetermined significance (ASC-US)
Cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL)
Encompassing: human papillomavirus/mild dysplasia/cervical
Intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)
Encompassing: moderate and severe dysplasia, carcinoma in situ
CIN 2 and CIN 3
Squamous cell carcinoma
Glandular cell
Atypical glandular cells (AGC) (specify endocervical, endometrial or not otherwise specified)
Atypical glandular cells, favour neoplastic (specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)

Table 5.2 Risk of CIN 3 based on cytology alone

Pap −ve (%)	ASC-US (%)	LSIL (%)	ASC-H (%)	AGC (%)	HSIL (%)
0.2	2.6	5.3	18	8.7	48

Table 5.3 Risk of CIN 3 based on cytology and HPV co-test

	Pap −ve	ASC-US	LSIL	ASC-H	AGC	HSIL
HPV −ve	0.08	0.45	2.1	3.8	1.1	29
HPV +ve	3.5	6.8	6.2	25	34	50

5.1.1 Atypical Squamous Cells of Undetermined Significance (ASC-US) [2, 6–8]

Management of Women Aged 25 Years or Older

Guidelines for workup of ASC-US are based on the following observations:

ASC-US is the most common cytologic abnormality. It carries the lowest risk of CIN 3+, partly because one third to two thirds are not HPV associated. In fact, the risk of CIN 3+ was 2 %, low enough to justify annual rather than semi-annual cytology to identify women with CIN 3+. Triage using HPV genotyping was considered. Women with ASC-US who also had HPV-16 or HPV-18 detected had approximately twice the risk of CIN 3+ as women with ASC-US and high-risk HPV types other than 16 or 18.

Management

Option 1

For women with ASC-US cytology, HPV testing is preferred. For women with HPV-negative ASC-US whether from reflex HPV testing or co-testing, repeat co-testing at 3 years is recommended. For women with HPV-positive ASC-US, colposcopy is recommended. Triaging ASC-US cytology with HPV reduces the referrals for colposcopy by 50 %.

When colposcopy does not identify CIN in women with HPV-positive ASC-US, co-testing at 12 months is recommended. It is recommended that HPV testing in follow-up after colposcopy not be performed at intervals of less than 12 months. If the co-test is HPV negative and cytology negative, return for age-appropriate testing in 3 years is recommended. If all tests are negative at that time, routine screening is recommended.

Option 2

For women with ASC-US cytology and no HPV result, repeat cytology at 1 year is acceptable. If the result is ASC-US or worse, colposcopy is recommended; if the result is negative, return to cytology testing at 3-year intervals is recommended.

In our centre, we opt for HPV test if the patient can afford, because this is not available in our hospital setting. Repeat Pap smear at 1 year is offered if patient is reliable for follow-up. Though guidelines don't suggest colposcopy as the first option for the work up of ASC-US cytology, we offer colposcopy as first choice to patients who cannot afford HPV testing and are noncompliant. Depending on the availability of facility at one's centre, one can individualize the management.

5.1.1.1 ASC-US in Special Populations

Women Aged 21–24 Years

For women aged 21–24 years with ASC-US, cytology alone at 12-month intervals is preferred, but reflex HPV testing is acceptable. If reflex HPV testing is performed with ASC-US and the HPV result is positive, repeat cytology in 12 months is recommended.

Immediate colposcopy or repeat HPV testing is not recommended. If reflex HPV testing is performed and is negative, return for routine screening with cytology alone in 3 years is recommended.

Follow-Up

For women with ASC-H or HSIL+ (HSIL, atypical glandular cells [AGC] or cancer) at the 12-month follow-up, colposcopy is recommended. For women with ASC-US or worse at the 24-month follow-up, colposcopy is recommended. For women with two consecutive negative results, return to routine screening is recommended.

Women Aged 65 Years and Older
Postmenopausal women with ASC-US should be managed in the same manner as women in the general population, except when considering exit from screening for women aged 65 years and older. HPV-negative ASC-US is considered abnormal for these women as they have a higher risk for cervical cancer during follow-up than women with negative co-testing, suggesting that they need continued screening. Additional surveillance is recommended with repeat screening in 1 year; co-testing is preferred, but cytology is acceptable.

Pregnant Women
Management options for pregnant women with ASC-US are identical to those described for nonpregnant women, with the exception that deferring colposcopy until 6 weeks postpartum is acceptable. Endocervical curettage in pregnant women is unacceptable. For pregnant women who have no cytologic, histologic or colposcopically suspected CIN 2+ at the initial colposcopy, postpartum follow-up is recommended.

5.1.2 Low-Grade Squamous Intraepithelial Lesion [2, 9, 10]

Low-grade squamous intraepithelial lesions are highly associated with HPV infection, with HPV positivity of 77%. High rate of HPV positivity in LSIL does not favour reflex HPV testing to select women for colposcopy. The ASC-US-LSIL Triage Study showed that the natural history of LSIL approximates that of HPV-positive ASC-US. Women with LSIL at ages 21–24 years carry a lower risk of CIN 3+ than older women.

Management of Women with LSIL
For women with LSIL cytology and either no HPV test or a positive HPV test, colposcopy is recommended. If co-testing shows HPV-negative LSIL, repeat co-testing at 1 year is preferred, but colposcopy is acceptable. If repeat co-testing at 1 year is elected and if the cytology is ASC-US or worse or the HPV test is positive (i.e. if the co-testing result is other than HPV negative, cytology negative), colposcopy is recommended. If the co-testing result at 1 year is HPV negative and cytology negative, repeat co-testing after 3 years is recommended. If all tests are negative at that time, routine screening is recommended.

5.1.2.1 LSIL in Special Populations

Women Aged 21–24 Years
For women with LSIL who are aged 21–24 years, follow-up with cytology at 12-month intervals is recommended. Colposcopy is not recommended. For women with ASC-H or HSIL+ at the 12-month follow-up, colposcopy is recommended. For women with ASC-US or worse at the 24-month follow-up, colposcopy is

recommended. For women with two consecutive negative results, return to routine screening is recommended.

Pregnant Women
For pregnant women with LSIL, colposcopy is preferred. Endocervical curettage in pregnant women is unacceptable. For pregnant women aged 21–24 years, follow-up according to the guidelines for management of LSIL in women aged 21–24 years is recommended. Deferring colposcopy until 6 weeks postpartum is acceptable. For pregnant women who have no cytologic, histologic or colposcopically suspected CIN 2+ at the initial colposcopy, postpartum follow-up is recommended. Additional colposcopic and cytologic examinations during pregnancy are unacceptable for these women.

Postmenopausal Women
Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing, repeat cytologic testing at 6 and 12 months and colposcopy. If the HPV test is negative or if CIN is not identified at colposcopy, repeat cytology in 12 months is recommended. If either the HPV test is positive or repeat cytology is ASC-US or greater, colposcopy is recommended. If two consecutive repeat cytology tests are negative, return to routine screening is recommended.

Many times cytologic abnormality of LSIL in menopausal women is due to vaginal mucosal atrophy; in that case, it is prudent to treat with local oestrogen cream for 3 weeks or oral conjugated oestrogens and then repeat the cytology.

5.1.3 Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) [2, 11]

ASC-H have a higher risk for CIN 3+ than ASC-US or LSIL although risk is lower than HSIL (Table 5.2). The risk of is also true for women aged 21–24 years, although their risk of CIN 3+ is lower than that for older women with ASC-H. There is high rate of HPV detection in women with ASC-H making reflex HPV testing unsuitable. Also, the 5-year cancer risk among women with HPV-negative ASC-H is 2 %, which is too high to justify observation.

For women with ASC-H cytology, colposcopy is recommended regardless of HPV result. Reflex HPV testing is not recommended.

5.1.3.1 ASC-H in Special Populations

Women Aged 21–24 Years
Colposcopy is recommended. Further management should follow guidelines for women aged 21–24 years with HSIL.

5.1.4 High-Grade Squamous Intraepithelial Lesion

For women with HSIL cytology, immediate colposcopy with endocervical assessment is recommended. Triage using either a programme of repeat cytology alone or HPV testing is unacceptable. If colposcopy is adequate, transformation zone is 1 or 2, or the lesion is seen in its entirety, one can treat the lesion with large loop electrosurgical excision (LEEP). This will provide the diagnosis and treatment as well. This is the only condition where "see and treat" policy can be given. If immediate treatment is not acceptable, colposcopically directed biopsy should be taken from most abnormal area and women with CIN 2, and CIN 3 should be managed according to the appropriate guidelines. If no lesion is identified on colposcopy or it is type 3 transformation zone, a diagnostic excisional procedure is recommended.

Ablation is unacceptable when colposcopy has not been performed, when CIN 2,3 is not identified histologically and when the endocervical assessment identifies CIN 2 or CIN 3.

5.1.4.1 HSIL in Special Populations

Women Aged 21–24 Years
Colposcopy is recommended. If CIN 2,3 is identified histologically, management is done accordingly. When CIN 2 or more is not identified histologically, observation for up to 24 months using both colposcopy and cytology at 6-month intervals is recommended, provided the colposcopic examination is adequate and endocervical assessment is negative or CIN 1.

If during follow-up a high-grade colposcopic lesion is identified or HSIL cytology persists for 1 year, biopsy is recommended. If HSIL persists for 24 months without identification of CIN 2+, a diagnostic excisional procedure is recommended. A diagnostic excisional procedure is recommended for this age group with HSIL when colposcopy is unsatisfactory or CIN 2, CIN 3, CIN 2,3 or ungraded CIN is identified on endocervical sampling. After two consecutive negative cytology results and no evidence of high-grade colposcopic abnormality, return to routine screening is recommended.

Pregnant Women with HSIL
Immediate colposcopy is recommended with biopsy of lesions suspicious for CIN 2,3 or cancer. Colposcopy should be repeated no earlier than 6 weeks postpartum if no CIN 2,3 is found. For pregnant women with CIN 2,3, repeat cytology and colposcopy may be performed every 12 weeks with repeat biopsy if the lesion worsens or cytology suggests invasion.

5.1.5 Atypical Glandular Cells, Cytologic Adenocarcinoma In Situ and Benign Glandular Changes [2, 12, 13]

AGC are uncommon. AGC are found with polyps, metaplasia and also neoplasias, including adenocarcinomas of the endometrium, cervix, ovary and fallopian tube. The risk of neoplasia is higher when AGC favour neoplasia or frank AIS are

reported. In women younger than 35 years of age with AGC, the risk of CIN 2+ is higher than carcinoma, so a thorough assessment of AGC is warranted at all ages. AGC are most commonly associated with squamous lesions, as glandular and squamous lesions often coexist.

Benign-appearing endometrial cells and stromal cells or histiocytes are rarely associated with premalignant lesions or cancer in young women. However, in postmenopausal women, these changes can be associated with an approximately 5 % risk of clinically important pathology including endometrial adenocarcinoma.

Management of Women with AGC or Cytologic AIS

For initial workup of women with all subcategories of AGC and AIS except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV result. Accordingly, triage by reflex HPV testing is not recommended, and triage using repeat cervical cytology is unacceptable. Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in women 35 years of age and older with all subcategories of AGC and AIS. Endometrial sampling is also recommended for women younger than 35 years with clinical indications suggesting they may be at risk for endometrial neoplasia. These include unexplained vaginal bleeding or conditions suggesting chronic anovulation. For women with atypical endometrial cells, initial evaluation limited to endometrial and endocervical sampling is preferred, with colposcopy acceptable either at the initial evaluation or deferred until the results of endometrial and endocervical sampling are known; if colposcopy is deferred and no endometrial pathology is identified, colposcopy is then recommended.

Subsequent Management

For women with AGC not otherwise specified cytology in whom CIN 2+ is not identified, co-testing at 12 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.

If CIN 2+ but no glandular neoplasia is identified histologically during the initial workup of a woman with atypical endocervical, endometrial or glandular cells not otherwise specified, management should be according to the 2012 consensus guidelines for the lesion found.

For women with AGC "favour neoplasia" or endocervical AIS cytology, if invasive disease is not identified during the initial colposcopic workup, a diagnostic excisional procedure is recommended. It is recommended that the type of diagnostic excisional procedure used in this setting provides an intact specimen with interpretable margins. Endocervical sampling after excision is preferred.

5.1.5.1 AGC or Cytologic AIS in Special Populations

Pregnant Women

The initial evaluation of AGC in pregnant women should be identical to that of nonpregnant women except that endocervical curettage and endometrial biopsy are unacceptable.

Women Aged 21–24 Years
It is recommended that ASCCP guidelines for management of AGC be followed for all women, including those aged 21–24 years.

Management of Benign Glandular Changes
For asymptomatic premenopausal women with benign endometrial cells, endometrial stromal cells or histiocytes, no further evaluation is recommended. For postmenopausal women with benign endometrial cells, endometrial assessment is recommended. For posthysterectomy patients with a cytologic report of benign glandular cells, no further evaluation is recommended.

5.2 Unsatisfactory Cytology [14–22]

5.2.1 Unsatisfactory Cytology

Unsatisfactory cytology is unreliable for detecting epithelial abnormalities. Studies have found a higher risk of disease in women with unsatisfactory cytology. Cytology is usually rendered unsatisfactory by obscuring blood, inflammation or other processes. Instead of conventional Pap smear, liquid-based media control obscuring factors in processing. Using liquid-based media, unsatisfactory results are because of insufficient squamous cells.

Specimen collection techniques effective to minimize unsatisfactory cytology are extended-tip spatulas, spatulas plus brushes and brooms.

With HPV co-testing although the risk of high-grade disease is low in women with negative HPV test result, some currently available HPV tests lack a control for epithelial cellularity, so a negative HPV test cannot be relied upon as the HPV test may be falsely negative because of an insufficient sample.

Management
For women with an unsatisfactory cytology result and no, unknown or a negative HPV test result, repeat cytology in 2–4 months is recommended. Triage using reflex HPV testing is not recommended. It is prudent to treat atrophy or obscuring inflammation when a specific infection is present.

For women aged 30 years and older who are co-tested and have unsatisfactory cytology and a positive HPV test, repeat cytology in 2–4 months or colposcopy is acceptable.

Colposcopy is recommended for women with two consecutive unsatisfactory cytology tests.

5.2.2 Cytology Reported as Negative But with Absent or Insufficient EC/TZ Component

In cytology reported as negative but with absent or insufficient EC/TZ (endocervical/transformation zone) component, the cellularity is adequate for interpretation,

but there is lack of endocervical or metaplastic cells, suggesting that the squamocolumnar junction may not have been adequately sampled. Missing the disease was a concern in the past in such cytology which is not logical. Prior guidelines had recommended early repeat cytology. However, women with absent or insufficient EC/TZ component not only have fewer cytologic abnormalities, they also do not have a higher risk for CIN 3+ over time than women with a satisfactory EC/TZ component. Instead, there are lower rate of cytologic abnormality as these women are usually older and have lower risk of CIN 3+. HPV testing offers an added margin of safety for women aged 30–64 years as it is independent of transformation zone sampling.

Repeat cytology in 3 years is acceptable if HPV testing is not performed.

If the HPV test is done and is negative, return to routine screening is recommended.

If the HPV test is positive, repeating both tests in 1 year is acceptable. Genotyping is also acceptable; if HPV type 16 or type 18 is present, colposcopy is recommended. If HPV type 16 and type 18 are absent, repeat co-testing in 12 months is recommended.

For women aged 21–29 years with negative cytology and absent or insufficient EC/TZ component, routine screening is recommended. HPV testing is unacceptable.

5.3 Negative Cytology with a Positive HPV Test [2–5]

HPV testing is not indicated for younger women but is the preferred screening modality for women aged 30–64 years. Even women with negative cytology and with oncogenic HPV are at higher risk for later CIN 3+ than women with negative HPV tests. This sufficiently justifies early return for retesting. Persistent HPV positivity increases the risk of CIN 3+ further. However, since most HPV infections are cleared, it is also logical to observe to allow clearance. Nevertheless, CIN 3+ does occur during observation, requiring balancing risks arising from intervention for HPV that may yet be cleared against the risks of disease. HPV-16 particularly increases the risk for CIN 3+. HPV-18 is associated with cervical adenocarcinomas, which are less efficiently detected by cytology.

Management of Women Testing HPV Positive But Cytology Negative

For women 30 years of age and older with HPV-positive but cytology-negative co-testing, repeat co-testing at 1 year is acceptable. At 1-year repeat co-test, if the HPV test is positive or cytology is ASC-US or worse, colposcopy is recommended. If the 1-year repeat co-test result is HPV negative and cytology negative, repeat co-testing in 3 years is recommended.

HPV genotyping is also acceptable. If HPV-16 or HPV-18 tests are positive, colposcopy is recommended. If HPV-16 and HPV-18 tests are negative, repeat co-testing in 1 year is recommended.

5.4 Summary of Essential Changes from Prior Management Guidelines

- More strategies incorporate co-testing to reduce follow-up visits. Pap-only strategies are now limited to women younger than 30 years, but co-testing is expanded even to women younger than 30 years in some circumstances. Women aged 21–24 years are managed conservatively.
- For ASC-US cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, not 6 and 12 months, and then if negative, cytology every 3 years.
- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 65 years.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Cytology reported as negative but lacking endocervical cells can be managed without early repeat.
- Genotyping triages HPV-positive women with HPV type 16 or type 18 to earlier colposcopy only after negative cytology; colposcopy is indicated for all women with HPV and ASC-US, regardless of genotyping result.

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