MANAGEMENT OF ABNORMAL PAP TESTS IN AN AGE OF CONFUSION

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Disclosures

- I have no financial conflicts of interest
Teaching objectives

• Be able to review with patients the pros and cons of the 2 strategies for cervical cancer screening
• Explain the appropriate use of HPV genotyping in clinical management
• Compare the differences in management of abnormal Paps in women younger than 25 years compared to older.
• Explain the management of atypical glandular cells on Pap
Case 1

- 32 yo G2P2 comes in for contraceptive counseling
- She asks if she needs screening today for cervical cancer
- She had her last Pap at age 29
- Paps have always been normal

How do you counsel her?
Cervical cancer screening

- The U.S. Preventative Services Task Force (USPSTF) recommends that women between the ages of 30 and 65 can be screened with:
  - cytology every 3 years or
  - cytology plus HPV testing (co-testing) every 5 years in women who want to extend their screening interval

Cervical cancer screening

- The American Cancer Society, American Society of Colposcopy and Cervical Pathology, and American Society of Clinical Pathology (ACS/ASCCP/ASCP) recommend that women between the ages of 30 and 65 can be screened with:
  - cytology-plus-HPV testing (co-testing) every 5 years (“preferred”)
  - cytology alone every 3 years (acceptable)

Saslow et al 2012, *CA Cancer J Clin*
Cytology plus HPV co-testing “preferred” for cervical cancer screening: by whom?

Health care systems

Patients

Guideline committees
The advantage of co-testing:

- The advantage is the negative predictive value

- Women with negative results on HPV and cytology have a very low risk of CIN3+

- The screening intervals can be safely extended to 5 years in these women
The disadvantage of co-testing: low specificity

• HPV infection is common in sexually active women, and the vast majority of infections will resolve spontaneously and are not associated with precancerous lesions

• Hence HPV testing inherently has low specificity, and can lead to harm eg. anxiety, overtreatment, increased cost.
Co-testing: new categories of uncertainty

- Cytology is associated with uncertainty in the clinical management of some mild abnormalities (e.g., atypia and low-grade).

- Co-testing introduces a new state of ambiguity: normal cytology with a positive HPV test.

- Occurs in 3-8% of screened women, as high as 11% in 30-34 year women in the U.S.
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative
  - ≥ASC or HPV positive
    - Repeat cotesting @ 3 years

- **HPV DNA Typing**
  - Acceptable
  - HPV 16 or 18 Positive
  - HPV 16 and 18 Negative
    - Repeat Cotesting @ 1 year

**Colposcopy**

- Manage per ASCCP Guideline
- Manage per ASCCP Guideline

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Use of HPV Genotyping

• The only role of genotyping in the new guidelines is in the triage of women with normal Pap and a positive HRHPV test.

• In those women it is “acceptable” to test for HPV 16/18, and perform colposcopy if HPV 16 or 18 is detected.

• If HPV 16/18 is NOT detected, the cotest should be repeated in 1 year

• If the Pap is abnormal OR the HPV is again positive, she should receive colposcopy
Co-testing versus cytology

• Women undergoing co-testing thus need to be made aware of the potential for uncertainty, increased surveillance, increased rates of colposcopy, and negative impact on their quality of life.

• Given these issues with co-testing, why did the ACS/ASCCP/ASCP recommend it as the “preferred” option?
Co-testing “preferred”

From the supplement page 21

Recommendations

1a. Women aged 30-65 should be screened with cytology and HPV testing (“cotesting”) every 5 years or cytology alone every 3 years. *(strong recommendation)*

1b. Cytology and HPV testing (cotesting) every 5 years is the preferred strategy over screening with cytology alone every 3 years. *(weak recommendation)*

Saslow et al 2012, *CA Cancer J Clin*
Co-testing “preferred”

• Weak recommendation
  • indicates that there is “substantial uncertainty surrounding the balance of benefits and harms, and further research is needed to increase confidence in the results, or that benefits and harms are closely balanced, with decisions based largely on individual preferences and values”

  Saslow et al 2012, *CA Cancer J Clin*

• Given these substantial reservations, it is puzzling that the guidelines did not disclose that the designation of co-testing as “preferred” was a weak recommendation.
14th for cancer deaths. This reduction in mortality through screening is due to 1) an increase in the detection of invasive cancer at early stages, when the 5-year survival rate is approximately 92%; and 2) the detection and treatment of preinvasive lesions, which reduces the overall incidence of invasive cancer. In 2012, an estimated 12,170 cases of invasive cervical cancer will be diagnosed, and an estimated 4220 women will die.

It is now understood that persistent cervical infection with high-risk HPV genotypes ("types") is necessary for the development of cervical cancer and its immediate precursor lesion ("precancer"), cervical intraepithelial neoplasia (CIN) grade 3 (CIN3). Epidemiologic case series have shown that nearly 100% of cervical cancer cases test positive for HPV. HPV type 16 (HPV16) is the most carcinogenic HPV genotype and accounts for approximately 55% to 60% of all cervical cancers. HPV18 is the next most carcinogenic HPV genotype, and accounts for approximately 10% to 15% of cervical cancers.

The relationship between cervical cancer and HPV infection is clear. HPV is a necessary condition for cervical cancer, and the presence of HPV in the cervix is a strong predictor of cervical cancer development. The main types of HPV that are associated with cervical cancer are HPV16 and HPV18. These two types are responsible for approximately 70% of all cervical cancer cases. Other HPV types, such as HPV31, HPV33, and HPV45, are also associated with cervical cancer but less frequently.

Cervical cancer screening using cytology and HPV testing is an effective way to prevent cervical cancer. Cytology, also known as the Pap test, is a simple procedure that involves collecting cells from the cervix using a cotton swab or a small brush. The collected cells are then examined under a microscope to detect any abnormal changes that may indicate the presence of cervical cancer or precursor lesions.

HPV testing is another important tool in cervical cancer screening. HPV tests detect the presence of specific HPV types in the cervix. There are two main types of HPV tests: the HPV DNA test and the HPV RNA test. The HPV DNA test detects the presence of HPV DNA in the cervix, while the HPV RNA test detects the presence of HPV RNA, which is the viral RNA that is needed for the virus to replicate and cause disease.

The combination of cytology and HPV testing is more effective than either test used alone. This is because HPV testing can detect HPV types that are not detected by cytology, and cytology can detect changes in the cervical cells that are not detected by HPV testing. By using both tests, the effectiveness of cervical cancer screening is increased, and more women are identified at an earlier stage of the disease, leading to a higher chance of successful treatment.

Saslow et al 2012, CA Cancer J Clin
Approximately 25% of committee members reported financial conflicts of interests with companies that make HPV tests, including research supplies, research funding, advisory and/or consulting roles, and speakers’ honoraria.

Many committee members have spent their academic careers studying HPV and may have had intellectual biases favoring HPV-based testing over cytology alone.
U.S. Preventive Services Task Force

- Members of the USPSTF are experts in evidence-based medicine and prevention
- Members “can have no substantial conflicts of interest, whether financial, professional, or intellectual, that would impair the scientific integrity of the work of the USPSTF”

http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/uspstf/nominate.html
USPSTF Recommendations

cO-testing is an option “for women who want to lengthen the screening interval” (reflects a patient preference)
Co-testing versus cytology: how to choose

• Our 32-year old patient has been getting screening every 3 years
• She thinks that screening every 5 years would simplify her life considerably.
• You explain that there is a risk of detecting an asymptomatic HPV infection requiring her to be tested annually and possibly resulting in colposcopy. Given her age, that risk could be as high as 11%.
• She is willing to accept that risk for the trade-off of 5-year intervals between screening tests, and therefore “prefers” co-testing.
Co-testing versus cytology: how to choose

• Our 32-year old patient has been getting screening every 3 years
• She had mild abnormalities on her Pap in her mid-20s and had several colposcopies but the Pap normalized and she never needed treatment.
• She thinks that screening every 5 years would simplify her life considerably.
• You explain that there is a risk of detecting an asymptomatic HPV infection requiring her to be tested annually and possibly resulting in colposcopy. Given her age, that risk could be as high as 11%
Co-testing versus cytology: how to choose

- She remembers the colposcopies she had in her 20’s as being painful and unpleasant, and does not want to choose an option that might increase her risk of needing colposcopy.
- She “prefers” cytology every 3 years.
Summary

• For women over the age of 30, cytology every 3 years or co-testing every 5 years are acceptable options for screening.

• The choice of co-testing as “preferred” should include a consideration of the patient’s preferences.
Other issues with co-testing

- Sometimes there is a mismatch of cytology and HPV results, which can result in confusion. For example:

- 33 yo woman with a co-test result of HSIL, HRHPV negative

- For HSIL, Atypical Squamous Cells favor High grade (ASC-H) and Atypical Glandular Cells (AGC):

  IGNORE THE HPV RESULT
  PATIENT NEEDS COLPOSCOPY
Atypical Glandular Cells (AGC)

AGC is an uncommon cytology diagnosis, but has a high association with dysplasia (both squamous and glandular)

Cytology results of AGC:
- AGC not otherwise specified (NOS)
- AGC favor neoplasia
- Adenocarcinoma in situ
- Cytology result may specify “atypical endocervical cells” or “atypical endometrial cells” or not specify the source “atypical glandular cells”
Management of Atypical Glandular Cells (AGC) on Pap

- Colposcopy is required in all cases, REGARDLESS OF AGE
- Endocervical sampling with ECC must be done
- Endometrial biopsy is also required in some populations (>35 years of age, abnormal uterine bleeding, or condition suggesting chronic anovulation)
- Women with AGC-favor neoplasia or AIS must have a diagnostic excisional procedure if cancer is not found on colposcopy
Subsequent Management of Women with Atypical Glandular Cells (AGC)

Initial Cytology is AGC - NOS

- No CIN2+, AIS or Cancer
  - Cotest at 12 & 24 months
    - Both negative
      - Cotest 3 years later
    - Any abnormality
      - Colposcopy

- CIN2+ but no Glandular Neoplasia
  - Manage per ASCCP Guideline
    - Any abnormality
      - Colposcopy

Initial Cytology is AGC (favor neoplasia) or AIS

- No Invasive Disease
  - Diagnostic Excisional Procedure *
    - *Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred

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Management of ASCUS and LSIL in 21-24 year olds

• Underlying principles of management in this age group:
  - DO NO HARM
  - Cancer is uncommon
  - HPV is common and usually resolves (so there is NO ROLE for HPV testing in this age group)
Management of ASCUS and LSIL in 21-24 year olds

• Repeat the Pap at 12 and 24 months:

• Perform colposcopy if the Pap test at 12 months is >LSIL

  OR

• Perform colposcopy if ASCUS/LSIL persists for 24 months
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

- Repeat Cytology @ 12 months Preferred
  - Negative, ASC-US or LSIL
    - Repeat Cytology @ 12 months
      - Negative x 2
        - Routine Screening
  - ASC-H, AGC, HSIL
    - HPV Positive

- Reflex HPV Testing Acceptable for ASC-US only
  - HPV Negative
    - Routine Screening

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Case 2

- 21 year old with ASCUS on her first Pap
- She has LSIL on her Pap at 12 month
- She has LSIL on her Pap at 24 month
Treatment of High Grade CIN

• Before the advent of colposcopy, abnormal Paps were treated by hysterectomy or conization
• With the advent of colposcopy, more conservative methods were adopted:
  • ablative methods such as cryotherapy, laser ablation, electrocautery or diathermy
  • excision with CO2 laser (laser conization)
Treatment of High Grade CIN

• With the introduction of the loop electrosurgical excision procedure (LEEP, LLETZ) in the 1990’s, the ablative methods were mostly abandoned.

• Advantages of treatment with LEEP:
  • provides a histological specimen
  • therefore can be used in a “see-and-treat” format
Treatment of High Grade CIN

• There is a misperception that cryotherapy is not as effective as LEEP: the evidence strongly supports the effectiveness of cryotherapy except in women over the age of 40
• The preponderance of the evidence suggests that excisional therapies are associated with adverse obstetrical outcomes related to preterm labor
Meta-analysis of studies on preterm birth (<37 weeks) in women treated with LEEP (LLETZ)
Principles of management of CIN 2 and CIN 2/3 in younger women

- 40-50% of CIN 2 lesions will regress spontaneously
- There may be harms from treatment
- Therefore in suitable patients, the new guidelines advise that these lesions can be followed rather than treated
Summary of new recommendations

• In “young women” with CIN 2 or CIN 2/3 and adequate colposcopy, surveillance at 6 month intervals is a preferred option over treatment
• If the high grade lesion persists for 2 years, treatment is indicated
• In “young women” with CIN 3, treatment is preferred
• Given potential harms from treatment of CIN, consider using ablative techniques (cryo, laser) over excision (LEEP) when possible in reproductive aged women
Management after negative colposcopy

- Many results lead to colposcopy, but high grade disease is not always found.
- Recommendation in these cases, and after treatment for HSIL, is to repeat the co-test in 1 year.
- If HPV+ or Pap abnormal (ASCUS or worse), the recommendation is to repeat the colposcopy.
- If the colposcopy is again negative, the recommendation is to repeat the co-test in one year.
- Can lead to an endless cycle of annual colposcopy in women with persistent HPV+.
- In these cases, after 2 negative colposcopies, I recommend doing Paps only (not co-test) for surveillance.
Cervical Cancer Screening

George F. Sawaya, MD, and Karen Smith-McCune, MD, PhD

Recent changes in cervical cancer screening and management guidelines reflect our evolving knowledge about cervical carcinogenesis. In the pursuit of precision, however, decision-making has become complicated. We provide an overview of cervical cancer screening with a focus on what clinicians can do to maximize screening benefits while minimizing screening harms. The approach relies on categorizing women at each step in the screening process by their estimated risk of high-grade precancerous lesions and cervical cancer. Current screening guidelines are designed to find a reasonable balance between benefits and harms by recommending less screening in most women. Current management guidelines are designed to assure consistent decisions regarding referral to colposcopy. After initial colposcopy, we outline three major management options based on risk assessment. For treatment, we recommend ablational procedures when appropriate because they are similarly effective, less costly, and potentially safer than excisional procedures. We advise caution in adopting new screening strategies until they demonstrate cost-effective patient-centered improvements compared with current strategies. Clinicians can maximize their effect on cervical cancer prevention by being attentive to guidelines, assuring that women have access to appropriate human papillomavirus vaccination and providing low-cost, high-quality screening and treatment.


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### Table 2. Management of initial screening test results

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory cytology</td>
<td>Repeat cytology in 2-4 months</td>
</tr>
<tr>
<td>Satisfactory cytology, but no endocervical cells</td>
<td>Repeat cytology in 3 years*</td>
</tr>
<tr>
<td>Atypical squamous cells, undetermined significance (ASC-US), hrHPV negative</td>
<td>Routine screening in 3 years</td>
</tr>
<tr>
<td>ASC-US, hrHPV unknown</td>
<td>Cytology in 12 months. Colposcopy for any abnormality. If normal, resume routine screening.</td>
</tr>
<tr>
<td>Normal cytology, hrHPV positive, HPV 16/18 negative</td>
<td>Cytology plus HPV testing in 12 months. Colposcopy for any abnormality. If both normal, repeat cytology plus HPV testing in 3 years.</td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL), hrHPV negative</td>
<td></td>
</tr>
<tr>
<td>ASC-US, hrHPV positive</td>
<td>Ages 21-24: Cytology in 12 months (colposcopy for ASC-H or HSIL+) and at 24 months (colposcopy for any abnormality). If all normal, routine screening.</td>
</tr>
<tr>
<td>Normal cytology, hrHPV positive on 2 consecutive tests</td>
<td></td>
</tr>
<tr>
<td>Normal cytology, hrHPV positive, HPV 16/18 positive LSIL, hrHPV positive or unknown</td>
<td>Age 25+: Colposcopy†</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
<td>Colposcopy†</td>
</tr>
<tr>
<td>Atypical squamous cells, cannot exclude HSIL (ASC-H)</td>
<td></td>
</tr>
<tr>
<td>Atypical glandular cells (AGC)§</td>
<td>Colposcopy with endocervical curettage; endometrial biopsy if abnormal bleeding, chronic anovulation or age 35+</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td></td>
</tr>
</tbody>
</table>

hrHPV indicates high-risk human papillomavirus. HSIL+ indicates HSIL, AGC, AIS or cancer.

*2012 ACOG/ASCCP: cytology plus hrHPV testing preferred over repeat cytology alone.

Colposcopy should be performed even if hrHPV is negative. Endocervical curettage should not be performed in pregnancy.

If atypical glandular cells are specified as endometrial, endometrial biopsy is indicated.

### Pregnant women

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>Age 21-24, manage as per non-pregnant women. Age 25+, if colposcopy indicated, may defer to 6 weeks post-partum.</td>
</tr>
<tr>
<td>LSIL</td>
<td>Age 21-24, manage as per non-pregnant women. Age 25+, colposcopy is recommended but may be deferred to 6 weeks post-partum.</td>
</tr>
</tbody>
</table>

### Women with HIV infection

manage as per average-risk women (as per ASCCP 2012)

All patients should be advised about smoking cessation and HIV testing should be offered.
Summary: Less is more

• screen every 3 years (cytology) or 5 years (co-test)

• Genotyping is only indicated in women with normal Pap and HRHPV+, to determine who needs colposcopy

• In 21-24 year olds with ASCUS or LSIL, follow with annual cytology for 2 years before colposcopy

• Consider ablative treatments rather than LEEP in reproductive age women
QUESTIONS?