Abnormal Pap Smears

Satellite Conference and Live Webcast
Wednesday, March 2, 2011
2:00 - 4:00 p.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Faculty

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Professional Affiliations

- **American Academy of Family Physicians**
- **American Society for Colposcopy and Cervical Pathology**

Professional Affiliations

- **Disclosure: I have no real or perceived vested interests that relate to this presentation nor do I have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas**

Objectives

- **At the conclusion of this presentation, the participants will be able to:**
  - **Describe the normal cervical histology and cytology**
  - **Discuss the epidemiology and relationship between HPV and cervical cancer and the natural history of cervical cancer**

Objectives

- **Describe how to obtain a Pap smear and its value and limitations**
- **Discuss the rationale of current treatment approaches based on the latest ASCCP guidelines**
- **Discuss appropriate counseling and referral of women with abnormal Pap smears**

Pap Smears

- Screening test
- Has led to decreased death rates from cervical cancer
- False-negative rate = 20%
  - Most are sampling errors, not lab errors

Pap Smears

- 50% of women with newly diagnosed cervical cancer have never had a Pap smear and 10% have not had one in the past 5 years

Pap Smear Screening Guidelines USPTF

- Begin 2-3 years after first sexual intercourse or at age 21
- Stop at age 65 for women with no risk factors for cervical ca and for those who had a hysterectomy for benign reasons

Pap Smear Screening Guidelines USPTF

- Screen every 3 years for women with no new risk factors and 2-3 consecutive normal paps

ACOG Practice Bulletin Number 109, December 2009

- Clinical considerations and recommendations:
  - When should screening begin?
    - "Cervical cancer screening should begin at age 21 years."

ACOG Practice Bulletin Number 109, December 2009

- The recommendation to start screening at age 21 years regardless of the age of onset of sexual intercourse is based in part on the very low incidence of cancer in younger women

ACOG Practice Bulletin Number 109, December 2009

- It is also based on the potential for adverse effects associated with follow-up of young women with abnormal cytology screening results

ACOG Practice Bulletin Number 109, December 2009

- Although cancer is rare in adolescents, dysplasia is not uncommon
- Recent studies have documented a significant increase in premature births in women previously treated with excisional procedures for dysplasia (Lancet 2006:367:589-98. Meta-analysis)

ACOG Practice Bulletin Number 109, December 2009

- Sexually active adolescents (younger than 21) should be counseled and tested for STI and counseled regarding safe sex and contraception

ACOG Practice Bulletin Number 109, December 2009

- What is the optimal frequency of cervical cytology screening?
  - Cervical cytology screening is recommended every 2 years for women aged 21-29, with either conventional or liquid based cytology

ACOG Practice Bulletin Number 109, December 2009

- Women aged 30 years and older who have had three consecutive cervical cytology test results that are negative for intraepithelial lesions and malignancy may be screened every 3 years

ACOG Practice Bulletin Number 109, December 2009

- Risk factors associated with CIN and thus women with these may require more frequent cervical screening
  - Infection with HIV
  - Immunosuppressed
  - Exposure to DES in utero
  - Previously treated for CIN2, CIN3, or cervical cancer

ACOG Practice Bulletin Number 109, December 2009

- At what age is it appropriate to recommend discontinuing screening?
  - Women aged 65 years and older represent 14.3% of the US population but have 19.5% of new cases of cervical cancer

ACOG Practice Bulletin Number 109, December 2009

- Different peaks in the rate of disease in different ethnic groups
  - When to stop screening must therefore take into consideration a woman's past screening history

ACOG Practice Bulletin Number 109, December 2009

- ACS recommends stopping screening at age 70 in low risk women after 3 consecutive negative cervical cytology screening tests in the past decade
- USPSTF recommends age 65 as the upper limit of screening

ACOG Practice Bulletin Number 109, December 2009

- When is it appropriate to discontinue screening for women who have undergone hysterectomy?
  - Total hysterectomy for benign reasons and no prior history of high grade CIN, routine cytology testing should be discontinued

ACOG Practice Bulletin Number 109, December 2009

- If she had a history of CIN2 or CIN3 (or in whom a negative history cannot be documented) should continue to be screened

ACOG Practice Bulletin Number 109, December 2009

- When is HPV testing appropriate?
  - Triage test for women 21 years and older with a diagnosis of ASC-US and postmenopausal women with a diagnosis of LSIL

ACOG Practice Bulletin Number 109, December 2009

- HPV testing should not be used in females younger than 21 years and if inadvertently performed, a positive result should not influence management

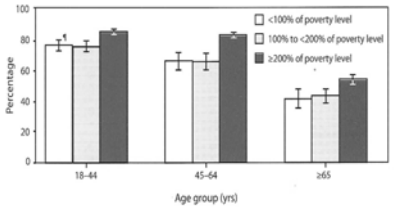
ACOG Practice Bulletin Number 109, December 2009

- When cervical cytology and HPV DNA testing are used together, can low-risk women be screened less frequently?
  - Co-testing is an appropriate screening test for women older than 30 years

ACOG Practice Bulletin Number 109, December 2009

- If both tests are negative, she should be rescreened no sooner that 3 years

Percentage of Women Aged ≥18 Years Who had a Papanicolaou (Pap) Smear Test* During the Preceding 3 Years, by Age Group and Poverty Status† — National Health Interview Survey, United States, 2008



* Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population. Responses are based on a series of questions in the cancer screening supplement of the 2008 National Health Interview Survey, including "Have you ever had a Pap smear or Pap test?" and "When did you have your most recent Pap smear or Pap test?" All women were included, regardless of whether they had had a hysterectomy.
† Poverty status is family income as a percentage of the federal poverty level and takes into account family size and composition.
¶ 95% confidence interval.

HPV

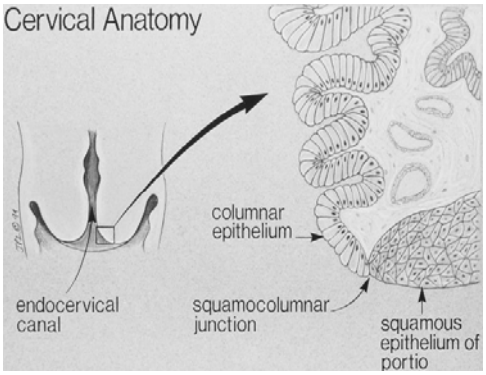
- Highly prevalent, sexually transmitted infection
- High risk types
  - HPV 16 and 18 (oncogenic)
- Low risk types
  - HPV 6 and 11 (genital warts)

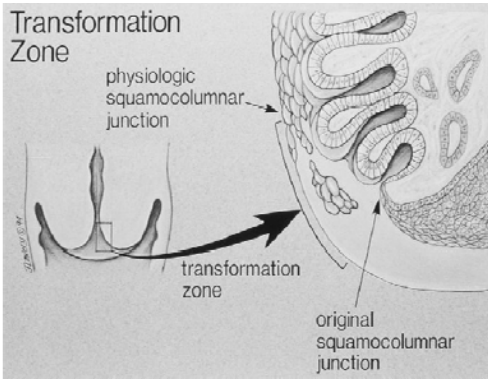
HPV

- Estimated 75% of adults will be infected with HPV during their lifetime

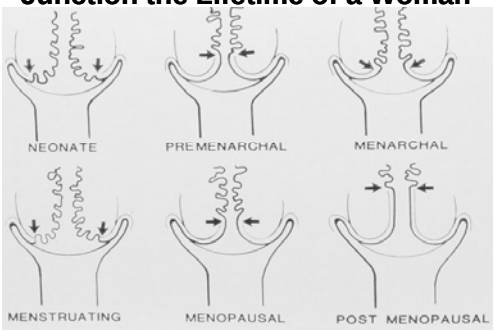
Risk Factors for HPV Infection

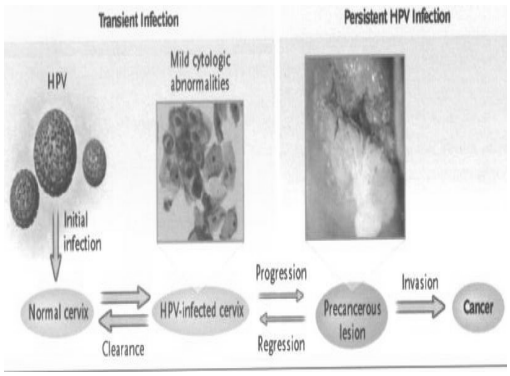
- **Higher number of recent sexual partners**
- **Previous infection with herpes simplex and genital warts**
- **Younger age at initiation of sexual activity**





The Location of Squamocolumar Junction the Lifetime of a Woman





Will HPV Resolve?

- **Median time to resolution:**
  - **Ho (1998) 8 months**
  - **Woodman (2001) 13.7 months**
  - **Richardson (2003) 13.2 months**
  - **Xi (2002) HPV16 17.2 months**

Ho. *N Engl J Med*. 1998; 338: 423-428.
Woodman. *Lancet*. 200;1.9:1831-1836.
Richardson. *Cancer Epidemiol Biomarkers Prev*. 2003;12:485-490.
Xi. *Cancer Epidemiol Biomarkers Prev*. 2002;11:343-51.

Quadrivalent Human Papillomavirus (Types 6,11,16,18)

- Recombinant Vaccine
  - Trade name: Gardasil (Merck & Co., Inc.)
  - Indication for use: vaccination in females 9-26 years of age for prevention of the following diseases caused by HPV Types 6,11,16 and 18

Quadrivalent Human Papillomavirus (Types 6,11,16,18)

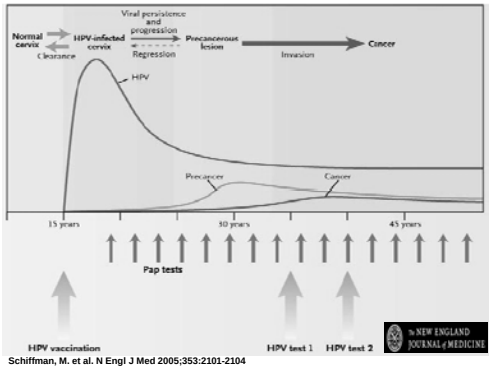
- Cervical cancer
  - CIN 2/3
- VIN 2/3
  - VaIN 2/3
- Genital warts
  - CIN 1
- AIS

HPV Vaccination

- Gardasil (Merck) is recommended for females 9-26 years old
- 3 dose series
  - Dose #2 given 2 months after dose #1
  - Dose #3 given 4 months after dose #2

HPV Vaccination

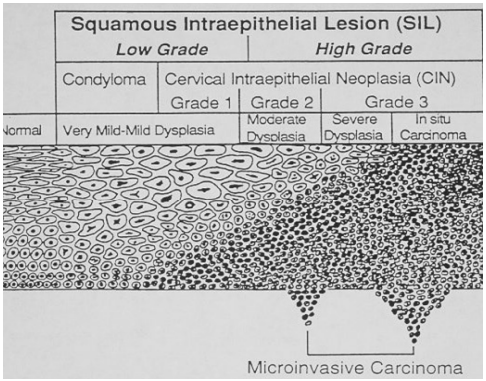
- Minimum interval between dose #1 and #2 is 4 weeks and between dose #2 and #3 is 12 weeks
- Given IM in the deltoid
- www.cdc.gov/mmwr/pdf/rr/rr56e312.pdf

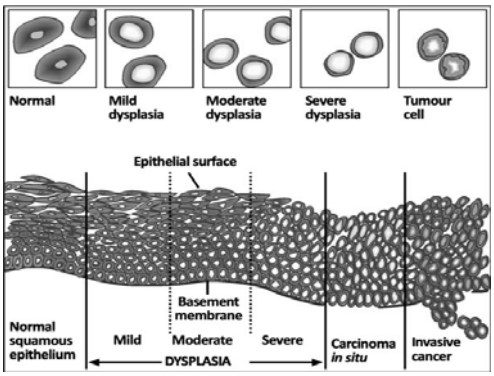


Schiffman, M. et al. N Engl J Med 2005;353:2101-2104

Evolution of Pap Smear Nomenclatures

PAPANICOLAOU		Intermediate Nomenclatures		BETHESDA SYSTEM (1988)
Class I	No abnormal cells	Normal		Normal
Class II	Atypical cells below level of neoplasia	Atypia – numerous types		ASCUS
Class III	Abnormal cells c/w dysplasia	Mild dysplasia	CIN 1	Low grade SIL (HPV/CIN 1)
		Moderate dysplasia	CIN 2	High grade SIL (CIN 2 and 3)
Class IV	Abnormal cells c/w CIS	Severe dysplasia Carcinoma in situ	CIN 3	
Class V	Abnormal cells c/w invasive squamous cell CA	Consistent with invasive cancer		Squamous cell CA



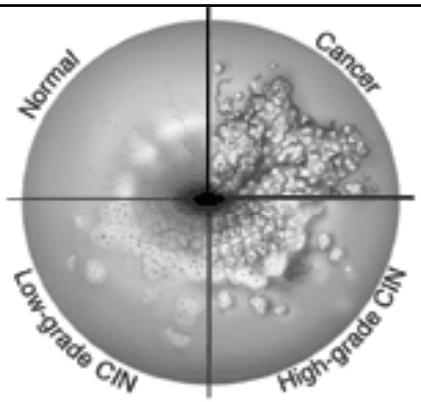


ASC-US

- **Atypical squamous cells of undetermined significance**
- **Slightly larger nucleor to cytoplasmic ratio**

ASC-US

- **A given woman with a cytological diagnosis of ASC has a 5-17% chance of having biopsy-confirmed CIN 2, 3**
  - **However, the risk that a woman with ASC has invasive cervical cancer is low**
    - **Approximately 0.1-0.2%**



Atypical Squamous Cells (ASC)

- **Several points need to be understood in order to interpret the consensus guidelines for the management of ASC**
  - **First, even with expert cytologists, the diagnosis of ASC is poorly reproducible**

Atypical Squamous Cells (ASC)

- Only 55% of the cytology specimens originally diagnosed as ASC in the ALTS trial were subsequently given a diagnosis of ASC by the pathology quality control group

Atypical Squamous Cells (ASC)

- Many of the slides initially interpreted as ASC were subsequently classified as normal
  - Adapted from Wright et. al., JAMA (2002;287; 2120-2129)

Pap Smear Tidbits

- Water-based speculum lubricant does not affect Pap screening
  - Hathaway JK, et al. Ostet Gynecol Jan 2006;107:66-70
- Right sided ectocervical lesions may be missed
  - Jeronimo, Jose et al ASCCP Journal of Lower Tract Genital Disease, Vol 7 Nov 2003; 175-183
- Tobacco carcinogens concentrate in the cervical mucous

ASCCP Consensus Conference for the Management of Women with Cervical Cytological Abnormalities and Cervical Cancer Precursors

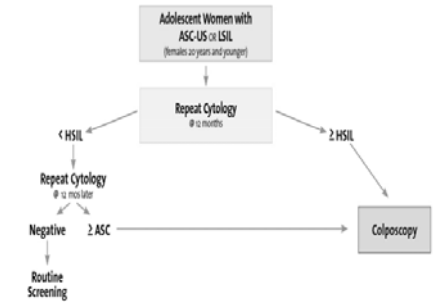
September 6-8, 2001
NIH Natcher Conference Center
Bethesda, Maryland

REVIEWS Oncology www.AJOG.org

2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests

Thomas C. Wright Jr, MD; L. Stewart Massad, MD; Charles J. Dunton, MD; Mark Spitzer, MD; Edward J. Wilkinson, MD; Diane Solomon, MD, for the 2006 American Society for Colposcopy and Cervical Pathology–sponsored Consensus Conference

Management of Adolescent Women with Either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)



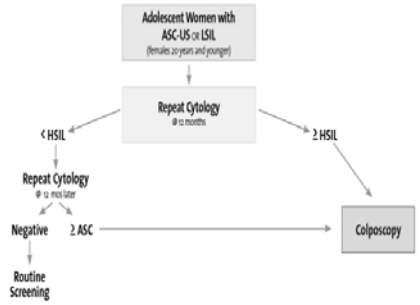
Cervical Cancer in Adolescents: Screening, Evaluation and Management

- ACOG Committee Opinion Number 463 August 2010
  - An adolescent with a history of normal cytologic screening the past should not be rescreened until age 21 years

Cervical Cancer in Adolescents: Screening, Evaluation and Management

- ACOG Committee Opinion Number 463 August 2010
  - If an adolescent has had a Pap test result of ASC-US or LSIL or CIN 1 in the past but has had 2 subsequent normal Pap test results, rescreening can be delayed until age 21 years

Management of Adolescent Women with Either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)



Cervical Cancer in Adolescents

- Screening, evaluation, and management
  - ACOG Committee Opinion Number 463 August 2010

Cervical Cancer in Adolescents

- For adolescents with HSIL or ASC-H or CIN2 or more severe, the current management guidelines detailed in the Committee Opinion should be followed
  - No "see and treat" leep

Cervical Cancer in Adolescents

- If on biopsy no CIN 2, 3 is found, observation with colposcopy and cytology at 6 month intervals is recommended for up to 2 years provided the result of the endocervical sampling is negative

Cervical Cancer in Adolescents

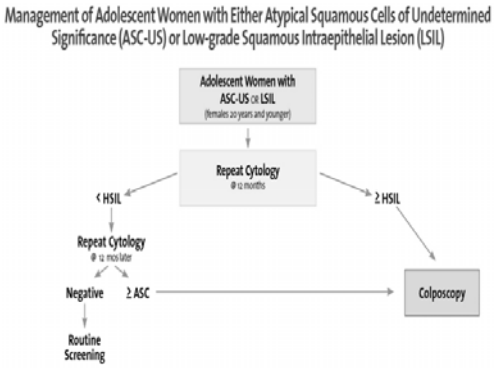
- ACOG Committee Opinion Number 463 August 2010
  - For adolescents with HSIL or ASC-H or CIN2 or more severe, the current management guidelines detailed in the Committee Opinion should be followed

Cervical Cancer in Adolescents

- If HSIL or high-grade colposcopic lesions persist at 1 year, repeat biopsy and thorough examination of the vagina is recommended

Cervical Cancer in Adolescents

- A diagnostic excisional procedure is recommended if HSIL persists at 24 months as confirmed by either cytology or colposcopy results and if the examination of the vagina does not explain the abnormality



ASC-US in Adolescents

"HPV DNA testing and colposcopy are unacceptable for adolescents with ASC-US. (EII) If HPV testing is inadvertently performed, the results should not influence management."

– 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Screening Tests

Atypical Squamous Cells (ASC)

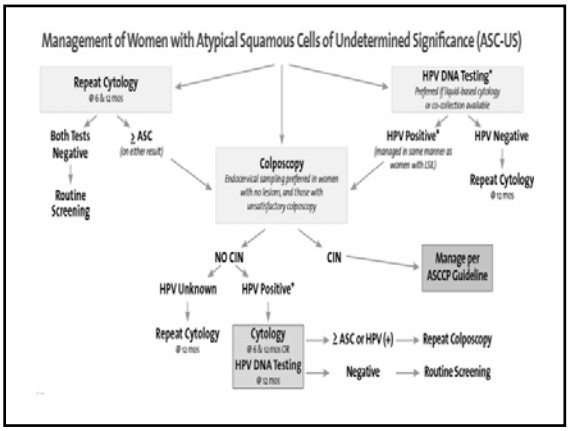
- A given woman with a cytological diagnosis of ASC has a 5-17% chance of having biopsy-confirmed CIN 2, 3
  - However, the risk that a woman with ASC has invasive cervical cancer is low
    - Approximately 0.1-0.2%

Atypical Squamous Cells (ASC)

- **The prevalence of CIN 2, 3 is considerably higher (24-94%) among women referred for colposcopy for the evaluation of ASC-H compared to women referred for the evaluation or ASC-US**
  - **Adapted from Wright et. al., JAMA (2002;287:2120-2129)**

Atypical Squamous Cells (ASC)

- **These risk factors confirm that:**
  - **A woman with ASC result requires some form of additional evaluation**
  - **But clinicians should attempt to prevent unnecessary anxiety, cost, inconvenience, and patient discomfort during work-up or follow-up**
  - **Adapted from Wright et. al., JAMA (2002;287:2120-2129)**



Immunosuppressed and Postmenopausal Women

- **"HIV-infected, other immunosuppressed women, and postmenopausal women with ASC-US should be managed in the same manner as women in the general population." (BII)**
  - **October 2007 American Journal of Obstetrics and Gynecology**

ASC-US in Special Circumstances

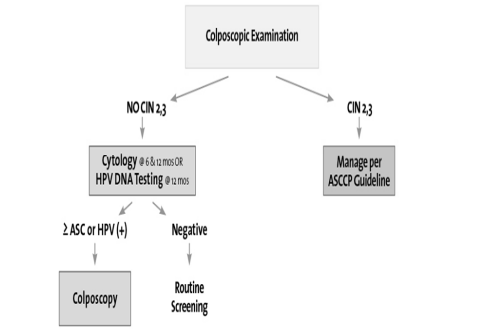
- **Pregnant patients**
  - **Management options for pregnant women over age 20 with ASC-US are identical to those described for non-pregnant women, with the exception that it is acceptable to defer colposcopy until at least 6 weeks postpartum. (CIII)**

ASC-US in Special Circumstances

- **Endocervical curettage is unacceptable in pregnant women. (EIII)**
  - **October 2007 American Journal of Obstetrics and Gynecology**

Management of Women with Atypical Squamous Cells

- Cannot exclude HSIL (ASC-H)



Low-grade Squamous Intraepithelial Lesion (LSIL)

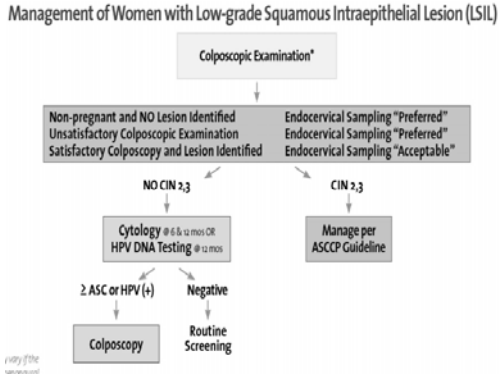
- General comments
  - The median LSIL rate in the US in 1996 was 1.6%
  - Rates as high as 7.7% have been reported from laboratories serving high-risk populations

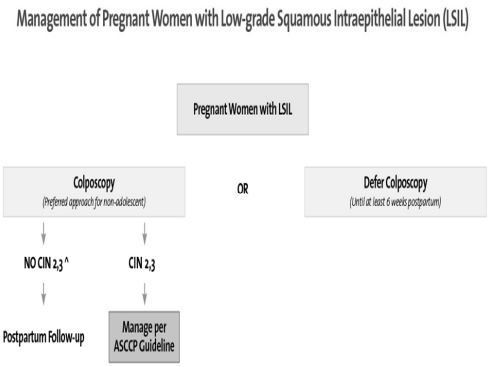
Low-grade Squamous Intraepithelial Lesion (LSIL)

- There is a relatively poor correlation between the grade of a lesion identified by cervical cytology and the grade of a lesion that is identified on a colposcopically directed biopsy

Low-grade Squamous Intraepithelial Lesion (LSIL)

- Biopsy-confirmed CIN 2, 3 is identified in approximately 15-30% of women undergoing colposcopy for a cytological result of LSIL
  - Adapted from Wright et. al., JAMA (2002;287:2120-2129)





LSIL in Special Circumstances

- Postmenopausal women
  - Acceptable options include:
    - "Reflex" HPV DNA testing
    - Repeat cytology testing at 6 and 12 months
    - Colposcopy

LSIL in Special Circumstances

- If HPV DNA is negative or CIN is not identified at colposcopy, repeat cytology in 12 months is recommended
  - If either the HPV DNA test is positive or the repeat cytology is ASC-US or greater, colposcopy is recommended

– October 2007 American Journal of Obstetrics and Gynecology

Recommendations for Managing Women with HSIL

- A cytological diagnosis of HSIL is relatively uncommon
  - The median rate of HSIL in the US in 1996 was only 0.45% according to a College of American Pathologists Intralaboratory survey

Recommendations for Managing Women with HSIL

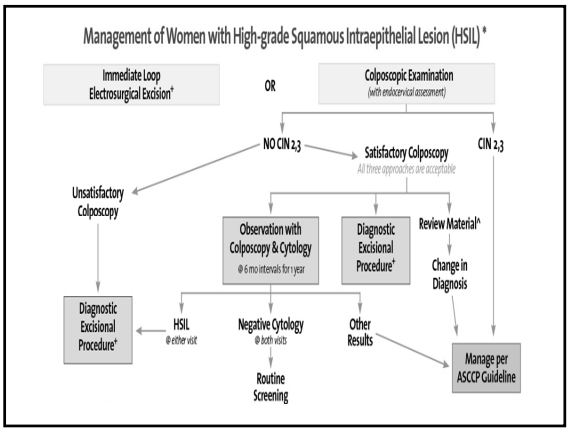
- A cytological result of HSIL is a significant finding since it identifies a subset of women who are at relatively high-risk for harboring a CIN 2, 3 or invasive cervical cancer

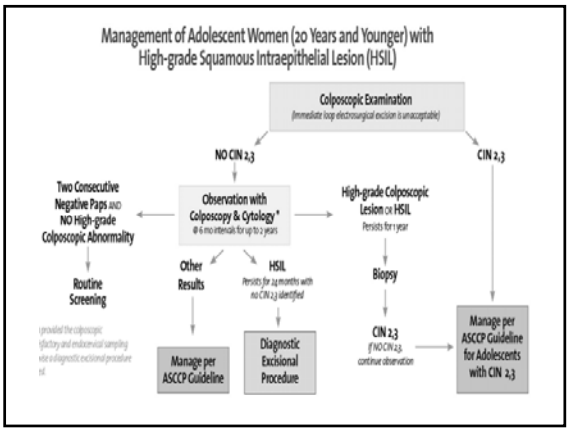
– Adapted from Wright et. al., JAMA (2002;287:2120-2129)

Recommendations for Managing Women HSIL

- Approximately 70-75% of women with HSIL will be found at colposcopy to have a biopsy-confirmed CIN 2, 3
- 1-2% have invasive cervical cancer

– Adapted from Wright et. al., JAMA (2002;287:2120-2129)



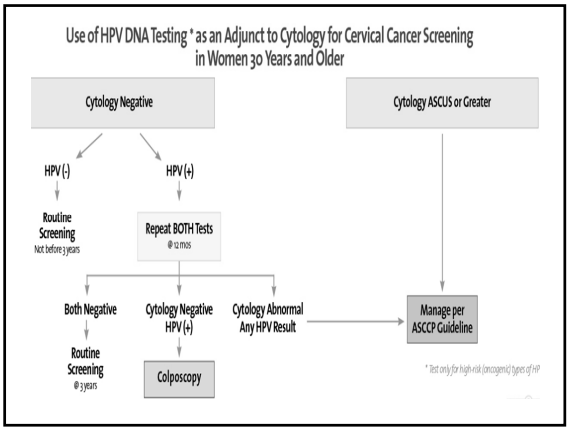


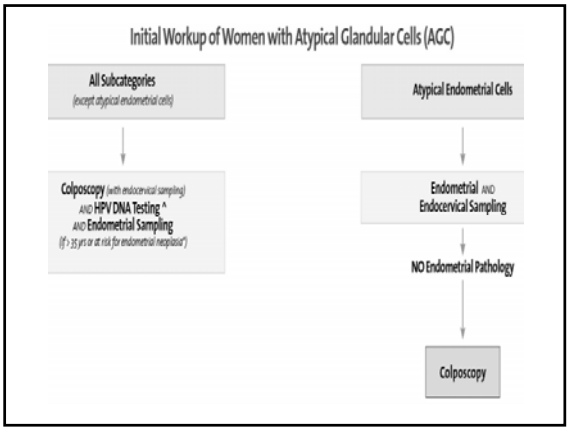
Case Study

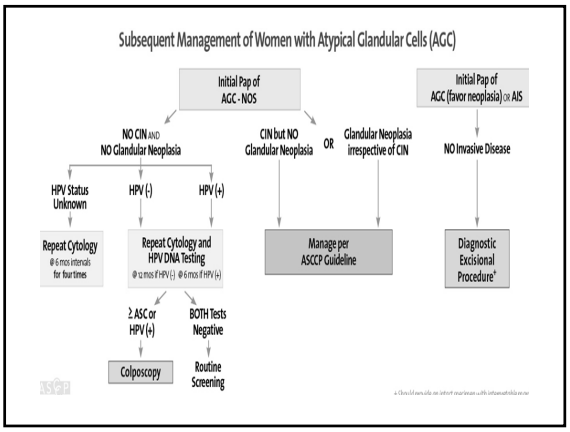
- **19 year old G2 P1 A0 (LC-1 age 18 months)**
- **Presents at 17 weeks gestation with initial pap HSIL**
- **Colposcopic exam done and biopsy results were "normal"**
  - **Repeat pap also done at that time was HSIL**

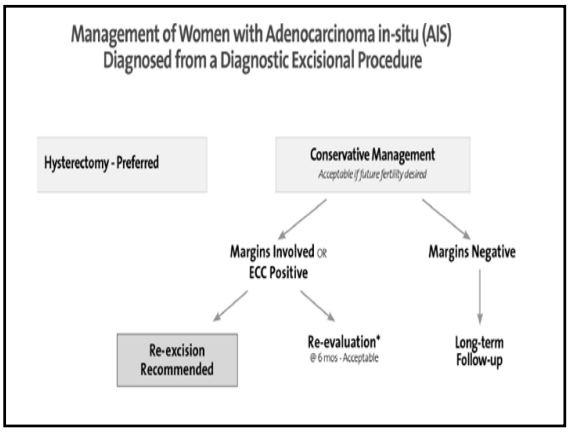
Case Study

- **Repeat colposcopic exam**
  - **"No lesions seen"**
- **Recommendation**
  - **Repeat pap and Colposcopy 3 months post partum**
    - **Which will be 6 months since last colpo and pap**









Key Educational Messages

- **Most women will have HPV at some point**
  - **But very few develop cervical cancer**
- **Most HPV infections are temporary and go away on their own**

Key Educational Messages

- **Only HPV infections that persist over many years can lead to cervical cancer**
  - **Cervical cancer is preventable**
  - **Early detection of abnormal cell changes is important**

Key Education Messages

- **Cervical cancer is rare and almost always prevented through regular Pap tests**
- **It can be helpful for women to know their HPV status if she is >30 years old**
  - **This may determine how often Pap/HPV testing is recommended**

Key Education Messages

- **Don't blame**
  - **Your HPV status is not a reliable indicator of your sexual behavior or that of your partner**
    - **Wright,T and Cox, J. Clincal Uses of HPV DNA Testing 2004**

The ASCCP Consensus Guidelines

- www.asccp.org
- beaslevl@dhec.sc.gov

Unique Pap Smear Scenarios

- Management of liquid based pap test with absent endocervical/transformation zone component?
  - Usually repeat yearly if this was a routine screening
  - Consider earlier screening-at 6 months-for:

Unique Pap Smear Scenarios

- Previous ASCUS or worse without 3 normal paps
- Prior pap with AGC
- High risk HPV result within the last year
- Patient is immunosuppressed

Unique Pap Smear Scenarios

- Clinician unable to see the cervix or sample the endocervical canal
- Patient has not had regular screenings

Unique Pap Smear Scenarios

- Normal Pap with high risk HPV?
  - If both tests are normal, repeat in 3 years
  - With a negative pap and a high risk HPV type, there is a 4% risk of CIN 2/3

Unique Pap Smear Scenarios

- This risk is lower than the risk with ASCUS cytology, therefore the recommendation is to not perform colposcopy but to repeat cytology and HPV testing in 6-12 months
- If HPV resolves, resume yearly testing

Unique Pap Smear Scenarios

- If HPV positivity persists or if abnormal cytology, perform colposcopy

Case Studies

1. 16 year old female with initial ASC-US pap

Case Studies

A. Perform HPV testing...”reflex” or otherwise

B. Perform Colposcopy

C. Repeat her pap smear in 3-4 months to make sure she doesn’t have cancer

D. Repeat her pap smear in one year

E. Suspend pap testing until age 21

Case Studies

A. Perform HPV testing...”reflex” or otherwise

B. Perform Colposcopy

C. Repeat her pap smear in 3-4 months to make sure she doesn’t have cancer

D. Repeat her pap smear in one year

E. Suspend pap testing until age 21

Case Studies

2. 24 year old female with initial LSIL pap

Case Studies

A. Schedule her for a colposcopy

B. Perform HPV DNA testing

C. Repeat her Pap in 6 months

D. Schedule her for a hysterectomy

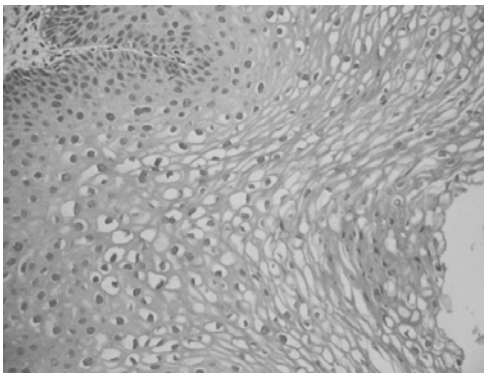
Case Studies

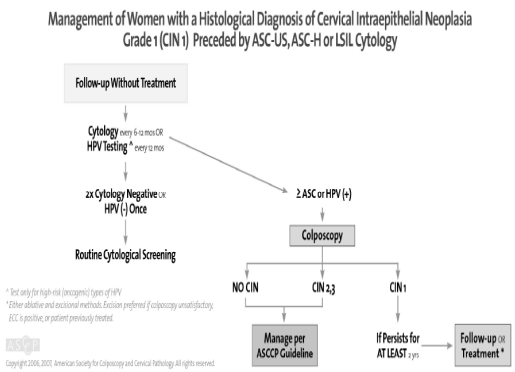
A. Schedule her for a colposcopy

B. Perform HPV DNA testing

C. Repeat her Pap in 6 months

D. Schedule her for a hysterectomy

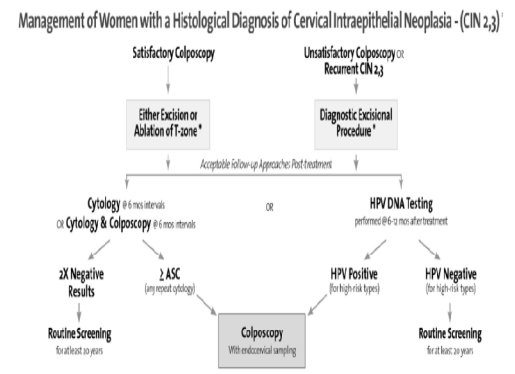




Case Studies

3. 25 year old female with follow-up ASC-US pap

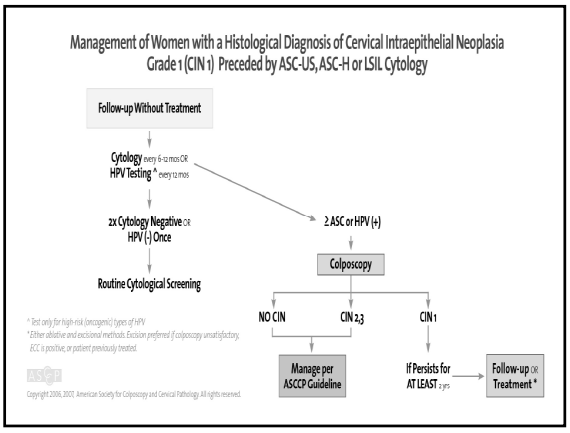
- **Previous pap was HSIL/pt had LEEP procedure 2 years ago for CIN III**



Case Studies

4. 22 year old female with "ASC-US"

- **PMH-cryo at age 16 for "? Abnormal pap"**
- **F/u pap…LSIL…had LEEP**
- **Normal pap x 3 years with "NEC"**

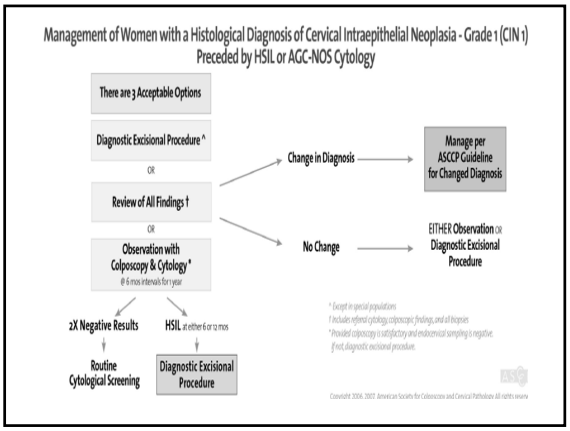


Case Study

- **25 year old Hispanic woman G2P1 A0**
- **Presents at 10 weeks gestation**
- **Initial pap HSIL**
- **Initial Colposcopy and Biopsy**
  - **CIN 1**

Case Study

- **At 30 weeks gestation**
  - **Repeat pap (HSIL) and Colposcopy**
    - **Unchanged, no evidence of invasive cancer**
- **6 weeks post partum**
  - **Pap: HSIL**
- **Colposcopy and Biopsy: CIN 1**



Case Study

- **19 year old comes to the clinic for her first pap smear**
- **She has been sexually active since age 16 and has had 4 partners**

Case Study

- **She desires birth control pills for contraception as she has just started college and isn't ready to have a baby yet**
  - **Although she confides to you she does someday want a "big family"**

Case Study

A. Refer her for immediate LEEP procedure to make sure she's "cancer free" when she decides to have children

B. Refer her for colposcopy

C. Do HPV DNA testing

D. Repeat pap smear in 6 months so she'll have a chance to heal that "HPV associated lesion"

Case Study

A. Refer her for immediate LEEP procedure to make sure she's "cancer free" when she decides to have children

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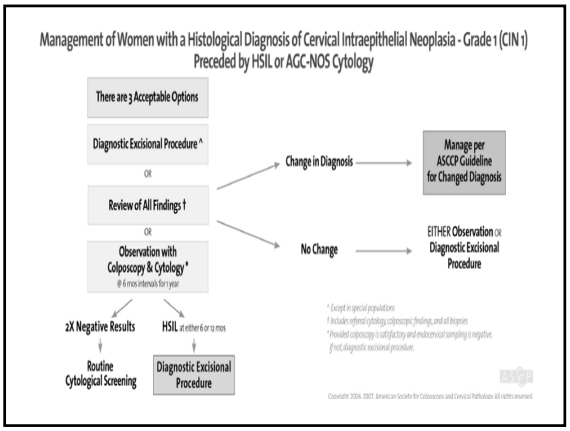

Cervical Cancer in Adolescents

- Screening, evaluation, and management
  - ACOG Committee Opinion Number 463 August 2010

Cervical Cancer in Adolescents

- For adolescents with HSIL or ASC-H or CIN2 or more severe, the current management guidelines detailed in the Committee Opinion should be followed
  - No "see and treat" leep

Cervical Cancer in Adolescents

- If on biopsy no CIN 2, 3 is found, observation with colposcopy and cytology at 6 month intervals is recommended for up to 2 years provided the result of the endocervical sampling is negative

Cervical Cancer in Adolescents

- ACOG Committee Opinion Number 463 August 2010
  - For adolescents with HSIL or ASC-H or CIN2 or more severe, the current management guidelines detailed in the Committee Opinion should be followed

Cervical Cancer in Adolescents

- If HSIL or high-grade colposcopic lesions persist at 1 year, repeat biopsy and thorough examination of the vagina is recommended

Cervical Cancer in Adolescents

- A diagnostic excisional procedure is recommended if HSIL persists at 24 months as confirmed by either cytology or colposcopy results and if the examination of the vagina does not explain the abnormality