Human Papillomavirus (HPV) and Management of Abnormal Pap Tests

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The Papanicolaou Test

- Developed by Dr’s. Papanicolaou and Traut in the 1940’s
- Consists of collecting cervical cytology from the cervix and depositing them onto a slide for microscopic evaluation
- Easy to collect and objectively interpret results
- Initially used to detect cervical cancer

Papanicolaou and Traut: Diagnosis of uterine cancer by the vaginal smear, 1943
The Papanicolaou Test

- The pap has dramatically decreased the incidence and mortality rate of cervical cancer in the United States
  - U.S. 10,000 new cases each year
    - 3700 deaths annually from cervical cancer
  - Worldwide 493,000 new cases
    - 293,000 deaths annually worldwide

The Papanicolaou Test

- Estimated 50 million paps performed in the U.S.
- 5% will be diagnosed as abnormal
- 2-3 million ASC-US paps
- 1 million LSIL paps
- 600,000 HSIL paps

Economics behind these numbers are staggering
Who Develops Cervical Cancer?

- 50% of women diagnosed with cervical cancer have not had a pap test in 5 years
- 25% of all cervical cancers are diagnosed in women older than 65
- In women older than 65, it is estimated that over 50% have not had a pap test in the past 10 years

Bottom Line – the majority of women with cervical cancer fail to get annual pap tests
Overview

- American Cancer Society guidelines for Pap testing
- Bethesda 2001 Pap nomenclature
- Human papillomavirus (HPV)
  - Types of HPV
  - Incidence of HPV
  - Incidence of HPV in cervical cancer and preinvasive disease
  - Mechanism for oncogenesis
  - Associated risk of cervical cancer with smoking
- Management of abnormal Pap tests
- Types of treatment
- Screening intervals after treatment
- HPV vaccines
American Cancer Society screening guidelines for Pap testing

- Begin testing 3 years after starting vaginal intercourse or no later than 21
- Interval is every year for a conventional pap test or every other year with liquid cytology

American Cancer Society screening guidelines for Pap testing

- At 30 years of age: IF > 3 normal/negative, satisfactory, consecutive pap tests then every 3 years IF no high-risk factors
- High-risk factors include: any abnormal pap tests, HPV infections, other STD’s – syphilis, HIV, gonorrhea and chlamydia

American Cancer Society screening guidelines for Pap testing

- Cease screening **IN**
  - Women > 70 with normal pap tests in the past 10 years
  - Women status post total hysterectomy for non-neoplastic diseases

Abnormal Pap Smears  
(Old Bethesda Nomenclature)

- **HPV** (Human Papilloma Virus)
- **LGSIL** (Low Grade Squamous Intraepithelial Lesion)
- **ASCUS** (Atypical Squamous Cells of Unknown Significance)
- **HGSIL** (High Grade Squamous Intraepithelial Lesion)
- **AGUS** (Atypical Glandular Cells of Unknown Significance)
- **AIS** (Adenocarcinoma In Situ)
- **CIS** or Carcinoma
2001 Bethesda Nomenclature, squamous cells

- **Mild dysplasia**
  - **HPV** effect (Human Papilloma Virus)
  - **ASC-US** (Atypical Squamous Cells of Unknown Significance)
  - **LSIL** (Low Grade Squamous Intraepithelial Lesion)

- **Severe dysplasia**
  - **ASC-H** (Cannot rule out HGSIL)
  - **HSIL** (High Grade Squamous Intraepithelial Lesion)
  - **CIS** (Squamous Carcinoma In-Situ)

Solomon et al. JAMA, 2002.
2001 Bethesda Nomenclature, glandular cells

- Glandular abnormalities
  - **Endometrial cells** in a woman 40 years of age or older
  - **AGC** (Atypical Glandular Cells of Unknown Significance)
  - **AIS** (Adenocarcinoma In-Situ)
  - **Adenocarcinoma**

- AGC and AIS should be handled with utmost caution

Solomon et al. JAMA, 2002.
Cytology versus Histology

- Cytology pertains to a sample of cells
  - Pap test
- Histology pertains to a tissue sample
  - Colposcopic biopsy

- Cervical intraepithelial neoplasia (CIN) is the nomenclature used for colposcopic/cervical biopsies
- Cervical intraepithelial neoplasia (CIN) and dysplasia are synonymous
Dysplasia

- Dysplasia is the medical term for preinvasive disease
- Dysplasia represents the POTENTIAL for abnormal cells to progress to invasive cancer
- This potential is subdivided:
  - CIN 1 = mild dysplasia
  - CIN 2 = moderate dysplasia
  - CIN 3 = severe dysplasia
  - Carcinoma in situ and CIN 3 are the same
Anatomy of Dysplasia

- **Moderate Dysplasia (CIN II)**
  - Abnormal cells

- **Severe Dysplasia, or Carcinoma-in-Situ (CIN III)**
  - Abnormal cells

- **Invasive Cancer**
  - Abnormal cells invading into stroma
  - Blood vessels or lymphatics

**Development of Cervical Cancer**
- Normal tissue
- Low grade smears
- High grade smears
- CIN 1, CIN 2, CIN 3
- Cancer
- 5-15 years
Human Papillomavirus

- Member of the Papovaviridae family
- Double Stranded DNA tumor virus
- 45-55 nm icosohedral capsid
- More than 100 types
- Specific for target epithelium
- Epitheliotrophic and causes proliferation
HPV and types of infection

- Mucocutaneous
  - Verruca plantaris 1,2,4
  - Verruca vulgaris 2,4,29,38
  - Verruca plana 3,10,28

- Anogenital
  - Condyloma 6,11
  - SIL and Cancer 16,18,31,33,35,45,51,56
Incidence of HPV

- 608 college aged women studied from 1992-1994
- Followed 3 years at 6 month intervals
- Incidence of infection 43%
- Median duration of any HPV infection, 8 months
- 70% cleared in one year, 90% in two years

Ho et al. NEJM 1998
Risk Factors for HPV

- African American and Hispanic races (RR 4.4 and 2.1)
- Etoh consumption > 4 times a month (RR 2)
- > 2-3 sexual partners in one year (RR 3)
- > 6 sexual partners of main regular partner (RR 10.1)

Ho et al. NEJM 1998
Incidence of HPV Types

- Most common types are high risk types 51, 66, 16, 18
  - Type 16 found in 7% of 514 women
  - Type 18 found in 4% of 525 women

Ho et al. NEJM 1998
HPV and SIL

- Persistent HPV more likely to progress to SIL
- High risk types take longer to clear (Median of 12 month)
- Women infected with high risk types documented at two 6 month visits were 38 times more likely to develop SIL

Ho et al. NEJM 1998
Incidence of HPV

- Winer et al. also studied 603 college women from 1990-2000
- Followed for 4 month intervals
- Incidence of HPV infection 32%
- Incidence among virginal women and sexually active women was the same
- Report of a new partner (5-8 months before a visit) was the greatest risk factor for acquiring HPV infection, RR 2.1

Incidence of HPV

- Richardson et al. studied 621 college students from 1996 to 2001
- Followed at six month intervals for 2 years
- Incidence was 36%
- Median time to regression was 13 months for high risk HPV

Incidence of HPV types

- HPV 16 most common
  - Ho et al. 7%
  - Kuhn et al. 6%
  - Winer et al. 10%
  - Richardson et al. 8%

- HPV 18
  - Roughly 3-4%

- HPV 33, 39
  - Roughly 3-4%
HPV and cervical cancer

- Bosch et al in 1995, accrued 932 cases of cervical cancer from around the world
- Using polymerase chain reactions (PCR), his group amplified HPV DNA from the tumor and recorded their findings
- 93% of cervical carcinoma had HPV DNA
- Common types included 16, 18, 31, 33, 35, 39, 45, 51 (high risk HPV subtypes)
Walboomers et al. repeated Bosch’s experiment using new PCR primers.

Those cancers that failed to test positive for HPV DNA were retested with these new primers.

Results showed that 99.7% of Bosch’s original cases tested positive for HPV DNA.
HPV and HSIL/CIN 3

- Severe cervical dysplasia can be described as the step before invasive carcinoma
- HPV is closely tied to the development of CIN 3
- ALTS group examined 136 women with histology proven CIN 3
- 126/136 or 93% tested positive for high risk HPV

HPV and LSIL, ASC-H, ASC-US

- ALTS group found that a significant number of patients were positive for high risk HPV with an LSIL Pap test (83%)
- ASC-H also tests positive for high risk HPV in 85% of liquid cytology Pap tests or 70% of conventional Pap test
- ASC-US has a 50% rate of testing positive for high risk HPV

HPV and oncogenesis

- Viral DNA E6 and E7 believed to be crucial in stimulating cellular proliferation
  - E6 acts by inhibiting p53 which is a crucial cell protein involved in programmed cell death (apoptosis)
  - E7 acts by binding the retinoblastoma (Rb) protein
  - Once bound, Rb releases E2F transcription factor which causes cellular proliferation
  - Combined they inhibit the regulatory mechanism for apoptosis while stimulating the cell to proliferate
HPV and oncogenesis
HPV and Smoking
Smoking and HPV

- Prior to understanding the role of HPV in cervical cancer, studies which focused on smoking as a risk factor were often contradictory.
- Once stratified for HPV status, many recent studies have shown that smokers with HPV are more likely to develop cervical cancer and CIN 3.
Smoking and Oncogenesis

- Two probable causes for oncogenesis
- Accumulation of carcinogens from tobacco smoke in cervical mucous
- Decreased host immune system
  - Decreased T cells more likely to lead to uncontrolled cell growth
Smoking and cervical cancer

Plummer et al. and the IARC performed a case-control study to determine if smoking was a cofactor for progression of HPV to cancer.

Included:
- 1463 squamous cell carcinomas
- 124 adenocarcinomas
- 211 CIN 3 cases
- 254 control women

Only women positive for HPV DNA were included.
Smoking and cervical cancer

- Results:
  - ever smoking and HPV had an OR 2.17 (95% CI 1.46-3.22)
  - Stronger risk for squamous cell carcinomas OR 2.3 (95% CI 1.31-4.04)
  - Ex-smokers also had an increased risk for developing squamous cell carcinoma, OR 1.8 (95% CI 0.95-3.44)
  - No increased risk for smoking and adenocarcinoma
Smoking and cervical cancer

- Lacey et al. performed a smaller case-control study in the US aimed at examining smoking and adenocarcinomas and squamous cell carcinomas of the cervix

- Included:
  - 124 adenocarcinomas
  - 139 squamous carcinomas
  - 309 control women

- All women were positive for HPV DNA

Lacey et al. Cancer Causes Control, 2001
Smoking and cervical cancer

Results:

- Women who smoked 1 pack per day were at an increased risk to develop squamous cell carcinoma OR 1.8 (95% CI 1.0-3.3)
- Women who smoked 1 pack per day had a decreased risk of developing adenocarcinomas OR 0.7 (95% CI 0.4-1.3)
Smoking and CIN 3

- The ALTS group examined smoking as a risk factor for developing CIN 3 or cervical cancer

- Included:
  - Originally 5,060 women with ASCUS or LSIL pap tests
  - 3,133 women with high risk HPV
  - 506 women with CIN 3 or cancer

McIntyre-Seltman et al. Cancer Epidemiol Biomarkers Prev, 2005
Smoking and CIN 3

Concluded:

- Current smokers (OR 1.7) and ex-smokers (1.7) had a mildly increased risk for developing >CIN 3
- Women who smoked more cigarettes and who smoked for a longer duration were at a higher risk for developing > CIN3
- Smoked more than 2 packs per day OR 3.3 (95% CI 1.5-7.5)
- Smoked greater than 11 years OR 2.1 (95% CI 1.5-2.9)
- Both the smoking duration and smoking intensity trended towards significance ($P_{trend} < 0.0005$)
Passive smoking and CIN 3

- Coker et al evaluated passive cigarette smoke exposure as a risk factor for developing CIN 3
- Small case-control study
- Women exposed to passive tobacco smoke were more likely to have CIN 3 (p <0.05)

Atypical Squamous Cells of Unknown Significance (ASC-US)

- COMMON
- 5% of all pap smears
- 2 million a year
- 20% - 30% have CIN (mild – severe) on any one ASC-US Pap
- 5% - 17% have CIN II and III
- Fortunately, invasive cancer is low 0.1% to 0.2%

Wright et al. JAMA, 2002.
Changes in management have come from two sources: technology and a NIH study

- Liquid cytology
  - ThinPrep (Cytyc Corporation)
  - SurePath/PrepStain (TriPath Corporation)
- ASC-US/LSIL triage study (ALTS) data
Liquid Cytology

- Wooden spatula replaced by cytobrush
- Cells collected in liquid medium instead of slide
- End result: fewer cells plated per slide, thus easier to interpret
Liquid Cytology

Conventional Pap Smear

ThinPrep Pap Test Slide
Liquid Cytology

- Several studies published documenting decreased rates of ASC-US and increased rates of SIL
- Vassilakos studied 15,000 women by conventional pap smear and 32,000 women by liquid cytology
- Concluded 130% reduction in ASC-US
- 275% increase in LSIL

Liquid Cytology

- Minge took 2156 patients and performed both conventional paps and liquid cytology paps
- Same-patient conventional and liquid cytology were given to separate cytopathologists
- Results: 78% of SIL discovered by thin prep versus 59% by conventional pap (p < 0.01)
- Discordant cases: thin prep found 88% more LGSIL lesions than conventional (p < 0.05)

Liquid Cytology

- Proven to be highly effective in reducing ASCUS and increasing SIL
- Should replace conventional pap smears
ALTS Trial

- Multicenter, prospective, randomized controlled study
- Took 3488 ASCUS referrals
- Each patient had thin prep and HPV typing prior to randomly being assigned a study arm
- Placed into three arms: immediate colposcopy; HPV screen, if positive then colposcopy; and conservative management with colpo only for HSIL

Solomon et al. JNCI 2001
Testing for HPV

- HPV is obtained with a cytobrush
- Hybrid capture II® (Digene) is the commercial test
- Detects 13 high risk strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
- Positive test > 1pg/ml of DNA content
All referral paps brought before pathology review board for quality control
3389 pap smears analyzed by this board
55% concurred ASC-US
45% changed !!!
- 31% NORMAL
- 14% LSIL
ALTS

- Immediate Colposcopy
  - Normal 539 (62.9%)
  - CIN I 167 (19.5%)
  - CIN II 72 (7.4%)
  - CIN III 59 (6.9%)
  - N 857
  - 35% are CIN

- HPV screening
  - Normal 237 (48%)
  - CIN I 111 (22.5%)
  - CIN II 59 (11.9%)
  - CIN III 77 (15.6%)
  - N 494
  - 50% are CIN

Solomon et al. JNCI 2001
ALTS

- 136 CIN III patients in both arms
- 125 of these were HPV positive
- Sensitivity 96.3%
- PPV 10%
- NPV 99.5%
ASC-US

- Benefit is NPV 99.5%
- Clinical Implications: If a patient is negative for high risk HPV then it is highly unlikely she will have CIN III
- Therefore: colposcopy and biopsies are unlikely to yield CIN III
ASC-US

1) Repeat Pap test in 6 months
   - If ASCUS or greater - Colposcopy
   - If normal repeat in 6 months; continue until two normal pap tests are achieved then place patient on yearly Pap test

2) Reflex HPV testing
   - If HPV positive – Colposcopy
   - If HPV negative – repeat Pap test in one year
   - Reflex HPV testing should only include high risk strains
ASC-H

- Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
- **NOT ASC-US!!!!**
- Pap test lacks conclusive cytology to be labeled as HSIL
- Significant rate of CIN 2-3 diagnosed on colposcopic biopsies (40%)
- High Risk HPV 85%
ASC-H

- COLPOSCOPY
- If colposcopy and biopsies are normal AND discussion with pathologist upholds ASC-H...
- Repeat Pap test in 6 months or HPV testing in 12 months
Low Grade Squamous Intraepithelial Lesion (LSIL)

- 1 million reported a year
- Usually histology confirms CIN 1
- High risk HPV associated with LSIL
  Pap tests 83% of time
- **Colposcopy** is the initial management
LSIL

- Common mistake made by practitioners is to equate LSIL with CIN 1
- LSIL is a cytologic specimen
- CIN 1 is a histologic specimen
- LSIL does not equal CIN 1
- 30% of LSIL paps actually harbor worse disease: CIN 2 or CIN 3
- COLPOSCOPY NEEDED
Colposcopic Findings

- Acetyl white plaques
- Bright white
- Clearly demarcated
- Fine punctations
- Acetic Acid - more is better
LSIL Pap and Colposcopy
LSIL Pap with Colposcopy
Natural Progression of CIN 1

- Ontario Cancer Registry conducted a study of Pap tests in a single cytologic laboratory
- 17,000 women identified between 1970 and 1980 with dysplasia
- Conservative treatment
Regression of CIN 1

- Mild dysplasia regressed to normal
- 44% in 2 years
- 74% in 5 years
- 88% in 10 years
Regression of CIN 1 in One Year

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<th>Variable</th>
<th>Mild Dysplasia</th>
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<tr>
<td>No. Studies</td>
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<tr>
<td>No. Patients</td>
<td>4500</td>
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<tr>
<td>Regress</td>
<td>62%</td>
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<tr>
<td>Persist</td>
<td>22%</td>
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<tr>
<td>Progress to CIS</td>
<td>16%</td>
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Wright. ACOG Colposcopic Course
2001
Progression of CIN 1

- Mild dysplasia progressed to invasive cervical carcinoma 0.1% in 2 years
- 0.3% in 5 years
- 1.6% in 10 years
Management of CIN 1

- Most cases of CIN 1 spontaneously resolve in one to two years
- Resolution similar to regression of HPV infection
- Follow with serial Pap tests every 4 to 6 months
- Persistence of LSIL for more than one year warrants repeat colposcopy
- Persistence of CIN 1 beyond 1.5 to 2 years should be treated
- Pap test progression to HSIL merits colposcopy and biopsy
High Grade Squamous Intraepithelial Lesion (HSIL)

- The most aggressive type of squamous cell dysplasia before invasive cancer
- Needs prompt evaluation and treatment (within 4 weeks of diagnosis)
- Easiest to manage: colpo, biopsy, treat
Colposcopic Findings

- Dull acetyl white plaques
- Cobblestoning
- Coarse punctuations
- Atypical vessels
- Mosaicism
Colposcopy
Colposcopy
Progression of CIN III

- Most CIN III lesions progress to carcinoma if left untreated
- This risk grows the longer it is left untreated
- CIN III has a RR 22 for progression to cervical cancer OR
- 12% of patients will develop cancer in 2 years
- 70% will develop cancer in 8 years

Holowaty et al. JNCI 1999
Atypical Glandular Cells (AGC)

- Old Bethesda system AGC was known as AGUS
- AGC was created to clear confusion between ASC-US and AGUS
- **THE TWO ARE NOT THE SAME !!!**
- Incidence is 0.1 to 1.5% of all Pap tests
- High risk HPV correlated with 38% of AGC Pap tests.
- HPV testing not recommended

AGC

AGC is worrisome for several pathologies: CIN, adenocarcinoma in situ, cervical adenocarcinoma and endometrial adenocarcinoma.

Many studies have documented the incidence of these disease processes:

AGUS system
- Eddy et al. 36%, 1997 Am J Obstet Gynecol
- Duska et al. 34%, 1998 Obstet Gynecol
- Veljovich et al. 32%, 1998 Am J Obstet Gynecol
- Manetta et al. 45%, 1999 Gynecol Oncol
- Tam et al. 31%, 2003 Gynecol Oncol

AGC system
- DeSimone et al. 38%, 2005 Obstet Gynecol
Management of AGC

- American Society for Colposcopy and Cervical Pathology (ASCCP) recommends:
  - Colposcopy with or without biopsies
  - An endocervical curettage (ECC)
  - Endometrial biopsy in women with menorrhagia or age greater than 35
  - OR referral to GYN or GYN oncologist
Management of AGC

- Does every patient need an endometrial biopsy?
- Age is important
- Premenopausal women more likely to have HSIL vs. postmenopausal women (30.4% vs. 7.4%) $p = 0.04$  
  \cite{Duska_1998}
- Women over the age of 40 were more likely to have adenocarcinoma than dysplasia (31% vs. 6%) $p=0.002$  
  \cite{DeSimone_2005}
Adenocarcinoma in-situ (AIS)

- Aggressive form of dysplasia for columnar cells
- AIS cytology associated with:
  - AIS histology (48-69%)
  - Cervical adenocarcinoma (38%)

AIS

- AIS cytology mandates colposcopic biopsies and an ECC
- AIS histology is managed with a cold knife cone (CKC)
- Numerous studies support CKC over loop electrosurgical excision procedure (LEEP) because of margin status
- CKC has fewer positive margins than LEEP
- Women with positive margins have 40-70% risk of residual AIS
- Women with negative margins have a 20 to 40% risk of residual AIS
AIS

- Recommend referral to GYN or GYN oncologist
- Nulliparous women are difficult to manage secondary to a high risk of residual disease
- Don’t underestimate the risk of invasive adenocarcinoma with an AIS Pap test
Treatment Modalities

- Cryosurgery
- Loop Electricosurgical Excision Procedure (LEEP)
- Laser Ablation
- Cold Knife Conization
- Hysterectomy
Cryosurgery

- Inexpensive, easy to perform, tolerated well by patients
- Cells are destroyed by (cold) thermal damage
- 3 minute freeze/ 1 minute thaw/ 3 minute freeze well documented technique
- Does cause 2 - 3 weeks of malodorous discharge
- Does hinder repeat colposcopy (SCJ often obscured)
LEEP

- Procedure of choice for most OB/GYN’s
- Easy to perform, well tolerated and provides specimen for pathologic evaluation (Margins)
- Concern that multiple excisions or one large excision will increase rate of preterm labor/incompetent cervix
Preterm Delivery and LEEP

- NO conclusive evidence that LEEP increases preterm labor or incompetent cervix
- 2 retrospective studies from 2004 show no difference between control and study patients
- However, most studies are small and retrospective
- Good rule to keep specimens less than 4 cm wide and 2 cm tall

Sadler, JAMA 2004 and Tan, J Obstet Gynecol 2004
Margins and LEEP

- Margin status helpful in predicting recurrence of cervical dysplasia
- Negative margins ~15%
- Positive margins ~ 30-60%
- Re-excision not needed. Follow patient with serial pap tests and treat accordingly if patient recurs

Dietrich, Obstet Gynecol 2002
Laser

- CO2 laser works by vaporizing cervical cells
- Very precise method; only need 5-7 mm of vaporization for treatment
- Heals great, spares cervical excisions
- COST major problem
- No pathology specimen
Cold Knife Conization (CKC)

- Used to be the treatment of choice before LEEP
- Surgically excises dysplasia with scalpel/scissors
- Large cost to patient from physician, anesthesia, and hospital charges
- Incompetent cervix an issue
- Indications to perform are few
Hysterectomy

- The final treatment for cervical dysplasia
- Comes with significant morbidity/ mortality and lengthy recovery (6 weeks)
- Complications include: hemorrhage, infections, bowel & bladder injuries, MI, pulmonary embolus, stroke, death
- 10-20% of patients will continue to have abnormal pap tests: vaginal dysplasia
Efficacy of treatment

- Randomized controlled trial between cryosurgery, LEEP and laser showed no statistical difference in efficacy
- Recurrences were measured from 6-37 months
- Cryosurgery 19%
- LEEP 13%
- Laser 13%

Which method to chose?

- Several factors to consider: age, desire for fertility, size of lesion, size of the cervix, severity of dysplasia, and prior therapies

- Generalizations:
  - Cryosurgery - best for young women with few finances and CIN 1 or 2.
  - LEEP - the majority of women with CIN 2 or 3. Women with endocervical lesions also suited for LEEP
Which method to chose?

- **Laser** - women who have had multiple recurrences of CIN 2 or 3 and who want to retain fertility. Example: a 19 year old G0 who has CIN 3, prior LEEP, and a small cervix.

- **CKC** - glandular abnormalities (AIS) or early invasive cancer

- **Hysterectomy** - women finished with childbearing and who have persistent CIN. Often best utilized with other gynecologic problems like pelvic pain or abnormal uterine bleeding
Post Procedure Surveillance

- **CIN 1**
  - Repeat Pap testing at 6 and 12 months
    - ASC-US or greater = colposcopy (referral 63%)
    - 2 normal Pap tests = annual cytology screening
  - High risk HPV testing at 12 months
    - Positive test = colposcopy
    - HPV 92% sensitive for detecting CIN 2-3 (referral 55%)

Post Procedure Surveillance

- CIN 2-3
  - Repeat Pap testing at 4 to 6 month intervals
    - If 3 consecutive normal Pap tests = annual cytology screening
    - Colposcopy if ASC-US or greater
  - High risk HPV testing at 6 or 12 months
    - If positive = colposcopy
    - If negative = annual cytology screening

HPV vaccines

- 3 published, double blinded randomized control trials
- 2 trials with Merck
- 1 trial with GlaxoSmithKline
- All trials target the L1 protein of the HPV virus
- L1 is the major capsid protein
HPV Vaccines

- First trial (Merck) studied HPV type 16
- HPV 16 chosen since it accounts for 50% of CIN 2-3 and carcinoma
- 2392 women randomized between Placebo or HPV 16 virus-like-particle (VLP) vaccine [40µg] given on day 0, month 2 and month 6
- Women had to be HPV 16 negative on enrollment
- Genital samples were obtained on enrollment, month 7 and then every 6 months to check for HPV 16 by PCR
- Primary endpoint was persistent HPV 16 infection defined as HPV 16 diagnosed on two or more visits
HPV Vaccines

- Results
  - Median follow up 17 months
  - Incidence of 3.8 per 100 woman-years, placebo
  - Incidence of 0 per 100 woman-years, vaccine
  - P=0.001
  - Nine cases of CIN, HPV 16 induced occurred in placebo group

HPV Vaccines

- 2nd study was funded by GlaxoSmithKline
- It evaluated a bivalent vaccine for HPV 16 and 18
- Together HPV 16 and 18 account for 70% of CIN 2-3 and carcinoma
- 1113 women were randomized to receive placebo or vaccine (0.5ml) at 0, 1 and 6 months
- Women were HPV 16 and 18 negative on enrollment
- Genital samples were obtained on enrollment and every 3 months to check for HPV 16 and 18 by PCR
- Primary endpoint was prevention of HPV 16 and 18 infection, secondary endpoint was prevention of cytologic (LSIL, HSIL) and histologic abnormalities (CIN 1-3)

HPV Vaccines

Results

- Vaccine efficacy 91.6% against incident infections
- Efficacy 100% against persistent infection
- Vaccine arm two cytologic abnormalities (ASC-US, LSIL)
- Placebo arm 30 cytologic abnormalities (15 ASC-US, 14 LSIL, 1 HSIL)
- Vaccine efficacy 93.5% (95% CI 3-99.1; p=0.002)
HPV Vaccines

- 3rd study (Merck) evaluated a quadrivalent vaccine HPV 16, 18, 6, 11
- HPV 6, 11 account for 90% of condyloma (genital warts)
- 552 women randomized to placebo or vaccine at 0, 2 and 6 months
- Women were HPV 6,11,16,18 negative on enrollment

HPV Vaccines

Results

- Vaccine 4/235 cases of infection or clinical disease
- Placebo 36/233 cases of infection or clinical disease
- Efficacy difference 90% (95% CI 71-97; p=0.0001)
- No cases of condyloma or CIN in vaccine arm
- 3 cases of CIN and 3 cases of condyloma in placebo arm

HPV Vaccines

- HPV vaccines are effective in preventing HPV infection and clinical infections such as condyloma and CIN
- Large study by Merck presented at the meeting for Infectious Diseases Society of America confirmed these three studies with 5,000 women per arm
- Vaccine will be a boon for 3rd world countries with high rates of cervical cancer
HPV Vaccines

- **Limits**
  - Vaccines not widely available yet. Projected for 8/2006
    - Estimated cost $600 for three shots
  - Who do we start immunizing?
    - FDA recommend girls
    - What about boys?
  - At what age do we start immunizations?
    - Age 9-21
    - Best to immunize before onset of coitarche (sex)
  - Length of duration?
    - Latest studies suggest activity at 36 months
  - What about cross over immunization between other HPV strains?
    - Latest reports suggest there is cross over immunization
  - Will Pap testing cease?
    - Not likely in the next 40 years
    - We will need to see wide spread acceptance of the vaccine and immunizing men and women before Pap testing can be discontinued
Summary

- HPV is **THE** cause of cervical cancer and dysplasia
- Majority of men and women will have been exposed to HPV before the age of 50
- Smoking is an important co-factor in oncogenesis
- Upcoming vaccinations are effective in preventing HPV infections and histologic abnormalities
Summary of Squamous Abnormalities

- **ASC-US** Pap tests should either be repeated in 6 months or a reflex HPV testing should be performed
  - On repeat cytology, women with ASC-US or greater or women with positive HPV testing should undergo colposcopy

- **LSIL /ASC-H /HSIL** Pap tests should undergo colposcopy
Summary of Glandular Abnormalities

- **AGC** Pap tests should undergo colposcopy, ECC and endometrial biopsy (women >35 or menorrhagia)
- **AIS** Pap tests should be referred to a GYN or GYN oncologist
Summary of CIN

- **CIN 1** should be followed with serial cytology every 6 months or HPV testing at 12 months
  - Women with 2 normal Pap tests can resume annual cytology screening
  - Women with HPV negative testing can resume annual cytology screening

- **CIN 2-3** should be treated with an excision procedure
  - Post procedure cytology should be evaluated every 4 to 6 months OR
  - HPV testing at 6 to 12 months