

Pap Smear Guidelines: Family Planning Update 2008 Part One

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Faculty

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Objectives

- **Discuss the epidemiology and etiology of cervical precancerous and cancerous disease**
- **Compare the effectiveness of conventional vs liquid based pap smears**
- **Describe the natural course of HPV infection and its role in the development of cervical cancer**

Objectives

- **Discuss HPV vaccination guidelines**
- **Discuss new pap smear recommendations and the rationale behind the new changes**

Cervical Cancer

- **Incidence of Cervical Cancer:**
 - **9.2 per 100,000 (age-adjusted for the US population) in 2000**
 - **US Cancer Statistics Working Group. United States Cancer Statistics: 2000 Incidence. Atlanta, Ga: Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2003**

Cervical Cancer

- **Cervical cancer incidence has decreased by 77.7% from 1950 to 2001**
- **Mortality reduced by as much as 70% due to pap smear screening**

Etiology of Cervical Cancer

- **Infection with High Risk HPV**
 - 16,18,31,33,35,39,45,51,52,56,58,59,68 and 69
 - Mostly 16,18,45 and 31

HPV Infection

- **The prevalence of genital HPV infection**
 - Highest among sexually active teens and women in their 20s
 - Decreases after age 30

HPV and Cervical Cancer

- **HPV infections usually resolve spontaneously within 1-2 years**

HPV and Cervical Cancer

- **Persistent infection with High Risk HPV infection is a prerequisite for the development of cervical cancer**

Cervical Cancer and HPV

- **Although HPV infection is necessary for the development of cervical cancer, majority of women who are infected with HPV do not develop cervical cancer**

Risk Factors for Cervical Cancer

- **Infection with high-risk HPV**
- **Smoking**
- **Immunosuppression**
- **Multiple sex partners**
- **Young age at first pregnancy**

Risk Factors for Cervical Cancer continued

- Low socioeconomic status
- Long-term oral contraceptive use

UK National Health Service: Cervical Cancer Screening Programs
October 14, 2004

HPV and Genital Cancer

- Cervical cancer, precancerous lesions, vulvar, vaginal and anal and to a lesser extent pharyngeal cancers are associated with high-risk subtypes of HPV
- There are more than 15 high risk subtypes associated with cervical cancer
- 70% of cervical cancers are associated with high risk subtypes 16 and 18

Precancerous Lesions of the Cervix

- Cervical Intraepithelial Neoplasia is a precancerous precursor of cervical cancer
 - CIN 1 (often self limiting)
 - CIN 2
 - CIN3CIN 2 and CIN 3 are considered to be precancerous lesions with potential to progress to cancer

HPV and Cervical Cancer

- Majority of women with High risk HPV infections clear the infections from the genital tract
- Only a small minority develop persistent HPV infection
- Those who have persistent HPV infection are at increased risk for cervical cancer

HPV and Cervical Cancer

- Most women with HPV infections do not develop cervical cancer
- However, mortality rates can be high in women with invasive cervical cancer
- Cervical cancer is a preventable sequel of a persistent high risk HPV infection of the genital tract

HPV and Genital Cancer

- Cervical cancer is rare in women who had never been infected with HPV
- In the U.S., cervical cancer used to be #1 cancer in women both in incidence and mortality
- Since the advent of Pap smears in 1950s, the number of cervical cancers and cancer deaths came down dramatically in the US

HPV and Cervical Cancer

- Cervical cancer is the 2nd most common cancer in the world.
- Close to 500,000 cervical cancers are seen in the world annually
- We still see about 10,000 cervical cancers in the U.S. annually

Genital Warts

- Genital warts are caused by low risk subtypes; most common are 6 and 11
- Genital warts are seen in 1% of US population
- Not all people infected with HPV develop genital warts

HPV Vaccine

- The U.S. FDA approved Gardasil, the HPV vaccine in June, 2006
- Gardasil is a recombinant vaccine made by genetic engineering
- It's a quadrivalent vaccine
- The genes that code for a specific protein from each of the four viruses are expressed in yeast to create large quantities of protein used as the vaccine

Gardasil

- Distributed in the U.S. by Merck Inc.
- A quadrivalent vaccine
 - HPV types 6,11,16,18
 - Does not protect against the types not included in the vaccine
 - Women are not protected if already been infected with one or more of the HPV types in the vaccine

Gardasil

- Most effective if administered before a woman has had any of the four subtype infections incorporated in the vaccine

Gardasil

- Prevents cervical cancer, precancerous lesions, and genital warts due to HPV subtypes in the vaccine
- Will not work as a treatment of existing precancerous lesions or genital warts
- May not be effective in preventing cancers and precancerous lesions from other subtypes of HPV

Gardasil

- The US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends routine vaccination with Gardasil for 11 and 12 year old girls
- Females 13-26 years of age can be vaccinated if not vaccinated previously
- ACIP states that children as young as 9 years can be vaccinated

Gardasil

- Currently not recommended for boys and women older than 26
- Being studied in males and older women

HPV Vaccine

- Given in 3 doses:
 - 1st visit
 - 2 months later
 - 6 months later

HPV Vaccine

- Ideal for women before becoming sexually active
- Can be given in sexually active girls
- Can be given even in women with
 - Abnormal pap smears
 - Existing HPV infections
 - Genital warts

HPV Vaccine

- No need to assess for HPV infections
- Can be given with other vaccines
- Can be given to immuno-suppressed women
 - HIV positive women

HPV Vaccine

- Most sexually active women under age 26 will benefit from vaccination
 - Most are not infected with all the 4 subtypes of HPV
 - Will be protected against the subtypes they were not exposed to
 - Protection against genital warts unless infected earlier

HPV Vaccine

- The benefit is lower for those who had abnormal pap smears and genital warts

HPV Vaccine

- Vaccinating women over 26:
 - It seems likely that sexually active women over age 26 will benefit from vaccination
 - Safety data are excellent

HPV Vaccine in Older Women

- Counsel older women about
 - off-label use of HPV vaccine
 - Immune system is generally more responsive in younger women
 - Obtain informed consent

HPV Vaccine

- Can an adolescent give her own consent?
 - Not clear
 - Depends on the individual state laws
 - Cancer vaccine
 - May need parental permission

Safety

- The vaccines are safe
- Side effects are minor
- Long-term surveillance studies are being conducted

Vaccine Efficacy Gardasil

- Gardasil prevents CIN 2/3 (the cervical cancer precursors) caused by HPV 16 and 18
 - 100% effective in women not currently infected with HPV 16 and 18

HPV Vaccine

- **Cost:**
 - \$120 per dose
 - \$ 500 for 3 doses including 3 office visits
 - Most insurance companies cover the vaccine

HPV Vaccine

- Currently not recommended for pregnant women
- HPV vaccine registry is maintained for those who are pregnant and received the vaccine
- In clinical trials, no adverse effects found in infants worth mentioning
- Safe in lactating women

Pap Smears

- Do women still need to receive pap smears even after they received 3 doses of HPV vaccine?
 - Yes
 - Other 13 high risk oncogenic subtypes associated with cervical cancer
 - How long the immunity lasts unknown

HPV Vaccine

- Most common reactions are site related:
 - Pain
 - Erythema
 - Swelling
 - Fever
 - The vaccine is generally safe

HPV Vaccine

- Individuals who are allergic to yeast or other components of vaccine should not take the vaccine
- Gardasil is not a live vaccine
- Infection does not occur with the vaccine

American Cancer Society Recommendations

- ACS guidelines for HPV vaccination:
 - Routine vaccination for girls 11 and 12 years of age
 - Girls as young as 9 may be vaccinated
 - Recommended for teenage girls 13-18 years of age

American Cancer Society Recommendations

- **ACS guidelines for HPV vaccination:**
 - Evidence is insufficient for or against vaccination of women between 19-26 years of age
 - Not recommended for women above 26 years of age and for men

HPV Vaccination

- **Data still lacking regarding:**
 - How long the immunity lasts
 - If boosters are needed

A Second HPV Vaccine

- **A second vaccine to prevent cervical cancer**
- **Bivalent vaccine HPV 16 and 18**
- **Cervarix TM**
- **GlaxoSmithKline**
- **Approved in September 2007**

A Second HPV Vaccine

- **Studied in girls between 10 and 25 years of age**
- **Long-term trial data showed 100% immunity against HPV 16 and 18 lasting up to 5.5 years**
- **Not approved in the US**

Vaccine Efficacy

- **It is expected that the protection against all CIN 2/3 lesions will remain close to 70% after 10 years for HPV naïve population of women between 15-23 years old because of cross-protection with other oncogenic HPV subtypes**

HPV Vaccines

- **Covered by**
 - Many private insurers
 - Medicaid
 - Federal vaccines for children program
- **Merck has a Patient Assistance Program that would pay for the vaccine on need basis**

Methods of Pap Screening

- **Conventional Method:**
 - Glass slide, wooden spatula and cytobrush
- **Liquid Based Method:**
 - Cervix brush or broom
 - Plastic spatula and cytobrush

Pap Screening

- **Conventional Pap smear is associated with a high rate of false-negative results**
- **The use of liquid based Pap testing has decreased the incidence of false-negative Pap results**

Liquid Based Pap Smears

- **The sensitivity of AGUS and adenocarcinoma was found to be significantly greater with the liquid-based test**
- **72.0% with LBP vs 41.5% with Conventional**

New Pap Guidelines

- **American Cancer Society proposed new Pap smear screening recommendations in 2002**
 - endorsed by:
 - United States Preventive Services Task Force
 - American College of Obstetrics and Gynecology

New Pap Guidelines

- **Begin screening approximately 3 years after the 1st vaginal intercourse or at age 21 whichever comes first**
 - Test every 1 to 2 years until age 30
 - * every 2 years with liquid-based pap (ACS)

New Pap Guidelines

- **Test every 2 to 3 years after age 30**
 - In well screened women with prior negative pap

New Pap Guidelines

- Consider discontinuing Pap after age 65 to 70 in well-screened women
 - With no history of significant dysplasia(age 65 according to USPSTF and 70 according to ACS)

New Pap Guidelines

- Discontinue Pap testing in women whose uterus and cervix have been removed for benign conditions
 - with no history of high-grade cervical dysplasia or cancer

New Pap Recommendations

- Continue annual pap screening in women with no cervix with:
 - History of cervical cancer/precancer
 - In utero exposure to diethylstilbestrol
 - Immunocompromised women
 - HIV positive individuals

The Main Questions

- Why wait 3 years after first intercourse for the first pap test?
- Why is the age 21 the “default” age for first pap test?
- What is the cost of screening women over age 65?

The Main Questions

- What is the harm in continuing Pap tests in all women regardless of the age?
- Will women return for annual exams as we advise, if we change their Pap routine?

Yearly Pap Smears

- The yearly Pap test was advocated long before data suggested one interval might be better than another

Why Wait 3 Years After Onset of Intercourse for First Pap Test?

- The goal of pap smear screening is to diagnose and treat precancerous lesions and prevent cancerous progression
- A 3 year delay is highly unlikely to compromise timely diagnosis of high grade lesions

Why Wait 3 Years After Onset of Intercourse for First Pap Test?

- It does allow discovery and eradication of dysplastic changes long before they become malignant

Rationale

- Cervical cancer develops only after persistent HPV infection, many years from the initial infection
- HPV infections in young women are usually transient
- Up to 90% of young women who test positive for HPV DNA will revert to negative within 2 years

Initial Screening

- Problems of screening too early:
 - Squamous cancer of the cervix is exceedingly rare under age 21
 - HPV infections are exceedingly common in women under age 21
 - Diagnosis of self limited HPV infections and transient low grade dysplastic lesions
 - Would lead to unnecessary repeat pap smears
 - Unnecessary colposcopies

STD Screening and Contraception

- Delaying pap by 3 years in sexually active young women does not mean that these women do not need routine gynecologic care
- They still need
 - STD screening and counseling
 - Contraceptive counseling

Why is Age 21 the “Default” for First Pap?

- Incidence of High Grade SIL increases with age
- Cervical Cancer is rare in teenagers and young women
- Cytology screening starting at age 21 would capture most women at risk
- A 21 year old who has never had vaginal intercourse may not need to be screened for cervical cancer

Aggressive Screening Until Age 30

- Screening
 - Every year with conventional pap smears
 - Every 2 years with liquid based pap smears
 - According to ACS guidelines
 - According to ACOG yearly screening regardless of the method is recommended

Rationale

- Frequent screening until age 30 allows us to identify and treat young women with histologic cervical intraepithelial neoplasia (CIN II and CIN III or worse) which may progress to cancer

Pap Screening: Ages 30-65

- Research indicates that it is reasonable to reduce the screening interval from every year to every 2-3 years in previously well-screened women over age 30

Pap Screening: Ages 30-65

- Both ACOG and ACS recommend annual screening regardless of age if following risk factors are present
 - History of cervical cancer/precancer
 - Immunocompromise (HIV)
 - DES exposure
 - Those not screened well under the age 30
 - Should have at least 3 negative pap smears

Pap Smears in Older Women

- If an older woman's sexual practices change, consider restarting screening

Postmenopausal Screening

- Women over 65 do get cervical cancer
- 25% of new cases of cervical cancer are in women above age 65
- 41% cervical cancer mortality is in women above age 65

Postmenopausal Women

- However, incident cases of squamous cancer among older women are seen in those “who have not been well screened previously”

Postmenopausal Screening

- An older woman in a long-term monogamous relationship who has a history of frequent negative pap smears is at such low risk for acquiring cervical cancer that the US Preventive Services Task Force recommends discontinuing screening at age 65

Postmenopausal Screening

- American Cancer Society recommends discontinuing screening at age 70 in low-risk previously well screened women

Postmenopausal Screening

- While acknowledging the recommendations of these other professional organizations, ACOG notes that there is no good evidence to establish an age to discontinue screening

Postmenopausal Screening

- Heart and Estrogen/Progestin Replacement Study:
 - 2,561 women
 - Pap every 1-2 years
 - 110 recalled for follow-ups
 - 231 interventions (repeat paps, colposcopies, cervical and endometrial biopsies and D&C)
 - Only one woman with histologic moderate dysplasia

Postmenopausal Screening

- Among low risk population, routine pap screening may lead to:
 - Additional tests
 - Unnecessary cost
 - Anxiety
 - Limited value of screening

Screening Among Women with Hysterectomy

- Since 1996, US Preventive Services Task Force has recommended against Pap screening in women who had uterus and cervix removed for benign reasons

Hysterectomy

- A recent study showed as many as 45.6% of such women were still having pap smears
- Cervical cancer screening among women without cervix

Pap Smear in Women Without Cervix

- For any screening procedure to be cost effective, there must be a threshold prevalence of the disease in the population to be screened

Pap Smear in Women Without Cervix

- While women with prior cervical cancer or high-grade dysplasia remain at increased risk for recurrences at the vaginal cuff, women with no history of such disease are at extremely low risk of cancer

Pap Smear in Women Without Cervix

- In essence, screening these women becomes a search for primary vaginal cancer
- Primary vaginal cancer is very rare- only 0.3% of cancers in women

Pap Smear in Women Without Cervix

- Pap testing in the absence of cervix
 - results in screening an unacceptably large number of women to diagnose a rare cancer

Pap Smear in Women Without Cervix

- Cytology screening in this group is far more likely to diagnose low grade vaginal intraepithelial neoplasia (VAIN 1) which reflects self-limited epithelial changes extremely unlikely to progress to cancer

HPV Testing

- Hybrid Capture DNA 2 assay to detect 13 high-risk HPV subtypes:
 - Triage of ASCUS pap smears
 - Combined PAP-HPV DNA

PAP-HPV DNA

- A combination Cytology+HPV DNA test
- US FDA approved PAP-DNA in 2003 for use in women over age 30
- Both ACS and ACOG approved the combination test
- Should be used every 3 years if both tests are negative

PAP-DNA

- PAP-DNA screening in women under 30 is not useful
 - High prevalence of high-risk HPV in this age group
 - Results in unacceptably high numbers of women testing positive whose risk of invasive cervical cancer is low

Women Under 30

- Women under 30 should be screened with pap smear alone
- Routine HPV testing is not indicated in this group

PAP-DNA

- Prevalence of HPV declines after age 30
- PAP-DNA test is valuable in this age group
- High negative predictive value of the combination test

PAP-DNA Test

- Women can be assured that if they test negative on the combination test, their risk of CIN3 or squamous cancer is negligible at least for 3 years

PAP DNA

- Both cytology and HPV are negative:
 - Repeat the test in 3 years

Putting New Guidelines into Practice

- Easier said than done
- Patients need a clear message
- Tell patients:
 - Don't stop annual exams
 - Breast exams and
 - Other health related check ups are necessary

Counseling HPV Patients

- Sexually transmitted
- High prevalence: >75% population of reproductive age
- Low risk of cancer for the partner
- Low risk of cervical cancer
- Importance of timely pap screening

References

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- The new HPV vaccine: What the ObGyn needs to know: OBG management: January 2007:40-48