Cervical Testing and Results Management

An Evidenced-Based Approach
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Debora Bear, MSN, MPH
Assistant Medical Director for
Planned Parenthood of New Mexico, Inc.

Burden of cervical cancer

PAP

- Physical
- Activity
- Prescription
Burden of Cervical Cancer

Why do we care about cervical testing?

Burden of Cervical Cancer

All Cancer in women: US Perspective
2009 ACS Estimates
www.cancer.org accessed April 2010

- Cases of Cancer
  713,220
- Deaths from all Cancer
  269,800
- Cancer Cases by site
  - Breast 192,370 27%
  - Lung/Bronchus 103,350 14%
  - Cervical 11,270 < 1.6%
- Cancer Death by site
  - Lung/Bronchus 70,490 26%
  - Breast 40,680 15%
  - Cervical 4,070 < 1.5%

Deaths from heart disease in women
25.8%
(2006 data from CDC accessed April 2010)
Burden of Cervical Cancer

All Cancer: World wide perspective

2004 WHO

- Around 13% of all deaths are from cancer
- Lung, stomach, liver, colon and breast cancer are the leading cancers in developing countries
- Eighty percent of cervical cancer is in less developed countries

www.who.accessed April 2010

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Burden of Cervical Cancer

Cervical Screening works to decrease Cervical Cancer

- **US**
  - cervical cancer incidence decreased by 50% from 1975 to 2005
  - ~36% in US die from cervical cancer

- **World-wide**
  - Developed countries: 525,120 : 2,336,986
  - Developing countries: 1,811,867: 2,336,986
  - ~48% die in developing countries
    (www.WHO accessed February 2010)
Burden of Cervical Cancer

- ~50% of women with cervical cancer have never been tested
- ~10% more have not been tested within 5 years
- About 14 adolescents develop cervical cancer every year
- Testing the same people who are already being tested will not decrease the burden of cervical cancer

Burden of cervical cancer

- Why patients think Pap smears are done:
  - Start birth control
  - Test for “everything”
  - Ovarian cancer
  - Breast discharge
  - So they won’t get vaginal warts
  - Irregular periods
  - New sexual partner
History behind cervical screening

Historical Perspective of “Pap” tests

- 1928 Dr. Papanicolaou worked with
- Dr. Stockard- dysplastic, malignant cells
  - Dr. Babes (first to publish) from the Romanian Cancer Institute. Dr. Babes published in the French medical journal, Presse Medicale. And with
  - Dr. Traut worked with Dr. Papaniolaou to identify lesions.
- Revision in labs over the years
- US peak between 1970 to mid 1990’s have led to yearly “annual” as the norm.

Colposcopy Principles and Practice,
Barbara Apgar, 2008

History behind cervical screening

Fifty-Five Million Pap tests yearly

- 3.5 million require follow-up
- Cost of liquid based cervical screening
  - Twice as much as conventional (glass)
- Impact of over-screening
  - Increased anxiety/morbidity
  - Dysplasia in adolescence is not uncommon
  - Cancer in adolescence is rare and rates did not decrease with screening
  - treatment on adolescent health
    - Premature birth?
    - Label an adolescent w/ STD & pre-cancer

ACOG Practice Bulletin, December 2009
### History behind cervical screening

#### US Cervical Screening Guideline

<table>
<thead>
<tr>
<th>Organization</th>
<th>Ages</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>21-29</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>ACS</td>
<td>3 years after sexual activity</td>
<td>Pap every 1-2 years</td>
</tr>
<tr>
<td></td>
<td>or age 21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>Pap and HPV test every 3 years</td>
</tr>
<tr>
<td>USPTF</td>
<td>3 years after sexual activity</td>
<td>Every 3 years with pap testing</td>
</tr>
<tr>
<td></td>
<td>or ages 21-65</td>
<td>only</td>
</tr>
</tbody>
</table>

#### Other Developed Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Ages</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>≥ 18</td>
<td>2 years</td>
</tr>
<tr>
<td>UK</td>
<td>25-64</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Canada</td>
<td>18-65</td>
<td>3 years</td>
</tr>
<tr>
<td>Finland</td>
<td>30-60</td>
<td>5 years</td>
</tr>
</tbody>
</table>
History behind cervical screening

- Finland
  - 1964 to 1994
  - 66% decrease in cancer
  - 7 cytology tests in a lifetime
  - 40% of invasive cancer was from women who were not screened

Pathophysiology of HPV

- HPV is a necessary factor in development of squamous cervical neoplasia
- Most HPV-infected females will not develop cervical disease
- HPV type and persistence are the most important determinants of progression
- Cigarette smoking and compromised immune system
Pathophysiology of HPV

- > 100 types of HPV
- 40 Infect the genital tract
- > 90% resolve within 2 years
- 60% acquire HPV within 5 years of having sex
- 75-90% of people will have HPV at some time (ASCCP Accessed April 2010)
- HPV is transmitted asymptptomatically
- A minority of HPV persists for 5-20 years
- Persistence of HPV, not incidence, is associated with disease
- CIN 3 peaks ages 25-30 and cancer at least 10 years later

Pathophysiology of HPV

- HPV types 16, 18, 45 cause 70-80% of invasive cervical cancer
- Cervical HPV is associated with squamous cell and adenocarcinoma
- Non-cervical consequences:
  - 35-50% of vulvar and vaginal cancer
  - VIN 2/3 and VAaIN 2/3 are precursors
  - Genital warts: HPV 6 & 11 cause 90% of genital warts
  - Anal cancer: HPV causes 90%
  - Head and neck: HPV causes ~40%
New Testing Standards

- Liquid-based vs. conventional glass
  - Costs more?
  - Not more sensitive, less specific
  - Cyto techs like it
  - Automated and computerized equipment
  - Reflex HPV
  - Possibly fewer unsatisfactories
- Reflex HPV
- Pap + HPV for women $\geq 30$
- Genotyping: Cervista 16/18

Bethesda System: Cytology

- The formation, structure, and function of cells
- The cervical screen (Pap) result
- Changes over the years to standardize
  - CIN since the 1960s- continuum of pre-cancerous lesions
  - Uniform terminology system lead to clear set of management guidelines
  - 2001: Result/interpretation not “diagnosis”
Cytology:

- Specimen type
  - Conventional vs. liquid-based

- Specimen Adequacy
  - Satisfactory (describe presence of T-zone)

- General Categorization (optional)
  - NILM

- Interpretation/Result
  - Negative for intraepithelial lesion or malignancy
  - Organisms
  - Other (endometrial cells)
  - Epithelial Cell Abnormalities
  - Other malignant neoplasms

ASC-H= Atypical squamous cells of undetermined significance, cannot exclude HSIL (this is not the same thing as ASC-US)

* Recommend colposcopy as at least 35% will have high-grade lesions
Histology: WHO Criteria

- Study of the microscopic tissue structure
- The biopsy result
- CIN 1 (low grade)
- CIN 2,3 (high grade)
- Squamous cell carcinoma
- Adenocarcinoma-in-situ
- Adenocarcinoma

Management of Abnormal Cervical Testing

Evolution of Therapy

<table>
<thead>
<tr>
<th>Decade</th>
<th>CIN 1</th>
<th>CIN 2,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950’s-60’s</td>
<td>not treated</td>
<td>cold cone, hysterectomy</td>
</tr>
<tr>
<td>1970’s</td>
<td>cryo</td>
<td>cryo, cone</td>
</tr>
<tr>
<td>1980’s</td>
<td>cryo, laser</td>
<td>cryo, laser, cone</td>
</tr>
<tr>
<td>Early 90’s</td>
<td>LEEP, cryo</td>
<td>LEEP, cone</td>
</tr>
<tr>
<td>Late 90’s</td>
<td>cryo, No Rx</td>
<td>LEEP, cryo, cone</td>
</tr>
<tr>
<td>2000</td>
<td>No Rx</td>
<td>LEEP, cryo, cone or follow-up</td>
</tr>
</tbody>
</table>
Management of Abnormal Cervical Testing
ASC-US Follow-Up Using HPV Testing
(reflex or sample co-collected at time of original Pap)

- HPV Test
  (Reflex ordered if possible)

  - HPV +
    - Colposcopy
  - HPV -
    - Repeat Cytology @ 12 mos

Management of Abnormal Cervical Testing
ASC-US Follow-Up without using HPV Testing

- Repeat Cytology @ 6 & 12 mos

  - Both Tests Negative
    - Routine Screening
  - ≥ASC (on either test)
    - Colposcopy
Management of Abnormal Cervical Testing

- ALTS: ASCUS/LSIL Triage Study for Cervical Cancer
- ALTS was a clinical trial designed to find the best way to manage the mild abnormalities that often show up on Pap tests
- HPV testing is not useful for women with a Pap test diagnosis of LSIL
- The sensitivity of the colposcopy procedure is increased when the colposcopist takes more than one biopsy

Management of Abnormal Cervical Testing

Post-colposcopy Strategies, LSIL or HPV+
ASCUS with ≤ CIN 1 on Initial Colposcopy

1539 women with LSIL or HPV+ ASCUS found to have CIN 1 or less on colposcopy
Followed over 2 years with q 6 mo. Cytology and HPV testing in ALTS study
10.6 found to have CIN 2,3 by 2 years f/u

<table>
<thead>
<tr>
<th>Effectiveness of follow-up options</th>
<th>Sens. For CIN 2+</th>
<th>Referral to colpo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap at 6 &amp; 12 mo.</td>
<td>88.0%</td>
<td>63.6%</td>
</tr>
<tr>
<td>HPV testing at 12 mo.</td>
<td>92.2%</td>
<td>55.0%</td>
</tr>
</tbody>
</table>
Management of Abnormal Cervical Testing

- Have references, such as ASCCP nearby
- History
  - When test was done (how old was she?)
  - What test was done
    - HPV < 21
    - Cytology?
    - Colposcopy?
      - Satisfactory colposcopy?
      - Follow-up plan from colposcopist?
- What test results
  - CIN 2,3
- What treatment
  - Cryo
  - LEEP
    - Margins clear?

Prevention: Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Gardasil</th>
<th>Cervarix</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV types</td>
<td>16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td></td>
<td>6, 11</td>
<td></td>
</tr>
<tr>
<td>What does it do</td>
<td>Protect against 70% of cervical cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90% of genital warts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protection against vulvar and vaginal cancers and pre-cancers</td>
<td></td>
</tr>
<tr>
<td>Who can get it</td>
<td>Women and girls 9-26+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men and boys 9-26+</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Merck 2009, GSK 2009, ACIP 2009
Prevention: Vaccines

- HPV vaccines do not treat HPV
  
  (JAMA 298 (7): 743-53, 2007)

- HPV vaccines can still be administered after an abnormal cytologic screening or manifestation of genital warts
  
  - It has not been tested in women that have had 4 or more sexual partners
  
  - It is unknown if it is cost effective in this age group
  
  (ACS, 3, 2007 accessed May 2008)

- Dosing
- Side Effects

Patient Education

- HPV
  
  - prevention
  
  - Vaccine
  
  - Warts
  
  - Sexual partners

- Cytology results
  
  - “pre-cancer”
  
  - Next-step

- Frequency and types of tests
Education

PAP

- Physical
- Activity
- Prescription