Cervical Cancer Screening

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Epidemiology

- Cervical cancer is the second most common cancer among women worldwide
- About 86% of the cases occur in developing countries
- Age adjusted incidence is about 27 cases per 100,000 women per year
- Cervical cancer has the highest incidence compared to other cancers in women of all ages in India (breast cancer being second)
- Cervical cancer mortality rate in India is approx 13 per 100,000 women per year
- Fully preventable if detected early

Facts from WHO India Information Center on HPV and Cervical Cancer, 2010
Cervical cancer screening

- Conventional Pap smear
- Liquid Based Cytology
- Molecular Diagnosis/HPV
Please submit!!!

• Patient’s history/Age
• Clinical findings
• LMP
• Systemic or Topical hormones & additional information that aids in preparing a comprehensive report.
3 Steps to accurate Cyto-diagnosis

**STEP 1:**
- Time and effort in preparing a good smear sample
- **WHAT IS NOT ON THE SMEAR CANNOT BE DIAGNOSED!!**
- Spreading and uniformity
3 Steps to accurate Cyto-diagnosis

STEP 2:

• Screener

• **THERE IS NO SUBSTITUTE FOR CAREFUL SCREENING**

• An atypical cell not seen or misinterpreted is possibly the only chance of avoiding the development of a potentially fatal disease

• **NO DEFINITE WHITES & BLACKS**
3 Steps to accurate Cyto-diagnosis

**STEP 3:**

- **POSITIVE OR ATYPICAL SMEAR SHOULD BE FOLLOWED UP BY AN ADEQUATE CONFIRMATORY TEST**
- Good liaison & dialogue between the clinician & cytology department
- Follow up
- **CYTO-HPV- HISTO- CORRELATION**
The Conventional Pap Smear
The Conventional Pap smear

The greatest challenge in cervical screening has been the tedious task of finding a needle in a haystack, where majority of haystacks have no needle!
The Goal of Pap testing

THE GOAL OF PAP TESTING IS TO IDENTIFY PRECANCEROUS CELL CHANGES BEFORE THEY PROGRESS TO CANCER
Challenges of conventional Pap smear

- Unsatisfactory specimen
- Non-representative sample
- Cervical cells obscured by inflammation and blood
- High false positive rate leading to unnecessary cervical biopsy
- 14%-33% false negative

More than 80% of the cells are not transferred to the slide in a conventional pap smear
Liquid Based Cytology
To address the shortcomings of the conventional smear, newer technologies were introduced.

In 1996, the **Thin Prep Pap** test by Hologic became the first LBC to be approved by the US FDA.

In 1999, a second LBC was approved by the FDA, the **SurePath Pap Test**.

**Thin Prep test procedure** uses a liquid based filtration process for slide preparation whereby the sample is dispersed, filtered and a representative sample is transferred to the slide.
Thin Prep Consumables
Thin Prep Sample Collection
**Improvement of LBC vs conventional Pap**

- More cells are collected
- Clearer slide because obscuring material is removed
- Increased disease detection rate
- Thin Prep provides a 65% increase in the diagnosis of LSIL or greater cytology
**Conventional Pap Smear**
- Majority of cells not captured
- Non-representative transfer of cells
- Clumping and overlapping cells
- Obscuring material

**ThinPrep Pap Test**
- Virtually all of the sample is collected
- Randomized, representative transfer of cells
- Even distribution of cells
- Minimizing obscuring material
LARGE, RETROSPECTIVE STUDY CONFIRMS SUPERIORITY OF THINPREP® PAP TEST

Two-period, retrospective analysis of approximately 2 million specimens showed with the ThinPrep Pap Test:

- Improvement was statistically significant after correcting for selection bias
- Significant decrease in false-negative proportion
- 233% improvement in the HSIL detection in high-risk cases
- Decrease in ASC-US to SIL ratio

SIL = squamous intraepithelial lesions.
Thin Prep Advantage

The **ONLY LBC test** approved by US FDA for

- Detection of glandular lesions and adenocarcinoma
- HPV DNA testing and genotyping
- Chlamydia and Gonorrhoea testing
- Reprocessing procedure for unsatisfactory specimen
Human Papilloma Virus (HPV) and Cervical Cancer
Why test for high risk HPV DNA

- HPV testing when combined with Pap test is more sensitive in determining the presence of disease than a Pap test alone
- HPV is sexually transmitted and is a major etiologic agent of cervical cancer
- HPV infection increases, by over 250 times, the relative risk of cervical cancer
- It helps to clarify ambiguous cytology results
Who should be tested – Latest Recommendations

New Cervical Cancer Screening Recommendations from the U.S. Preventive Services Task Force and the American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology

*March 15, 2012, issue of Annals of Internal Medicine*

- 1st time that USPSTF has recommended the combined use of cervical cytology and high-risk human papillomavirus (HPV) DNA testing (“co-testing”).
- CS/ASCCP/ASCP finds that co-testing every 5 years is *preferred* to cytology alone but that cytology alone every 3 years is an *acceptable* strategy. In choosing to make co-testing the preferred strategy, ACS/ASCCP/ASCP focused on evidence from multiple randomized trials showing that co-testing has improved performance compared with cytology alone.
- Specifically, co-testing has increased sensitivity for detecting cervical intraepithelial neoplasia grade 3 or greater (CIN3+), and women who have undergone co-testing have a lower risk of CIN3+ and invasive cancer after the first screening round.
Summary of Recommendations

I. Women under 21 years
Females under the age of 21 should not be screened.

I. Women ages 21-29 years
Women ages 21-29 years should be screened with cytology (cervical cytology testing or Pap testing) alone every three years. Screening intervals should not be changed based on the number of previous normal results.

Women ages 21-29 years should:

- Not be screened every year or more frequently than recommended
- Not be tested for HPV alone or in combination with cytology, unless for the triage of ASC-US results

Notes on Follow-up: Women ages 21-29 years screened with cytology alone who have **ASC-US cytology results associated with negative HPV test results** should continue to be screened every 3 years with cytology.
Summary of Recommendations (cont.)

III. Women ages 30-65 years

Women ages 30-65 years should be screened with cytology and HPV testing (“cotesting”) every 5 years (preferred) or cytology alone every 3 years (acceptable). Screening intervals should not be changed for either modality based on the number of previous negative screening results.

In most clinical settings, women ages 30-65 years should not be screened with HPV testing alone as an alternative to cotesting at 5-year intervals or cytology alone at 3-year intervals.

Women ages 30-65 years should not be screened every year or more frequently than recommended.

Notes on Follow-up: Women ages 30-65 years testing HPV positive, cytology negative should have one of the following two follow-up options:

1. Repeat cotesting in 12 months
   - If the follow-up cotest is positive, women should be referred to colposcopy.
   - If the follow-up cotest is negative, women should be screened again with cotesting in 5 years.

2. Immediate, HPV genotype-specific testing for HPV16 or HPV16/18.
   - Women testing positive for either HPV16 or HPV18 should be referred directly to colposcopy.
   - Women testing HPV16 or HPV16/18 negative should be cotested in 12 months.
     o If the follow-up cotest is positive, women should be referred to colposcopy.
     o If the follow-up cotest is negative, women should be screened again with cotesting in 5 years.

A positive cotest is HPV positive OR LSIL or more severe cytology. A negative cotest is HPV negative AND ASC-US or negative cytology.
Summary of Recommendations (cont.)

III. Women ages 30-65 years

Women testing **HPV positive, cytology negative** should:

• **Not** be referred directly to colposcopy

• **Not** be tested for individual HPV genotypes other than HPV16 and HPV18 or for non-HPV biomarkers.

Women ages 30-65 years with **ASC-US cytology results associated with a negative HPV test** should continue to **be screened** with cotesting in 5 years or with cytology alone in 3 years.

IV. Women over 65 years of age

Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN2 or more severe diagnosis or cervical cancer within the last 20 years should not be screened for cervical cancer with any modality. Once screening is discontinued it should not resume even if a woman reports having a new sexual partner.

*Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the last 10 years before ceasing screening, with the most recent test performed within the past 5 years.*
Summary of Recommendations (cont.)

V. Women with a history of CIN2 or a more severe diagnosis

Following spontaneous regression or appropriate management of CIN2 or a more severe diagnosis, routine screening should continue for at least 20 years (even if this extends screening past age 65).

VI. Women post-hysterectomy for benign reasons

Women at any age following a hysterectomy with removal of the cervix for benign reasons (i.e., no history of CIN2 or more severe diagnosis or cervical cancer) should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. Once screening is discontinued it should not resume even if a woman reports having a new sexual partner.

VII. Women with a history of HPV vaccination

Women at any age with a history of HPV vaccination should be screened according to the age-specific recommendations for the general population.
Both Cytology and Molecular Tests are Possible from the ThinPrep® Vial

*ThinPrep is the only liquid-based Pap FDA-approved for use with molecular diagnostics tests*
**CISH (Chromogenic in situ hybridization)**

- CISH, or chromogenic in situ hybridization, is a process in which a labeled complementary DNA or RNA strand is used to localize a specific DNA or RNA sequence in a tissue specimen.
- CISH utilizes conventional peroxidase or alkaline phosphatase reactions visualized under a standard bright-field microscope, and is applicable to formalin-fixed, paraffin-embedded (FFPE) tissues, blood or bone marrow smears, metaphase chromosome spreads, and fixed cells.
- Chromogen in situ hybridization (CISH) offers a real advantage by providing a cytomorphologic link in assessing HPV Positivity, which is seen as either in or not in, the abnormal cells.
- It also provides additional information as to whether the virus is integrated or not in the host genome (discrete nuclear dots imply that virus is in the chromosomal DNA & now able to effect the genetic aberration almost always a marker of a high risk HPV).
- It is even possible to detect and localize single or very few HPV copies within infected nuclei.
Transformation of Gynecologic Cytology @ Metropolis
Aims and Objectives

• To study gynaecologic cytology with respect to conventional and liquid based preparations.

• To compare abnormal results obtained by these methodologies.

• To study the role of HPV co-testing.
Materials and Methods

• **Duration of Study**: July 2009 to September 2012 (39 months).

• A total of 10135 conventional and 3895 Liquid based preparations (THIN PREP) were included in this study.

**CONVENTIONAL CYTOLOGY**: 

• *Prefixed smears* were received along with the requisite clinical details.

• These were stained using the conventional Papanicoloau staining method.
Cytology No : ML G 2225/12
Clinical details: C/o Leucorrhea

**Specimen Type**: Liquid based cytology (Preserve Cyt vial received)

**SPECIMEN ADEQUACY**: Adequate
- Superficial cells: Present
- Intermediate cells: Present
- Parabasal cells: Present
- Deep parabasal/Basal cells: Present
- Endocervical cells: Present
- Metaplastic cells
- Others

**Inflammation**: Moderate

**Organisms**:
- Doderlein bacilli: Present
- Trichomonas vaginalis: -
- Fungal organisms: -
- Others: -

**EPITHELIAL CELL ABNORMALITIES**: DETECTED
Squamous: Cells with a high N:C ratio, hyperchromasia, raisinoid nuclei & perinuclear halo are present.

**RESULT INTERPRETATION**

Low grade Squamous Intraepithelial lesion (LSIL)

HPV: Detected: Genotype: 16
Distribution of Abnormal & negative smears (July 2009 to September 2012)

<table>
<thead>
<tr>
<th></th>
<th>Conv</th>
<th>LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NILM</td>
<td>9981 (98.45%)</td>
<td>3825 (98.2%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>154 (1.55%)</td>
<td>70 (1.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Conv</th>
<th>LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>64</td>
<td>21</td>
</tr>
<tr>
<td>LSIL</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>ASC-H</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>HSIL</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>AGUS</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>70</td>
</tr>
</tbody>
</table>

*NILM – Negative for Intraepithelial Lesion or Malignancy*
% of distribution of Abnormal findings in Conventional and LBC

A significant increase in LSIL in LBC Compared to conv cyto is evident

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Conv cyto</th>
<th>LBC</th>
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</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>0.63%</td>
<td>0.54%</td>
</tr>
<tr>
<td>LSIL</td>
<td>0.37%</td>
<td>0.95%</td>
</tr>
<tr>
<td>ASC-H</td>
<td>0.07%</td>
<td>0.05%</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.31%</td>
<td>0.23%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0.08%</td>
<td>0.03%</td>
</tr>
<tr>
<td>AGUS</td>
<td>0.07%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
Other findings

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>177 (1.77%)</td>
<td>45 (1.18%)</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>6 (0.06%)</td>
<td>1 (0.02%)</td>
</tr>
<tr>
<td>Reactive cellular changes a/w</td>
<td>736 (7.37%)</td>
<td>331 (8.65%)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>42 (0.5%)</td>
<td>5 (0.13%)</td>
</tr>
</tbody>
</table>

Two cases of granulomatous cervicitis were also reported which on histology were compatible with tuberculous cervicitis. One of them presented as a mass lesion.
HPV RESULTS

- 116 of 177 cases showed the high risk genotypes 16 & 18 i.e. 66%

- 21 of 31 cases were positive for low risk genotypes 6 & 11 i.e. 68%

- The average HPV infection rate was 10 – 11%

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases for HPV screening</th>
<th>Abnormal findings in Cytology</th>
<th>HPV detected in</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>43</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2011</td>
<td>66</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>2012</td>
<td>340</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>
## Data Summary

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of pap</td>
<td>3182</td>
<td>3553</td>
<td>4411</td>
<td>4311</td>
</tr>
<tr>
<td>Conventional pap</td>
<td>1637</td>
<td>2745</td>
<td>3092</td>
<td>2661</td>
</tr>
<tr>
<td>LBC</td>
<td>111</td>
<td>846</td>
<td>1288</td>
<td>1650</td>
</tr>
<tr>
<td>% positive Conventional pap</td>
<td>2.01%</td>
<td>2.3%</td>
<td>0.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>% positive LBC</td>
<td>8.1%</td>
<td>1.5%</td>
<td>1.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>HPV screening</td>
<td>NA</td>
<td>NA</td>
<td>899</td>
<td>989</td>
</tr>
<tr>
<td>% positive in HPV</td>
<td>NA</td>
<td>NA</td>
<td>11.01%</td>
<td>10.31%</td>
</tr>
</tbody>
</table>
Summary

- 75% of cases with epithelial abnormalities were in the age group of 30-60 yrs.

- There was a slight increase in the detection of epithelial abnormalities in LBC (1.8%) compared to conventional cytology (1.55%).

- The detection of LSIL was higher in LBC preparations, in concordance with other studies.

- There was a slight increase in detection of SCC in conventional smears which is attributed to slides received for a second opinion rather than first referrals.

- A distinct added advantage is the ability to perform HPV DNA testing which allows to adhere to the latest recommendation of co-testing in the 30-65 yrs group.
Cervical Cancer Screening @ Metropolis

• Pap smear – LBC

• HPV screening – LBC (Pap by Thin Prep + HPV DNA)

• HPV screening – LBC with reflex CISH* (Pap + HPV DNA with reflex CISH)

* CISH is done only when HPV DNA is positive for the high risk subtypes