VISUAL INSPECTION WITH ACETIC ACID AS A CERVICAL CANCER SCREENING TOOL FOR DEVELOPING COUNTRIES

Maria Julieta V. Germar, M.D.
Section of Gynecologic Oncology
Department of Obstetrics and Gynecology
University of the Philippines
Philippine General Hospital

Tutor:
Mario Merialdi, M.D.
Department of Reproductive Health and Research
World Health Organization
Cervical Cancer

Worldwide

- 231,000 women die of cervical cancer every year
- 12% of all cancers in women
- 80% from developing countries

Cervical Cancer
466,000 New Cases Year 2002

THE TEN LEADING CANCER SITES IN THE PHILIPPINES

Philadelphia Cancer Facts and Estimates, 1998
TEN LEADING CANCER SITES IN WOMEN

1. BREAST
2. CERVIX
3. LUNG
4. THYROID
5. OVARY
6. LEUKEMIAS
7. COLON
8. LIVER
9. STOMACH
10. UTERUS

Philippine Cancer Facts and Estimates, 1998
Cervical Cancer Problem in the Philippines

- Incidence rate remains unchanged from 1980-1995 – 22 per 100,000 women
- 56% of Filipino women with cervical cancer will die within 5 years (44% overall survival rate)
  - About 2/3 of cervical cancer is diagnosed in the advanced stage, where mortality is high.
Cervical Cancer is PREVENTABLE

- Screening detects PREINVASIVE STAGE
- Developed countries with well-organized screening programs – invasive cervical cancer incidence reduced by as much as 90%
- Community based screening programs require sophisticated infrastructure, highly trained personnel, adequately equipped laboratories, good referral systems
In the Philippines

- Geographic limitation- 7,100 islands
- Lack of cytological facilities and expertise
- Lack of treatment facilities in rural areas
- Lack of patient’s compliance in rural areas
- Lack of knowledge among women on symptoms associated with cervical cancer
- A fatalistic attitude toward cancer in general

*Philippine Knowledge, Attitude and Practices Behavior Modification Study, 2000*
Cervical Cancer Screening
Situation in the Philippines

389 of 946 Philippine Hospitals surveyed
(118 primary; 167 secondary; 104 tertiary)

- 42% claimed they offer screening & early detection services for cervical cancer; only 8% have clinics dedicated to cervical cancer screening
- Cotton swab – common smear collection tool
- MD – usual person performing Pap smear
- Cytology technician is available in only 21% of hospitals
Cervical Cancer Screening
Situation in the Philippines

389 of 946 Philippine Hospitals surveyed
(118 primary; 167 secondary; 104 tertiary)

- Pathologist available (part-time) in 45% hospitals
- Colposcopy in 22% tertiary hospitals, 16 % of secondary hospitals, none in primary hospitals
- Only 11 % of hospitals with treatment facilities for cervical cancer

University of the Philippines-Department of Health
Cervical Cancer Screening Study Group.
Delineation of an Appropriate and Replicable
Cervical Cancer Screening Program for Filipino Women.
Manila. 2001
Cervical Cancer Screening Situation in the Philippines

- 47 +/- 11 days (mean/sd) days – for a patient to travel from her residence to the clinic for a Pap smear to the time she is told of the result

University of the Philippines-Department of Health
Cervical Cancer Screening Study Group.
Delineation of an Appropriate and Replicable Cervical Cancer Screening Program for Filipino Women.
Manila. 2001
Cervical Cancer Screening

- Alternatives to cervical cytology
  - Automated pap screening
  - VIA (visual inspection with acetic acid)
  - HPV testing
  - Polar probe
VIA

- Inexpensive
- Requires supplies locally obtainable
- Can be competently performed by non-physicians with proper training
- Result is immediate
Visual Inspection with Acetic Acid

3-5% Acetic acid

Inspection with naked eye
With 100 watt lamp as light source

Colposcopy
Objectives

- To review the evidence on VIA as a cervical cancer screening tool in terms of its sensitivity and specificity in detecting pre-invasive lesions compared to cervical cytology, which is the standard of screening at present.

- To evaluate how this evidence can be used to implement a feasible screening program in a low resource setting like the Philippines.
Materials and Methods

All relevant articles were retrieved from 1980 to March 2003. Studies were identified by a MEDLINE search.

- Manual searches of relevant journals,
- Reference lists of retrieved articles,
- Direct communication with other researchers
  - Unpublished data from the
    - World Health Organization (WHO)
    - International Agency for Research on Cancer (IARC)
<table>
<thead>
<tr>
<th>Authors/ Year (Reference)</th>
<th>Type of study</th>
<th>Purpose</th>
<th>No of women screened</th>
<th>Setting</th>
<th>Technique (VIA) done by</th>
<th>Independence of assessments</th>
<th>Key Statistics</th>
<th>Reference Standard</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Megevand et al 1996 (20)</td>
<td>Cross sectional</td>
<td>VIA as an alternative to cytology</td>
<td>2426</td>
<td>Community-based (Mobile clinics in a squatter area in Cape Town, South Africa)</td>
<td>described</td>
<td>Trained Nurses, Community Health workers</td>
<td>Cytotechnologist not blinded to result</td>
<td>Positive Predictive Value</td>
<td>Colposcopy with or without a biopsy</td>
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<td>2 Sankaranarayanan et al 1998 (21)</td>
<td>Cross sectional</td>
<td>Compare performance of VIA and cytology</td>
<td>3000</td>
<td>Community-based (Open access cancer detection clinics in Karala, India)</td>
<td>described</td>
<td>Trained cytotecnologists</td>
<td>Sensitivity ratio, approximate sensitivity, approximate specificity</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference test not applied to women who were screening test negative</td>
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<td>3 Sankaranarayanan et al 1999 (22)</td>
<td>Cross sectional</td>
<td>Compare performance of VIA and cytology</td>
<td>1351</td>
<td>Community-based (in Emakulam, India)</td>
<td>described</td>
<td>Trained nurses</td>
<td>Sensitivity ratio, approximate sensitivity, approximate specificity</td>
<td>Colposcopy with or without a biopsy</td>
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<td>4 University of Zimbabwe/JHPIEGO 1999 (26)</td>
<td>Cross sectional</td>
<td>Test qualities of VIA</td>
<td>10934 phase 1- 8731 phase 2- 2203</td>
<td>Community-based (151 clinics in Chitungwiza and Greater Harare Area, Zimbabwe)</td>
<td>described</td>
<td>Trained nurse-midwife</td>
<td>Sensitivity/Specificity</td>
<td>Colposcopy with or without a biopsy</td>
<td>Phase 1- work up bias, Phase 2- all women underwent gold standard</td>
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<td>5 Denny et al 2000 (23)</td>
<td>Cross sectional</td>
<td>Compare performance of cytology, VIA, VIA with magnification and HPV DNA in detecting HSIL</td>
<td>2944</td>
<td>Community based (clinics in Khageliska, South Africa)</td>
<td>described</td>
<td>Trained nurses</td>
<td>Sensitivity ratio, approximate sensitivity, approximate specificity</td>
<td>Colposcopy with or without a biopsy</td>
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<td>Cronje et al 2000 (27)</td>
<td>Cross sectional</td>
<td>Compare cytology, cervicography, VIA</td>
<td>6301 Community based (Volunteers throughout Free State Province of South Africa)</td>
<td>described</td>
<td>Trained Nurses</td>
<td>Blinded</td>
<td>Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value</td>
<td>Colposcopy with biopsy</td>
<td>Gold standard done on all women</td>
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<td>Belinson , Quia et al 2001 (28)</td>
<td>Cross-sectional</td>
<td>Determine accuracy of 6 screening tests: conventional cytology, liquid based cytology, VIA, colposcopy, HPV testing, fluorescence spectroscopy</td>
<td>1997 Community-based (Rural Shanxi Province, China)</td>
<td>described</td>
<td>Gynecologic Oncologists</td>
<td>Blinded</td>
<td>Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value</td>
<td>Colposcopy with biopsy</td>
<td>Gold standard done on all women Result may not be reproducible VIA performed by Gynecologic Oncologists</td>
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<td>Ngelangel et al 2001 (29)</td>
<td>Cross sectional</td>
<td>VIA alone, VIA with magnification compared to cytology</td>
<td>13,710 Hospital based (6 Metro Manila Hospitals and 6 regional Hospitals Philippines)</td>
<td>described</td>
<td>Trained nurses, midwives, physicians from community centers</td>
<td>Blinded</td>
<td>Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference standard used was colposcopy not applied to the women who were screening test negative</td>
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<td>Benny et al 2002 (24)</td>
<td>Cross Sectional</td>
<td>Compare VIA and VIA with magnification to cytology</td>
<td>2754 Community based (Periurban settlement in Cape Town, South Africa)</td>
<td>described</td>
<td>Trained Nurses</td>
<td>Blinded</td>
<td>Sensitivity ratio, approximate sensitivity, approximate specificity</td>
<td>Colposcopy with or without a biopsy</td>
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- Verification bias
- Non-independence of assessments
<table>
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<tr>
<th>Authors/ Year (Reference)</th>
<th>No of women screened</th>
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<th>Key results (Sensitivity,Specificity,PPV,NPV when available)</th>
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<tr>
<td>Megevand et al 1996 (20)</td>
<td>2426</td>
<td>20-83</td>
<td>Sensitivity of VIA 65 % vs 100 % for cytology Specificity 97 % vs 89 % for cytology PPV 72.4 % vs 88.9 % for cytology</td>
<td>Colposcopy with or without a biopsy</td>
<td>Cytotechnologist not blinded to study results, limited by lack of information on those patients negative on VIA and cytology</td>
</tr>
<tr>
<td>Sankaranarayanan et al 1998 (21)</td>
<td>3000</td>
<td>25-70</td>
<td>Sensitivity ratio to cytology= 1.05, p=0.25 Estimated Sensitivity 90 % for VIA vs 86 % for cytology Estimated specificity 92 % for VIA vs 91 % for cytology PPV 17.0 % vs 17.2 % NPV 99 % vs 99 %</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference test not applied to women who were screening test negative</td>
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<td>Sankanarayanan et al 1999 (22)</td>
<td>1351</td>
<td>22-70</td>
<td>Sensitivity ratio to cytology= 1.54, p&lt;0.001 Estimated Sensitivity 96 % for VIA vs 62 % for cytology Estimated specificity 68 % for VIA vs 90 % for cytology PPV 15 % vs 25 % NPV 99 % vs 97 %</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference test not applied to women who were screening test negative</td>
</tr>
<tr>
<td>University of Zimbabwe/JHPIEGO 1999 (26)</td>
<td>10934 phase 1-8731 phase 2-2203</td>
<td>25-55</td>
<td>Sensitivity of VIA 77 % (70.3-82.3) vs 44 % (37.3-51.4) for cytology Specificity 64 % (61.9-66.2) vs 91 % (89.2-91.9) for cytology PPV 19 % vs 33 % NPV 96 % vs 94 %</td>
<td>Colposcopy with or without a biopsy</td>
<td>Phase 1- work up bias, Phase 2- all women underwent gold standard</td>
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<tr>
<td>Denny et al 2000 (23)</td>
<td>2944</td>
<td>35-65</td>
<td>Sensitivity ratio to cytology= 0.85, p=0.16 Estimated Sensitivity 67 % for VIA vs 78 % for cytology Estimated specificity 83 % for VIA vs 94 % for cytology PPV 11 % vs 27 % NPV 99 % vs 99 %</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference standard not applied to the women who were screening test negative</td>
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Table 2 Data from Studies Reviewed (VIA)

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<tr>
<td>Cronje et al 2000 (27)</td>
<td>6301</td>
<td>Ave age 34.4</td>
<td>Sensitivity 49.4 % (44.1-54.7) for VIA vs 19.3 % (15.1-23.5) for cytology Specificity 48.5 % (45.9-51.2) for VIA vs 99.3 % (98.7-99.7) for cytology PPV 18.9 % vs 86.8 % NPV 99 % vs 97 %</td>
<td>Colposcopy with biopsy</td>
<td>Reference standard done on all women</td>
</tr>
<tr>
<td>Belinson , Quia et al</td>
<td>1997</td>
<td>35-45</td>
<td>Sensitivity 71 % for VIA % vs 77 % for cytology Specificity 74 % vs 98 % for cytology PPV 11 % vs 61 % for cytology NPV 98 % vs 98 % for cytology</td>
<td>Colposcopy with biopsy</td>
<td>Reference standard done on all women Result may not be reproducible VIA performed by Gynecologic Oncologists</td>
</tr>
<tr>
<td>Ngelangel et al 2001 (29)</td>
<td>13,710</td>
<td>20-65</td>
<td>Estimated Sensitivity 50.3 % (45.2-55.5) for VIA vs 8.5 % (5.5-11.5) for cytology Estimated specificity 94.1 % (93.4-94.9) for VIA vs 97.3 % (97.1-98.2) for cytology</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference standard used was colposcopy not applied to the women who were screening test negative</td>
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<tr>
<td>Denny et al 2002 (24)</td>
<td>2754</td>
<td>35-65</td>
<td>Sensitivity 69.8 % (59.4-78.5) for VIA vs 57.4 % (46.8-67.4) for cytology Specificity 79.3 % (77.8-80.8) for VIA vs 96.3 % (95.5-97.0) for cytology PPV 12.9 % vs 34.5 % NPV 96.3 % vs 95.8 %</td>
<td>Colposcopy with or without a biopsy</td>
<td>Reference standard not applied to the women who were screening test negative</td>
</tr>
</tbody>
</table>
VIA

- Range of sensitivity: 49.4 % - 96 %
- Range for specificity: 48.5 % - 97 %
- Positive predictive value: 11% - 26 %
- Negative predictive value: 95.5% - 99 %.
Variations

- Definitions for a positive VIA test
- Personnel who performed VIA
- Age range among study participants: 20-83
  - Less than 35 vs older than 35
    - Sensitivity of pap smear and VIA increased
Conclusions

- VIA has better or similar sensitivity to that of cervical cytology in detecting pre-invasive disease but has lower specificity.
- VIA should be evaluated further with regard to:
  - Improving specificity, without compromising sensitivity.
  - Standardization of criteria as to disease categories.
  - A comprehensive competency based training of personnel involved in screening must be done.
  - Long term follow up of women and the consequent impact on disease burden deserve further research.
Table 3: On-going IARC collaborative studies on VIA for cervical cancer screening

<table>
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<tr>
<th>Program design</th>
<th>Interventions evaluated</th>
<th>Location of the study</th>
<th>Number of participants</th>
<th>End points of the program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, controlled intervention study</td>
<td>VIA, cervical cytology, HPV testing</td>
<td>Osmanabad district, India</td>
<td>160,000 women 30-59 years</td>
<td>Cervical cancer incidence/ mortality; Cost-effectiveness; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Randomised, controlled intervention study</td>
<td>VIA</td>
<td>Dindigul District, India</td>
<td>7,000 women aged 30-59 years</td>
<td>Detection rates of CIN2-3; Cervical cancer incidence/mortality; Cost-effectiveness; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>VIA, VILI</td>
<td>Burkina Faso, Republic of Congo, Guinea, Hyderabad, India, Laos, Mali, Niger, Mauritania, Tanzania</td>
<td>5000 women aged 30-59 in each location</td>
<td>Test characteristics; Acceptability, efficacy, complications of cryotherapy; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>VIA, cytology</td>
<td>Nigeria</td>
<td>2000 women aged 30-64 years</td>
<td>Test characteristics; Acceptability, efficacy, complications of cryotherapy; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>VIA, VILI, cervical cytology</td>
<td>Trivandrum and Jaipur, India;</td>
<td>6000 women 30-59 years in each location</td>
<td>Test characteristics; Acceptability, efficacy, complications of cryotherapy; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>VIA, VIAM, VILI, cervical cytology, HPV testing</td>
<td>Calcutta, India</td>
<td>12,000 women aged 30-64 years</td>
<td>Test characteristics; Acceptability, efficacy, complications of cryotherapy; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>Cervical cytology, HPV testing, VIA, VIAM, VILI</td>
<td>Bombay, India</td>
<td>5000 women aged 30-59 years</td>
<td>Test characteristics; Acceptability, efficacy, complications of cryotherapy; establishment of a service and training platform for cervical cancer prevention.</td>
</tr>
</tbody>
</table>

VIA: Visual inspection with acetic acid; VIAM: Magnified visual inspection with acetic acid; VILI: Visual inspection with Lugol’s iodine

Sankaranarayanan R. The current work of the International Agency for Research on Cancer (WHO/IARC) in cervical cancer control in developing countries. (Unpublished; Personal communication with the author)
In areas where resources are scarce, VIA may find a place as a low technology, low cost method of screening; particularly in regions like the Philippines - without extensive cytology laboratory facilities.
Good Morning.