

## Review-II

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# Is the Aided Visual Inspection of Cervix: A Promising Alternative to Screen for Uterine Cervical Cancer

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### ABSTRACT

Absence of cervical cytology screening programmes in developing countries has resulted in need to explore alternative strategies to screen women at risk of uterine cervical cancer. Current alternative screening methods are-aided visual (viz., Visualization inspection after the application of acetic acid (VIA), Visual inspection after Lugols iodine (VILI), visual inspection after acetic acid under magnification (VIAM) and HPV to compare and to define more reliable and feasible screening tool. Though considered accurate, the establish methods of HPV are expensive and time consuming while the aided visual methods involving simple methodology and low cost should be preferable for low resource settings. We have made an attempt to review the current literature to highlight the performance of these screening strategies. This review indicate that there are overall comparable performances between cytology and aided visual screening methods in various studies excepting few study settings and laboratories where low sensitivities were observed perhaps due to quality considerations. Performance observed for VIA for example could yield 60 to 92% of true positive lesions by referring of only 7 to 17% of test positives resulted from screening. However, the performance of the test is influenced by the magnitude of the disease while the accuracy of a test is

influenced by test quality, training and quality assurance. It was reported that VIA along with VILI as parallel screening method enhanced the performance of the test. The value of visual screening through VILI in fact improves the test performance by checking false negatives and indecisiveness in VIA, if it exists. Based on review findings, a flow chart for visual screening is suggested with combined use of VIA and VILI. Thus, the aided visual inspection method appears to be a simple, feasible, and promising screening tool for cervical cancer. Implementation of this aided visual screening in the existing health care infrastructure could reduce the load of the disease in the long run.

### INTRODUCTION

Cervical cancer is the commonest form of malignancy among Indian women. This could be detected at pre-invasive stage by regular cytology screening. It is known that screening of women by Papanicalagu (Pap) smear test lowers the incidence and facilitates early detection of cervical cancer. Organized cervical cytology screening programmes do not exist in most developing countries including India due to lack of required resources and manpower. As there are other gripping health problems especially control of infectious diseases and population explosion, it is not possible to launch a nation wide cytological screening programme in India for this disease. To overcome these limitations there was a need for alternative strategies to cytology screening. The methods such as unaided Visual inspection (VI) of the cervix, aided visual inspection and HPV DNA

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testing have been studied as alternatives to cytology screening. This communication attempts to highlight the performance of these strategies in screening women for early detection of cancer of uterine cervix and to state its usefulness in evidence based practice.

The principle of alternative screening methodology other than HPV screening is basically the visualization of the cervix through per speculum examination in the presence of good light source. On careful inspection one may find a normal cervix, or a low risk clinical signs viz., cervicitis, cervical erosion, hypertrophied cervix, cervical polyp and prolapse of the uterus and high risk signs, such as unhealthy cervix, erosion that bleeds on touch, small growth and suspicious looking cervix. These three groups were formed after examining a large population<sup>1</sup> called unaided visual inspection (VI) method. As there was problem of high false positivity and low pick up rate of precancerous lesions in VI screening, perhaps due to subjectivity in identifying the clinical signs, to delineate the high risk and low risk population, there was a definite need for improvement in the unaided visual inspection method. Thus, this resulted into aided methods of examination of cervix such as Visual Inspection after the application of Acetic acid (VIA) or Lugols Iodine (VILI) and VIA under Magnification (VIAM). In other words, the visual screening methods rely on visualizing the cervix for gross lesions (downstaging or unaided visual inspection) or for aceto white lesions (VIA) or iodine non-uptake areas (VILI) while cytology relied on adequately collecting and studying the morphology of both squamous and epithelial cells.

An outline of methodologies of various alternative screening methods reported in literature are given below.

*VIA (Visual Inspection after the application of Acetic acid):* VIA is done by visualization of cervix after applying cotton swab at cervix with 3-5% acetic acid and sufficient time is allowed to occur the color changes, abnormal lesions tend to become aceto-white against the pinkish back ground of normal epithelium.<sup>2</sup>

*VIAM (VIA under Magnification):* In this method VIA is done under low magnification to visualize the cervix more clearly.

*VILI (Visual Inspection after the application of Lugols Iodine):* VILI is similar to VIA except the application of lugol's iodine instead of acetic acid. VILI is considered positive if yellow iodine non-uptake areas were visualized close to the squamo-columnar junction or the entire cervix or a growth on the cervix turned yellow. In a normal cervix, normal squamous epithelium will be strongly stained as mahogany brown due to iodine uptake. However, the columnar epithelium of central endocervical areas will not take the iodine stain and remain pale. Further details of criteria for interpretation of VILI and VIA are available in literature.<sup>2,3</sup>

#### *HPV:*

The other method is Human papilloma virus (HPV) detection as screening for cervical cancer. This is considered as a screening tool to define the role of persistent viral infection with oncogenic types of HPV in the etiology of cervical cancer.<sup>4,5</sup> Cervical samples are assessed as HPV positive for DNA from high risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) if the relative light unit (RLU) reading obtained from the luminometer of the Hybrid Capture II (HC II) assay equipment is equal to or greater than the mean of the positive control values supplied by HCII kit.<sup>6</sup>

A brief summary of review findings on the performance of various screening tools is discussed in the following paragraphs.

#### VALIDITY OF VARIOUS SCREENING TESTS

A review of studies<sup>6-21</sup> that reported tests characteristics on various alternative-screening modalities was done to summarize comparability of quality of tests. Sensitivity and specificity that indicate the inherent qualities of the screening test for various studies were depicted in Table-I. Sensitivities

**Table-1. Test performances of various modes of screening in different studies.**

AUTHOR (ref)	Cytology		VIA		VIAM		VILI	
	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY
De Vuvst et al 2005(7)	83.3	94.6	73.3	80.0	-	-	-	-
Goel et al. 2005 (8)	50.0	97.0	96.7	36.7	-	-	-	-
Ghaemmaghami et al 2004, (9)	72.0	90.2	74.3	94.0	-	-	-	-
Sankaranarayanan et al, 2003 (15)	72.1	91.6	93.4	85.1	-	-	-	-
Singh et al, 2001 (12)	73.3	99.0	86.7	94.3	-	-	-	-
Lancet 1999 (13)	44.3	90.6	76.7	64.1	-	-	-	-
Sankaranarayanan et al, 1998 (14)	86.2	91.3	90.1	92.2	-	-	-	-
Shastri et al 2005(6)	57.4	98.6	56.9	88.4	64.9	86.3	75.4	84.3
Basu et al 2003 (10)	29.5	92.3	55.7	82.1	60.7	83.2	-	-
Sankaranarayanan et al, 2003 (11)	81.9	87.8	82.6	86.5	-	-	87.2	84.7
Parashari et al, 2000 (20)	78.9	99.0	-	-	82.9	94.3	-	-
Sankaranarayanan et al, 2004 (18)	-	-	76.8	85.5	-	-	91.7	85.4
Sankaranarayanan et al, 2004 (19)	-	-	60.3	86.8	64.2	86.8	-	-
Denny et al 2002 (16)	-	-	70.0	79.0	74.0	77.0	-	-
Belinson et al, 2001(21)	-	-	71.0	74.0	-	-	-	-
Winkler et al 2003 (17)	-	-	-	-	60.0	69.0	-	-

and specificities for HPV ranged from 45.7 to 80.9 and 91.7 to 94.6 respectively.<sup>22,23</sup> The comparisons of different methods of screening such as cytology, VIA, VILI, VIAM and HPV were assessed with the reference standard of biopsy

or colposcopy with biopsy. The threshold against which the test characteristics computed was CIN-II and worse.

Sensitivities observed for cytological screening in four of eleven studies

reviewed<sup>10,13,8,6</sup> were as low as 29% to 57.4%. It was well known that cytology achieved moderate to low sensitivities in many laboratories and study settings. In VIA screening out of fourteen studies reviewed, three<sup>6,10,19</sup> showed a sensitivity of 60% or lower. VILI screening performed in limited studies showed good sensitivities of the test. Except in few study settings reported above, the sensitivities of all the three modes of screening viz., cytology, VIA and VILI are comparable. When the test quality is comparable in most studies, the low quality in some studies might be attributed to training and quality control aspects.

As clearly observed from Table-I, cytology is very specific tool as compared to aided visual methods. In VIA screening, leaving apart a single study<sup>8</sup> which reported an unacceptably low specificity of 36.7% and another study<sup>13</sup> with 64%, all the remaining studies reported acceptable magnitudes of specificities. In the case of VILI mode of screening, specificities were observed to high in all the three studies. So far as use of magnification in the visual screening is concerned, the anticipated advantage was not achieved.

In addition to specificity and sensitivity, validity of the screening test is assessed by positive and negative predictive values. To evaluate predictive values, test positives and test negatives among women screened are assessed for presence or absence of the disease. Test positive rates percent observed in various studies reported for cytology, VIA, VILI, VIAM and HPV were ranged from 2.7 to 10.2, 6.9 to 16.1, 16.4 to 17.0, 14.2 to 17.7 and 7.6 to 10.3 respectively. The positive predictive values of cytology, VIA, VILI, VIAM and HPV for various studies reviewed were ranged from 8.2 to 37.8, 5.9 to 25.9, 6.5 to 10.9, 6.3 to 17.7 and 10.9 to 12.1 respectively. The negative predictive value is as high as 99% in most studies. The positive predictive values indicate that out of 100 women found to be test positive, a minimum of 6 to 11 true lesions would be detected. That is a maximum of 89 to 94 would potentially be over treated or referred for colposcopy and tissue diagnosis in various screening methods including cytology. In a study<sup>13</sup> where the incidence of the disease is high, the positive

predictive value of VIA was as high as 25.9%. That means only three fourth of women were over treated. Thus, it is clear that performance of the screening test is influenced on the magnitude of the disease while the accuracy of the test is influenced by test quality, training and quality assurance.

The treatment generally takes place is with cryotherapy for women diagnosed with low and high-grade lesions. LEEP, cold knife conization and simple hysterectomy are the other methods of treatment adopted for women those are not appropriate for cryotherapy.<sup>25</sup> A cluster randomized trial conducted in south India<sup>25</sup> reported that 71 % women with CIN I and 80% women with CIN II and III lesions accepted cryotherapy provided by nurses and surgical treatment by middle level clinicians. As it was known that low morbidity associated with the conservative treatment modalities such as cryotherapy, laser vaporization and loop electro-surgical excision (LEEP) in well trained hands, the over treatment in women with abnormal screening results could be judged to be ethical because of reduction in risk of the disease.<sup>24</sup>

Some important aspects of the comparative picture of various screening tests are given below.

#### COMPARISON OF VARIOUS SCREENING TESTS

A study on test characteristics of VIA and VILI<sup>11</sup> showed comparable performance in detecting CIN-II or worse disease. Another study<sup>6</sup> reported that VILI had a significantly higher sensitivity than VIA in detecting HSIL but specificities were similar. VILI was found to perform well by detecting three quarters of all cases of HSIL compared to VIA which detected less than two third of all HSIL cases.<sup>18</sup> A study on accuracy of visual screening reported the positive predictive value for VIA and VILI as 9.4% and 10.9% respectively. The ability of VIA and VILI to correctly predict the presence of the disease is marginally different by 1.5%.The use of both VIA and VILI in parallel was also recommended for low resource settings.<sup>18</sup>

On the question of whether VIA after magnification (VIAM) can improve test performance, it was observed that the

performance was similar with or without magnification. The positive predictive values were 5.9% and 6.3% for VIA and VIAM with equal negative predictive value of 99.4% for both.<sup>19</sup> In another study VIAM identified a higher (16.3%) population of women with a cervical abnormality than VIA (3.4%).<sup>26</sup> A study<sup>20</sup> indicated an increase in the sensitivity for detecting low-grade lesion (CIN I) with magnification device as compared to VIA. However, for high grade lesions the results were comparable.

HPV testing was found to give similar sensitivities to detect CIN II lesions as compared to cytology and VIA in a multi-centric study in India. On the other hand a randomized control trial in India indicated that there was no improvement of HPV over cytology.<sup>25</sup> The currently available HPV testing (HCII) is expensive and requires a relatively sophisticated laboratory infrastructure. Thus, it is not feasible screening tool for low resource settings.

One randomized control trial (RCT) by Sankaranarayanan et al<sup>25</sup> compared the methods of screening for cancer cervix viz. VIA, cytology and HPV in a rural Indian setting by screening 142,701 women aged 30-59 years. The test positive rates observed were 14% for VIA, 7% for cytology and 10.3% for HPV. The detection rates for higher-grade lesions were found to be similar in all the three methods. The study supported the need for training requirements and quality control aspects for the appropriate use of screening tools. The findings observed by investigators were important in the context of varying test positive rates and sensitivities in studies conducted by different authors. The test positive rates of VIA declined from 17% at the beginning of the study to 10% after a second retraining. This study showed that the cytology method also influenced due to inadequate training and quality control of laboratories and reported a decline in cytology positivity from 22% in the first year of training to 5% after retraining without loss in case detection.

In another study,<sup>27</sup> it was shown that VIA was useful for detection of precancerous lesions of cervical cancer not only in low-resource settings but also in well-equipped health centers

and cancer centers. This study reported test positive rates 6.9% and 4.2% in VIA and cytology methods respectively. The positive predictive values for detection of CIN II or worse was 8.3% for VIA and 6.3% for cytology.

#### EVALUATION OF DIAGNOSTIC PERFORMANCE

Predictive values, both positive and negative indicate the practical performance of the test and authenticate the validity of the screening test. Consider a hypothetical cohort of 10,000 women for screening of cancer of uterine cervix and apply the rates of validity of various screening modalities. The rates used for this purpose were from the recent studies.<sup>6,23</sup> The diagnostic performance assessed is obtained as follows. The test positives that could be observed from the cohort were 7000, 14000, 17000, 14800 and 10300 for cytology, VIA, VILI, VIAM and HPV respectively. The yield in terms of actual cases with the presence of disease by applying positive predictive values on test positives would be 1330, 1050, 1598, 1421 and 1123 for cytology, VIA, VILI, VIAM and HPV respectively. Thus, this exploration shows that the yield in cytology screening is comparable to visual screening by referring only 7 to 17% out of a large cohort of 100000 women.

#### CONCLUSION

The review suggests that aided visual methods such as VIA and VILI are simple, and promising alternatives to cytology for screening cancer of cervix. The performance of the alternative screening methods is comparable with exceptional difference in few study settings. Hence it is desirable to adopt a simple and acceptable test. Training and quality control aspects need special consideration in the use of screening techniques. VILI as a parallel test along with VIA could enhance the performance further. Combined use of these visual methods by performing VILI in VIA negative or indecisive cases would help in picking-up the lesions that are likely to be missed. A flow chart suggested for such a screening to detect test positives and further flow of diagnostics and management is shown in Fig-1. The implementation of this combined mode of screening with VIA and VILI for cervical cancer at primary and community level health settings would be beneficial for control of the disease.

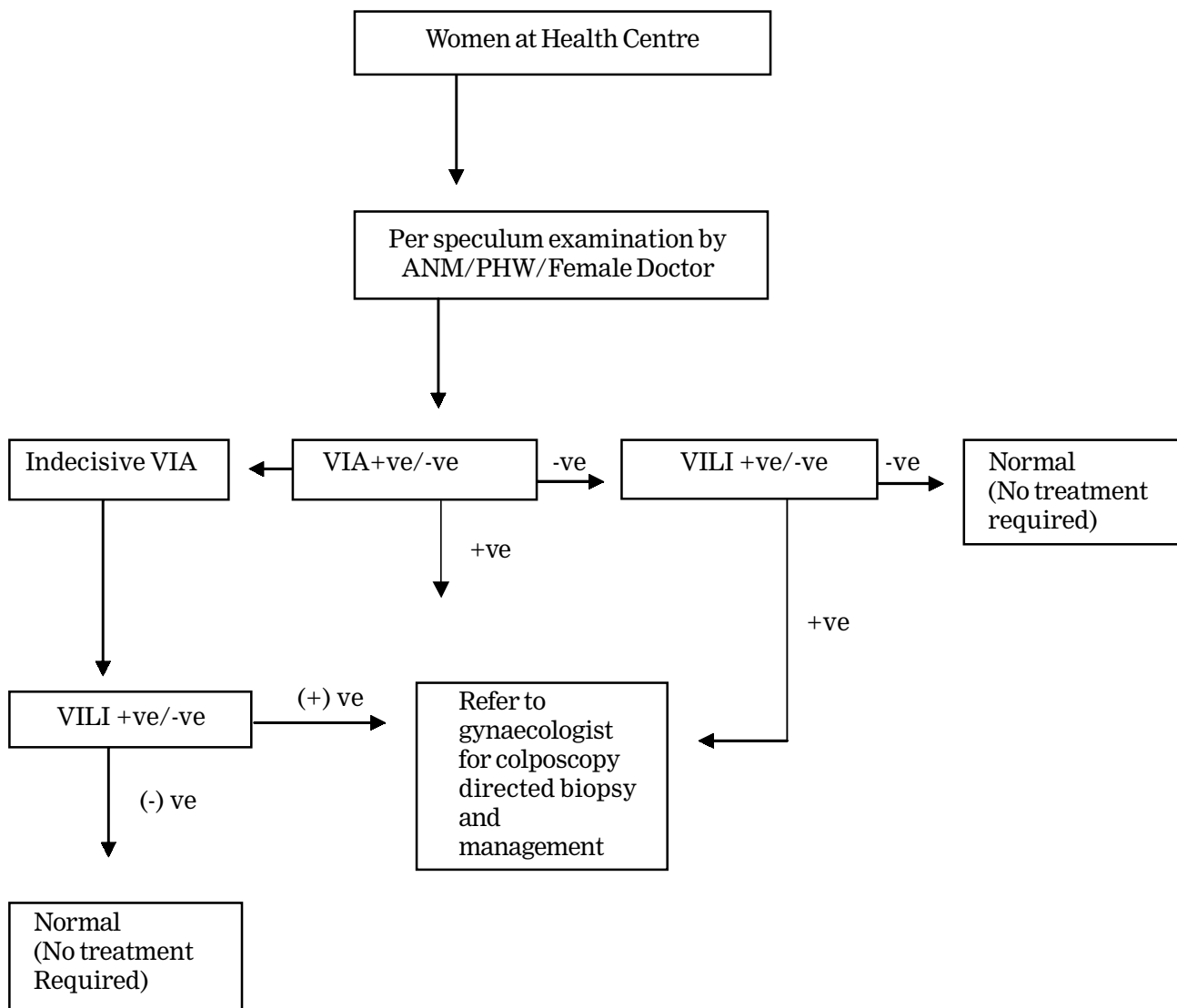


Fig.1: Flow chart for cervical cancer screening with the help of aided visual inspection with acetic acid (VIA) and with Lugol’s iodine (VILI)

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