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To compare the efficacy of pap smear & visual inspection of cervix with acetic acid (VIA) in early diagnosis of cervical intraepithelial neoplasia (CIN) & early cancer cervix

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Abstract
Background: Cervical cancer is the cancer in the lining of the cervix. Cervical cancer does not form suddenly, gradual changes takes place from a normal cervix to pre-cancerous to cancer. Cervical cytology has become the main diagnostic tool to detect cervical cancer. Colposcopy is essential for evaluation of all patients with abnormal cervical smears. In the present study we compare the effectiveness of Pap smear and VIA with acetic acid in diagnosing the cervical cancer.
Method: This is a prospective study where 100 patients with risk factors for cervical cancer were evaluated in gynecology OPD from January 2021 to May 2021 and standard protocol followed in Shri Vinoba Bhave civil hospital, Silvassa. Pap smear and VIA with acetic acid was carried out and colposcopy was done in all patients irrespective of Pap smear finding.
Results: Pap smear had sensitivity only 25.71% but the specificity was 96.92%. While VIA with acetic acid had sensitivity and specificity of 74.26% and 76.92%, respectively. Colposcopy had high sensitivity and specificity rates, 82.86% and 93.85%, respectively.
Conclusion: Pap smear still remains a well-established and perhaps the best studied screening test as of date.

Keywords: Pap smear, colposcopy, cervival cancer, VIA with acetic acid

Introduction
Cervical cancer is the most common cause of death among women in developing countries despite the fact the cervical cancer is preventable [1-3]. There are numerous risk factors for cervical carcinoma which are young age at first intercourse (<16years), Human papilloma virus infection (HPV), multiple sexual partners, cigarette smoking, race, high parity, and low socio-economic status.[1-2]Age interval 35-44 years is at high risk of CIN III and invasive cancer of the cervix [4].
Cervical cancer is mainly caused by infection with the oncogenic subtypes of HPV [5-6]. Moderate increase in the risk of cervical cancer (1.3- 1.8 fold) is seen among women who have used Oral contraceptive pills for more than 5 years [7] Cervical cytology is a simple, safe, non-invasive method of detecting precancerous changes in cervix. It is accepted as a screening tool for healthy woman for evidence of CIN
VIA involves naked eye examination of the 3% acetic acid swabbed uterine cervix without any magnification with illumination provided by a bright light source such as halogen lamp. A positive test is the detection of well defined, dull acetowhite lesions on the cervix. The objective of VIA is to detect acetowhite lesions leading to the early diagnosis of high grade cervical intraepithelial neoplasia and early preclinical, asymptomatic invasive cancer. CIN may be identified by microscopic examination of cervical cells in a cytology smear stained by the Papanicolaou technique; also known has Pap smear. In cytological preparations, individual cell changes are assessed for the diagnosis of CIN and its grading. Nuclear enlargement with variation in size and shape is a regular feature of all dysplastic cells. Increased intensity of staining (hyperchromasia) is another prominent feature. Irregular chromatin distribution with clumping is always present in dysplastic cells. Mitotic figures and visible nucleoli are uncommon in cytological smears. Abnormal nuclei in superficial or intermediate cells indicate a low-grade CIN, whereas abnormality in nuclei of parabasal and basal cells indicates high-grade

CIN. The amount of cytoplasm in relation to the size of the nucleus (nuclear-cytoplasmic ratio) is one of the most important bases for assessing the grade of CIN [8].

Colposcopy is essential for evaluation of all patients with abnormal cervical smears. It is used to identify the site, severity and extent of the abnormality as well as to aid directed biopsy, plan treatment and to allow use of conservative methods to treat the precursor lesions. Colposcopy, however, has no role as a primary screening procedure for cervical cancer although it may enhance cervical screening in women with other wise negative Pap smear [9-10].

Recurrence even after treatment of CIN is more common in patients who have had high-grade lesions emphasizing the importance of more intensive and prolonged follow-up for these patients. It is imperative that screening and treatment be strongly linked so that women who are identified as having precancerous lesions are able to get treatment they need to prevent the development of cancer.

Inclusion criteria

1. All women above 25 years of age.
2. Marital life more than 3 years. All patients are subjected for screening irrespective of the purpose of OPD visit.

Exclusion criteria

1. Unmarried women.
2. Women with frank invasive cancer cervix (with visible growth on cervix)
3. Women with bleeding per vaginum.
4. Pregnancy.

Methodology

After a brief history and a general examination the subjects were counselled and consent obtained for undergoing the study. Pap smear, VIA, colposcopy and biopsy was performed on all women of the target population attending Shri Vinoba Bhave civil hospital, Gynecology OPD.

Speculum examination was performed which included direct visual inspection of the cervix (without any magnification) and macroscopic abnormalities such as cervicitis, cervical warts, polyps, erosions, nabothian cysts, bleeding erosions, stippled cervix, irregular edematous elongated cervix, growths and ulcers were identified and noted.

Cervical Pap smear using a wooden Arye's spatula for cytological examination was performed which was immediately fixed in a mixture of 95% ethyl alcohol and 5% ether.

Pap smear reportings were done according to the Bethesda classification. After taking Pap smear, the same patients were subjected to visual inspection of the cervix with acetic acid using a cotton swab soaked in acetic acid for 1-2 minutes, 3% acetic acid were applied on the cervix and then the cervix were carefully inspected for any acetowhite lesions, particularly in the transformation zone.

The test outcome were considered positive on the basis of following criteria -

1. Intensity of the white color of acetowhite lesion.
2. Borders and demarcation of the white lesion.
3. Whether the lesion is uniformly white in color or variation in the color intensity across the lesion.
4. Location of the lesion.
5. Size and number of the lesion.

Results

In the present series 100 subjects who attended gynecological outpatient department check-up and who were sexually active were studied. All the women included in the study were subjected to the screening tests e.g. Pap smear, visual inspection after acetic acid application, colposcopic examination, and biopsy for histopathological examination (HPE), after general examination

1A. Distribution according to age

Majority of the subjects were in the 31 to 40 years and 41 to 50 years age group (30% and 31% respectively). The minimum number was in the 21-30 years age group.

1B. Age Distribution and HPE finding

It showed that more subjects in 40 and above age group were positive for CIN 1 and above lesions, compared to age group less than 40, but were not statistically significant

2. The age range and characteristics of distribution of the subjects

The mean age of the subjects was 44.51 years and the median age in years was 45. All the women were married and majority of the subjects (85%) were married by 25 years of age. The mean age of marriage was 20.93 years and the median was 20 years.

3. The distribution according to parity

Highest numbers were seen n parity 5 (19%). Majority of the subjects were between parity 2 to 6. The mean parity was 3.9.

4. Distribution according to location.

Majority of the subjects were from a rural setting (64%) compared to 36% from urban areas.

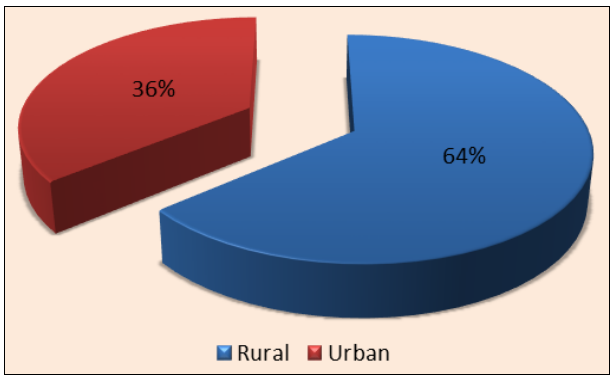

Fig 1: Area distribution according to HPE findings

More subjects from rural area had HPE positive lesion compared to urban subjects which was found to be statistically significant (p value=0.004) thus suggesting that subjects residing in rural areas were more likely to have CIN lesions.

5A. Distribution of VIA results.

Majority of the subjects (59%) were acetonegative, and 41% were acetopositive, which was defined as well-defined, demarcated, densely opaque acetowhite lesions located in the transformation zone (TZ) close to the squamocolumnar junction.

5B. Distribution of VIA findings according to HPE results.

It showed that the VIA positive group had more CIN 1 and above lesion on HPE. This means that subjects are more likely to have CIN lesions (p=0.003) if they are VIA positive than compared to VIA negative subjects.

6A. Distribution according to Pap smear results.
Of the total 100 subjects, 11 subjects had findings suggestive of CIN 1 or worse lesions on cytology.

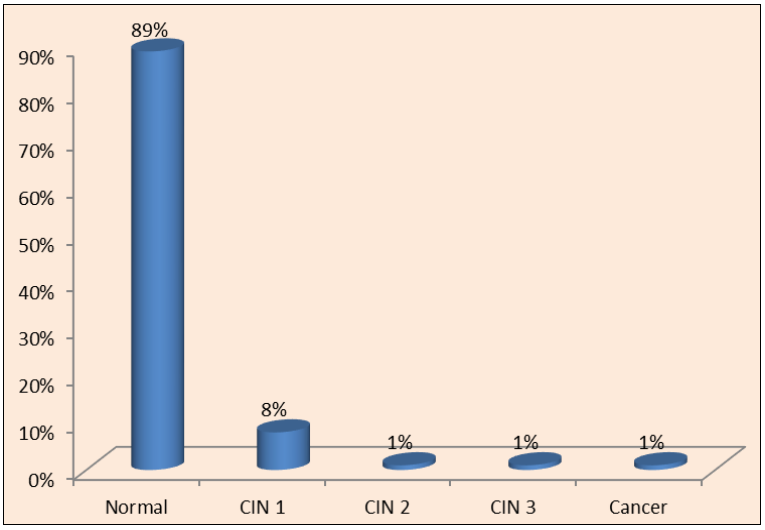

Fig 2: Distribution according to Pap smear results

6B. Distribution of Pap smear findings according to HPE results
It showed that more subjects in Pap smear negative group had lesions CIN 1 or worse lesions on HPE compared to Pap smear positive group and was found to be statistically significant (P=0.001)

7A. Distribution according to Colposcopic findings
33 out of the 100 cases were found to be having positive colposcopic findings defines as Grade 1 or worse lesions (which corresponds to CIN 1 or worse lesions on HPE).

7B Colposcopic findings according to HPE results
29 out of 33 were HPE positive compared to 6 in the colposcopy negative group and was found to be statistically significant (P value <0.0001).

8. Distribution according to Histopathology results
35 subjects (35%) had positive lesions defined as CIN 1 or worse lesions. Of the 65 subjects, 11 subjects had no lesions, 14 subjects showed chronic cervicitis and 40 subjects had squamous metaplasia (all were defined to have negative lesion for the purpose of statistical calculations).

9. Distribution of histological findings by Results of screening test
Out of 11 positive pap smear findings, defined as CIN 1 or worse lesions 9 were histopathologically positive.
Among the 100 women screened, 41 of them were VIA positive, out of which 12 had biopsy proven CIN 1, 6 had CIN 2, 5 had CIN 3, and 3 had cancers. Among the 100 patients who underwent colposcopic examination 29 of the subjects had CIN 1 or worse lesions on biopsy.

Table 1: 2x2 contingency table for Pap smear and Histopathology results

Pap smear	HPE		Total
	(+)	(-)	
(+)	9	2	11
(-)	26	63	89
Total	35	65	100

Sensitivity : 25.71%
Specificity : 96.92%
Positive predictive value : 81.82%
Negative predictive value : 70.79%

Table 10 shows a 2x2 contingency table for Pap smear and histopathology results. Pap smear could detect 25.71% of the true positive cases (sensitivity). The calculated specificity, positive and negative predictive values were 96.92%, 81.82% and 70.79%, respectively.

Table 2: 2x2 table of colposcopy and histopathology results

Colposcopy	HPE		Total
	(+)	(-)	
(+)	29	4	33
(-)	6	61	67
Total	35	65	100

Sensitivity : 82.86%
Specificity : 93.85%
Positive predictive value : 87.88%
Negative predictive value : 91.04%

Table 11 shows a 2x2 contingency table for colposcopy and histopathology results. The calculated sensitivity was 82.86% and the specificity was 93.85%. The positive predictive value was 87.88% and the negative predictive value was 91.04%.

Table 3: 2x2 table of VIA and histopathology results

VIA	HPE		Total
	(+)	(-)	
(+)	26	15	41
(-)	9	50	59
Total	35	65	100

Sensitivity : 74.26%
Specificity : 76.92%
Positive predictive value : 63.42%
Negative predictive value : 84.75%

Table 12 shows a 2x2 contingency table for VIA and histopathology findings. Sensitivity was 74.26%, specificity was76.92%, positive predictive value was 63.42%, and negative predictive value was 84.75%.

10. Test performance of Pap smear, VIA and colposcopy

CIN 1 or worse lesions were considered as positive results for comparison between the various tests modalities.

Pap smear had the highest specificity (96.92%) compare to 93.85% by colposcopy and 76.92% by VIA.

Colposcopy showed the highest sensitivity (82.86) for detecting CIN 1 and above lesions. It also exhibited better positive and negative predictive value compare to Pap smear and VIA.

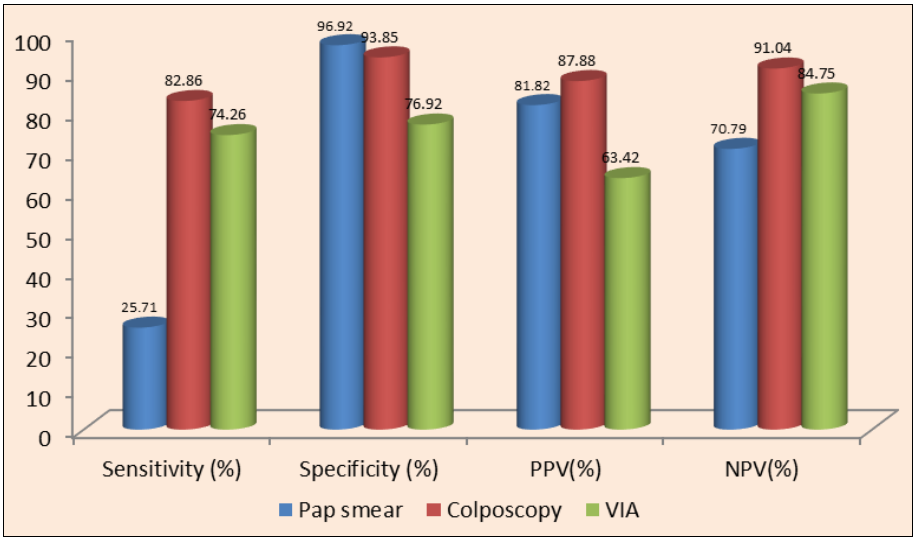

Fig 3: Comparative sensitivity and specificity figures and p value

When compared to Pap smear, colposcopy (82.86% vs. 25.71%) and VIA (74.26% vs. 25.71%) were more sensitive in detecting CIN or worse lesions (p<0.0001).

Pap smear with a specificity of 96.92% could screen out more CIN negative cases when compared to VIA with a specificity of 76.92% (p<0.00001). Colposcopy was also more accurate than VIA n detecting cases that were not having CIN lesions (93.85% vs. 76.92%, p=0.008).

Table 4: Test findings distribution according to CIN lesions

Test	CIN (+)	CIN(-)	
Pap Smear	11	89	Chi-square 24.57 df 3 p<0.0001
VIA	41	59	
Colposcopy	33	67	
Histopathology	35	65	

Table shows the screening results of the three tests and the histopathology results. VIA diagnosed more subjects to be having CIN 1 or worse lesions (41%) compared to colposcopy (33%) or Pap smear (11%) and the difference was significant (p<0.0001).

Conclusion

Pap smear could detect only 11 of the total 35 CIN I lesion or worse. CIN I lesion was seen in 8 subjects, and one subjects each had CIN 2 and CIN 3 and one of the subjects had true cancer of histology. The calculated sensitivity was only 25.71% but the specificity was 96.92%.

41 of the 100 subjects had acetowhite lesions on VIA out of which 26 were found to have CIN I or worse lesion on HPE giving positive predictive value of 63.42%. It had a sensitivity and specificity of 74.26% and 76.92%, respectively.

Colposcopy findings suggested 33 out of 100 cases to be having CIN I or worse lesions thus could detect 29 of the HPE confirmed CIN lesions giving a high sensitivity and specificity rates, 82.86% and 93.85%, respectively. The positive predictive value was 87.88%.

Histopathological diagnosis was the gold standards against which the performances of screening test *viz*. Pap smear, VIA, colposcopy were compared. HPE diagnosed 35 subjects to be having CIN I or worse lesions. Chronic cervicitis was seen in 14%, CIN I in 16%, CIN 2 in 9%, CIN 3 in 7%, and squamous metaplasia in 40%. Three subjects were found to have true cancer on HPE.

Colposcopy had the highest sensitivity (82.86%) in detecting CIN I or worse lesions. Pap smear had the highest specificity rate (96.92%) compared to 93.85% by colposcopy and 76.26% by VIA. The comparative PPV rates for Pap smear, VIA and colposcopy were 81.82%, 87.88% and 63.42%, respectively. The NPV were 70.79%, 91.04% and 84.75%, respectively.

VIA diagnosed more subjects to be having CIN I or worse lesions (41%) compared to colposcopy (33%) or Pap smear (11%). HPE of the cervical biopsy diagnosed 35 of the 100 samples as having CIN I or worse lesions. VIA observed more subjects as having CIN I or worse lesions (41%) compared to colposcopy (33%) or Pap smear (11%) and thus may be employed as a rule-out test in view of its acceptable sensitivity, ease of performing the test, low cost and instant feedback although it runs of over-diagnosing the disease condition.

Even though VIA has a promising option as a screening tool for detection of cervical cancer precursors, Pap smear still remains a well-established and perhaps the best studied screening test as of date. In fact, it is the only tool recommended by the WHO as a screening test for early detection of cervical cancer. Colposcopy in view of its high cost and the need for an expert in interpreting the findings will still retain its role as a procedure for confirmation and treatment of CIN lesions

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