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Validity and Overall Performance of Per Speculum, Visual Inspection of Cervix with Acetic Acid (VIA) and Lugol's Iodine (VILI) Versus Cytology as Screening Test for Cancer Cervix in the Presence of Infection

Dr. Deepika H. K.[1], Prof. Tamkin Khan[2], Prof. Fatima Khan[3], Dr. Nazia Ishrat[4], Prof. Kiran Alam[5]

[1] Assistant Professor, Obstetrics and Gynecology, MVJ Medical College
[2]Professor, Obstetrics and Gynecology, Jawaharlal Nehru Medical College, AMU
[3]Professor, Microbiology, Jawaharlal Nehru Medical College, AMU
[4]Assistant Professor, Obstetrics and Gynecology, Jawaharlal Nehru Medical College, AMU
[5]Professor, Pathology, Jawaharlal Nehru Medical College, AMU

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Corresponding Author:

Dr. Deepika H. K

Assistant Professor, Obstetrics and Gynecology, MVJ Medical College

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ABSTRACT

Background: Cervical cancer, despite being a preventable disease endangers the lives of a significant number of women every year and also its incidence is growing with time. Cervical cytology is a well-accepted standard screening tool in developed countries but in developing countries like India, it fails not only due to the lack of awareness but also due to financial and technical constraints. Visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) have been evaluated in several large clinical trials and is considered to be a possible alternative to cervical cytology for primary cervical cancer screening in low-resource settings. The present study aimed to compare the efficacy of VIA and Lugol's iodine with Pap smear and per speculum examination in screening for cancer cervix and evaluate their usefulness as tools for screening of premalignant and malignant lesions of the cervix. **Methodology:** This clinical study was conducted on 330 gynecological patients who were nonpregnant or who had no history suggestive of cervical intraepithelial neoplasia or carcinoma cervix. After taking informed and written consent each woman who fulfilled the inclusion criteria was subjected to Per speculum examination, Pap smear examination, VIA, and VILI. A biopsy was taken in patients with abnormal findings or suspicious findings on VIA/VILI. **Results:** The sensitivity of VIA and VILI was 78.94%, specificity 81.41% and 80.53%, positive predictive value was 41.6% and 40.54, and negative predictive value was 96% with biopsy as the reference standard. The sensitivity of per speculum and pam smear cytology in our study were 78.94% and 73.6%, specificity was 5.3% and 93.8%, positive predictive value was 60% and 95.4% and negative predictive value was 60 % and 90.9%, respectively. **Conclusion:** VIA and VILI are simple, inexpensive, and low-technology tests. Both when combined have high sensitivity as well as specificity. This can be practiced by clinicians and paramedics on a wide scale. Another advantage is the immediate availability of results and hence that treatment can be started during the same visit.

Keywords*: Cervical cancer, screening, Per speculum, Pap smear, visual inspection with acetic acid, visual inspection with Lugol's iodine*

INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally, with an estimated 604 000 new cases and 342 000 deaths in 2020. About 90% of the new cases and deaths worldwide in 2020 occurred in low- and middle-income countries.[1] More than 85% of the cases occurred in developing countries, where it accounts for 13% of all female cancers.[2,3] If precancerous lesions are found early through good screening programs, cervical cancer can be prevented. However, establishing and successfully implementing these programs is difficult in low-income nations. Successful cervical cancer screening in resource-limited settings requires that screening, diagnosis, and treatment be performed on-site or in clinics accessible to the majority of women at risk. Seeking a simple and low-cost screening method for cervical cancer prevention in resource-poor settings, visual acetic acid (VIA) and visual Lugol's iodine (VILI) were compared with conventional tests. It is considered a technically less complex alternative test to conventional cytology. However,

the diagnostic accuracy in detecting high-grade precursor lesions and invasive cervical cancer varies between studies. The sensitivity and specificity of VIA ranged from 55% to 96% and 49% to 98%, respectively, and the sensitivity and specificity of VILI ranged from 44% to 98% and 75% to 91%, respectively.[4-8]. The diagnostic performance of VIA and VILI for early detection of cervical cancer and their positive determinants have been extensively evaluated.[5,7-13] However, no studies have examined how patient characteristics affect diagnostic accuracy. The objective of the present study is to study the sensitivity and specificity of VIA and VILI test in the detection of premalignant and malignant lesions of cervix in the presence of infection, in a cross-sectional comparative clinical study conducted at the department of Obstetrics and Gynaecology in JNMCH, Aligarh.

MATERIALS AND METHODS

Study design and population

Briefly, 330 women aged 30 years were included at the Department of Obstetrics and Gynaecology in JNMCH, Aligarh. Women were interviewed using a structured, standardized questionnaire to collect information on sociodemographic, reproductive, clinical, lifestyle, and sexual behavior characteristics. Women were screened by conventional cytology, VIA, VILI, and colposcopy. Cytological diagnoses were based on the Bethesda system [15], i.e., negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and cancer (no other findings were recorded in this study). Per speculum examination and pap smear test were carried out. Cytology smears were read by a cytotechnologist and reviewed by a gynecologic cytopathologist without knowledge of disease status or results of the other screening tests. VIA and VILI were independently performed by an experienced gynecologist. Colposcopy-directed biopsies were obtained from women with cervical abnormalities. Cervical biopsies were also performed in a random sample of women (~20%) who had normal colposcopic findings. Biopsy slides were read in a research capacity by an experienced gynecologic pathologist. All patients were evaluated for infection through cervical culture. The data were statistically analyzed and presented as frequency and percentages. The Chi-square and p-value were calculated. The sensitivity, specificity, positive predictive value, and negative predictive value of per speculum examination, pap smear test, VIA, and VILI were compared.

RESULTS

Patients with gynecological conditions who attended the outpatient department of obstetrics and gynecology at JNMCH, Aligarh, were included in this study. Per speculum examination, cervical cytology, VIA, and VILI as screening methods for the detection of pre-cancerous and cancerous lesions of the cervix were used to screen 330 patients who met the inclusion and exclusion criteria for the current study. Additionally, cervical swabs were taken for culture to check for infection. Colposcopy and biopsy were performed on 149 patients who had been diagnosed as positive by any of the methods.

In the present study, the minimum age of patients screened was 21 years and the maximum age was 60 years, the greater part of patients was in the fourth decade of life, 197 (59.6%). We had 167 (50.6%) patients from the rural population and 163 (49.3%) from the urban population. 200 (60.6%) out of 330 patients were literate and had completed their primary education. 132(39.3%) were uneducated people. Most of the patients in our study belonged to class III socioeconomic status 156 (47.2%) and there were 240 Muslims (72.7%) and 90 Hindus (27.2%). Most of the patients had high parity, para. Around 125(37.8%) were sexually active before the age of 20. The length of marriage in most of our patients was between 11 to 20 years (67.5%), 325 (98.4%) were not addicted to any tobacco items, and 5 (1.5%) cases were addicted to tobacco.

Among 330 patients, about 159 underwent each of the four screening tests—Per speculum, Pap smear, VIA, and VILI and were identified as positive by a combination of these tests; On histopathological examination, 35 (or 10.6%) of these 159 positive cases had precancerous and cancerous lesions. Patients over the age of 40 had a higher rate of positive biopsies (26.7%), followed by those between the ages of 21 and 30 (21%) and 31 to 40 (21%) However, the difference was statistically not significant, $\chi 2$ =0.468, P value =0.7. About 21 (28.4 percent) of the biopsy-positive cases came from the rural population, which was the maximum compared to the urban population, while 14 (16.5%) came from the urban population. Biopsy results were more positive in the rural population by 28.4%. However, there was no statistically significant difference. $\chi 2$ =3.2, P=0.07.

Illiterates had a higher rate of biopsy positivity (34.5% vs. 14.9%), which was statistically significant (2 = 8.37, P=0.004). Biopsy positive was more in the low financial class 44.4% compared with the working class 16.5 % and 13.3% in the high financial class with $\chi 2$ =13.8, P esteem =0.01 and was found to be statistically significant. Biopsy positive was more among Hindus 27% compared with Muslims 18.8%. However, there was no statistically significant difference. P = 0.22 and 2 = 1.5. Positive biopsies were more common in paras four and above (44.4%), three (16.5%), and one to two (13.3%) with P value = 0.5, 2 = 1.2. However, there was no statistically significant difference.

Patients who started having sexual activity before the age of 20 had a positive biopsy result at a rate of 22.7 percent, compared to 18.5% of patients who started having sexual activity after the age of 20 ($\chi 2$ =0.2, P value =0.6). However, there was no statistically significant difference. Biopsy was positive in a more number of patients (31%) who were married for more than 21 years ($\chi 2$ = 1.2, P value = 0.5), but there was no statistically significant difference. Biopsy

results were more positive for tobacco users (25%) than for non-addicts (22.1%) with P value =0.8, $\chi 2$ =0.3. However, statistically speaking, it was insignificant. Out of the 330 patients, 136 (41.2%) had er speculum examination, whereas 194 (58.7%) had a normal one. On each speculum, aberrant findings included erosions, bleeding upon contact, growth, polyps, hypertrophy, cervicitis, and a Nabothian follicle. 27 patients (66.6%) had normal Pap smear findings; 65 (19.6%) had inflammatory smear results; 13 (4.2%) had ASC-US; two (0.6%) had ASC-H; 26.6% had LSIL; and five (1.5%) had HSIL. 57 (17.2%). Results from Pap smears above the ASC-US were regarded as positive. Visual inspection with acetic acid yielded positive findings in 57 (17.2%) patients; visual inspection with Lugol's iodine yielded positive results in 61 (81.5%) patients; and visual inspection with acetic acid yielded negative results in 273 (82.7%) individuals on colposcopy.

Out of the 136 cases that showed positive for per-speculum examination, 27 had precancerous and cancerous lesions on histopathology, 17 had CIN 1, 8 had CIN 2, 2 were squamous cell carcinoma, and 8 were normal on per-speculum examination had CIN1 on biopsy but were missed by per-speculum examination. The sensitivity of per speculum examination was 77%, specificity was 12.8%, positive predictive value was 19.8%, and negative predictive value was 65.2%. Out of 40 cases with a positive Pap smear, 28 had histologically confirmed precancerous and cancerous lesions, nine had precancerous CIN-1 lesions, two had precancerous SCC-2 lesions, and seven cases did not have a positive Pap smear. The Pap smear test had a sensitivity of 80%, a specificity of 90%, a positive predictive value of 70%, and a negative predictive value of 94%. Out of 57 VIA positive cases, 26 had Precancerous and carcinogenic sores on histopathological assessment, seventeen had CIN 1, nine had CIN 2, two had squamous cell carcinoma and 9 cases that were not picked by VIA test had CIN1 on biopsy. The sensitivity of the VIA test was 74.2%, specificity was 75%, positive predictive value was 45.6%, and negative predictive value was 91.1%. Out of 61 VILI positive cases, 28 had precancerous and malignant sores on histopathological assessment seventeen had CIN1, nine had CIN2, two had squamous cell carcinoma and 7 cases that were not picked up VILI test had CIN 1 on biopsy. The sensitivity of the VILI test was 80%, specificity was 73.3%, positive predictive value was 45%, and negative predictive value was 92%. (Tables 1 and 2)

Table 1: Test characteristics of Pap smear and visual inspection with acetic acid as a screening method

Per speculum	**BIOPSY**	
	Positive	**Negative**
Positive (136)	27 (19.9)	109 (80.1)
Negative (23)	8 (34.8)	15 (65.2)
Total (159)	35 (22)	124 (78)
χ^2=2.55, p=0.1		
Pap smear	**BIOPSY**	
	Positive	**Negative**
Positive (40)	28 (70)	Positive (40)
Negative (119)	7 (5.9)	Negative (119)
Total (159)	35	Total (159)
χ^2 =68.1, p=0.001		
VIA	**BIOPSY**	
	Positive	**Negative**
Positive (57)	26 (45.6)	31 (54.4)
Negative (102)	9 (8.8)	93 (91.2)
Total (159)	35	124
χ^2 =26.6, P value =0.001		
VILI	**BIOPSY**	
	Positive	**Negative**
Positive (61)	28 (45)	33 (54.1)
Negative (98)	7 (7.1)	91 (92.9)
Total (159)	35	124
χ^2=30.4, p=0.001		

Table 2: Comparison of tests characteristic of various screening tests in detecting precancerous and cancerous lesions of the cervix (n= 159)

Statistical values	**Per speculum**	**Pap smear**	**VIA**	**VILI**
Sensitivity	77	80	74.2	80
Specificity	12.8	90.3	75	73.3
Positive predictive value	19.8	70	45.6	45
Negative predictive value	65.2	94	91.1	92
Accuracy	26.4	88	74.8	74.8

Among 330 patients evaluated for infection through cervical culture, 132 (40%) were positive for the disease, remaining 198 (60%) were negative for contamination. Beta hemolytic streptococcus 7 (5.3%), *Escherichia coli* 40 (30.3%), *Staphylococcus aureus* 57 (41.3%), *Enterococcus faecalis* 15 (11.3%), *Klebsiella oxytoc* 6 (4.5%), and *Citrobacter ferundii* 7 (5.3%) were the microorganisms that were found in cervical cultures. The most prevalent type *is S. aureus.*

All screening tests (per speculum examination, Pap smear, VIA, and VILI) were performed on 132 patients who had a positive cervical culture; 122 patients were identified as positive by a combination of these tests; Histopathological examination revealed precancerous and cancerous lesions in 19 (14.3%) of these 132 cases.

About 122 (92.4%) out of 132 patients who received a positive cervical culture resulted in a positive per speculum examination, while 10 (7.5%) were negative. On histopathological examination, 15 out of 122 positive per-speculum cases had precancerous and cancerous lesions, and four cases were missed. The per speculum examination had a sensitivity of 78.9%, a specificity of 5.3 percent, a positive predictive value of 12.6%, and a negative predictive value of 60%.

66 patients (50%) had a normal Pap smear, 45 (34 %) had an inflammatory smear, 6 (4.5 percent) had an ASC-US, 2 (1.5 %) had an ASC-H, 10 (7.5 %) had LSIL, and 3 (2.2 %) had HSIL. On histopathological examination, 14 out of 21 cases with a positive Pap smear had precancerous and cancerous lesions, and 5 cases did not have a positive Pap smear. The Pap smear test had a sensitivity of 73.6 percent, a specificity of 93.8%, a positive predictive value of 70 percent, and a negative predictive value of 95.4%.

On histopathological examination, 15 out of 36 VIA-positive cases had precancerous and cancerous lesions, and the VIA test failed to identify four of the cases. The VIA test had a sensitivity of 78.9 percent, a specificity of 81.4%, a positive predictive value of 41.6%, and a negative predictive value of 95.8%.

Out of 37 VILI positive cases, histopathological examination revealed precancerous and cancerous lesions in 15 cases, and the Pap smear did not detect cancer in 4 cases. Awareness of the VILI test was 78.9%, explicitness was 80.53%, positive prescient worth was 40.5%, and negative prescient worth was 95.8%.

Per speculum examination had a sensitivity of 78.9 percent, a specificity of 5.3 %, a positive predictive value of 12.5 %, and a negative predictive value of 60 percent when infection was present. The Pap smear test had a sensitivity of 73.6 %, a specificity of 93.8%, a positive predictive value of 70 %, and a negative predictive value of 95.4%. The VIA test had a sensitivity of 78.9 %, a specificity of 81.4%, a positive predictive value of 41.6%, and a negative predictive value of 95.8%. The VILI test had a sensitivity of 78.9 %, a specificity of 8.5 %, a positive predictive value of 40.5%, and a negative predictive value of 83.3%. Per speculum accuracy was 15.9%, Pap smear accuracy was 90.9%, VIA accuracy was 81%, and VILI accuracy was 80.3% overall. (Table 3)

Table 3: Cervical Culture test results of all patients (n=330), test characteristics of Per speculum, Pap smear, and visual inspection with acetic acid and Lugol's iodine as a screening method among cervical culture positive patients and comparison of tests characteristic of various screening tests in detecting pre-cancerous and cancerous lesions in among cervical culture positive patients

Cervical Culture test results of all patients (n=330)		
Culture Results	**Number**	**Percentage**
Negative culture	198	60
Positive culture	132	40
Beta hemolytic streptococcus	7	5.3
Escherichia coli	40	30.3
Staphylococcus aureus	57	43.1
Enterococcus faecalis	15	11.3
Klebsiella oxytoc	6	4.5
Citrobacter ferundii	7	5.3
Per speculum among cervical culture positive patients		
Per speculum	**BIOPSY**	
	Positive	**Negative**
Positive (122)	15 (12.3)	107 (87.7)
Negative (10)	4 (40)	6 (60)
Total (132)	19	113
χ^2 =30.6, p =0.016		
Pap smear among cervical culture positive patients		
Pap smear	**BIOPSY**	
	Positive	**Negative**
Positive (20)	14 (70)	6 (30)
Negative (112)	5 (4.5)	106 (107)

Total (132)	19	113
χ^2 =59.1, p=0.001		
Visual inspection with acetic acid among cervical culture positive patients		
VIA	**BIOPSY**	
	Positive	**Negative**
Positive (36)	15 (41.7)	21 (58.3)
Negative (96)	4 (4.2)	92 (95.8)
Total 132	19	113
χ^2 =29.8, p= 0.001		
Visual inspection with Lugol's iodine among cervical culture positive patients		
VILI	**BIOPSY**	
	Positive	**Negative**
Positive (37)	15 (40.5)	22 (59.5)
Negative (95)	4 (4.2)	91 (95.8)
Total (132)	19	113
χ^2 =28.5, p=0.001		

Comparison of tests characteristic of various screening tests in detecting pre-cancerous and cancerous lesions among cervical culture positive patients

Statistical values	Per speculum	Pap smear	VIA	VILI
Sensitivity	78.94	73.6	78.94	78.94
Specificity	5.3	93.8	81.41	80.53
Positive predictive value	12.5	70	41.6	40.54
Negative predictive value	60	95.4	95.8	95.8
Overall performance	15.9	90.9	81	80.3

DISCUSSION

Cervical cancer is a potentially preventable cancer. It is preceded by premalignant lesions which may take 5–15 years to progress to invasive cancer. If detected and treated timely, the pre-invasive disease has a nearly 100% cure rate with the simple surgical procedure while advanced cancers have <35% survival rates.[14] However, in developing countries like India, universal screening has not been achieved. The main screening method (Pap smear) is available to a small percentage of the population. Cytology-based screening programs are difficult to organize due to limited infrastructure, trained personnel, and funds.[15] Patients find it unnecessary to come and collect cytology reports in subsequent visits and are usually lost to follow-up. It is also difficult for them to pay the charges of cytology. It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime.[16] Moreover, screening programs in India are mostly institution based and are restricted to urban centers.[17] Thus, in developing countries, there is a need for alternative strategies for early detection of premalignant cervical lesions. Most of the patients in our study belonged to class III socioeconomic status 156 (47.2%) and there were 240 Muslims (72.7%) and 90 Hindus (27.2%). Like the above fact, there was a study from Lahore in 2007 that showed that most women with positive lesions and those at higher risk of malignancy belong to a very low socioeconomic class. A similar study which was conducted in Lahore in 2007 concluded that most women with CIN were between 35-45 years of age and also positive results in those who marry early and have their first intercourse before the age of 20. We found that younger age, higher parity, pre-menopausal status, HPV positivity, and Pap cytology test results can be important influences on the performance of VIA and VILI tests in this study population which is similar to the study of Amidu et al.[18]

The worldwide prevalence of HPV infection is high (9-13%) and is the most common sexually transmitted infection, with no specific treatment.[19] Mostly Genital HPV infections are asymptomatic and unapparent and studies indicate that nearly all cervical cancer cases are caused by genital infection with specific high-risk HPV types. In India, women do not have access to effective screening programme, and it has been estimated that without a major improvement in cytology services, it will not be possible to screen even 25 per cent of the population once in a lifetime in the near future.[20] With use of the cervical smear Pap test or VIA, or application of effective HPV-DNA detection procedures, precursors of cervical cancer can be easily detected and successfully treated at an early stage. Thus, cervical cancer can be easily prevented with regular screening programmes. Routine cytological screening should be continued to be used to detect and treat women who are infected before vaccination or with other HPV types not covered by the vaccine.

Although previous studies have investigated predictors of VIA positivity,[10-12] they focused on estimating odds ratios, an approach that is better suited for the evaluation of effectiveness rather than the diagnostic accuracy of screening tests.[21] Hence, it may be difficult to compare our findings with previous reports, especially for VILI which has been less extensively studied. Nonetheless, an effect of age on the VIA positivity rate was repeatedly observed.[6,10,11, 22]

The sensitivity of VIA and VILI is 78.94%, specificity 78.94%, positive predictive value was 41.6% and 40.54, and negative predictive value for both was 95.8% with biopsy as the reference standard. The sensitivity of pre-speculum and pap smear in our study are 78.94% and 73.6% and specificity was 5.3% and 93.8% respectively. The study is in contrast to the study findings of the study done by Consul *et al*. in which the sensitivity of VIA and VILI was 94.70%, specificity was 48.30%, and the sensitivity of cytology was 84.20%, and specificity was 62%.[21] Our study also correlates with Cronjé *et al*. study,[24] wherein sensitivity was 78.9% and specificity was 48.9% which is in contrast to our study results, taking biopsy as the reference standard. Basu *et al*.[25] in their study comparing the performance of VIA and cytology for the detection of high-grade cervical cancer precursor lesions, found VIA to have a sensitivity of 57.7% and specificity of 82.1% and cytology with a sensitivity of 29.5% and specificity of 92.3%. Megevand *et al*.[26] in their study found VIA to detect 54% of high-grade lesions and hence concluded that in locations where access to cytopathologist is limited, naked eye visual examination of the cervix after application of dilute acetic acid can be a good alternative. In a study done by Ghosh *et al*.,[27] it was concluded that in low-resource settings, cervical cancer screening by Pap smear can be replaced by visual methods like VILI, which has the highest sensitivity (100%) to detect any grade of dysplasia, and good specificity (93.3%).[27] According to the study done by Consul *et al*. named comparative study of the effectiveness of Pap smear versus visual application of acetic acid and VILI for mass screening of premalignant and malignant lesions of the cervix showed that VIA and VILI had sensitivity comparable to Pap smear and can thus be a suitable potential alternative/adjunctive screening test not only in poor resource setting but also in well-equipped centers.[23] In a study by Yadav *et al*., VIA when compared with histopathological report (HPR) had sensitivity and specificity of 80% and 67%, respectively while that of VILI was found to be 80% and 87%, respectively.[28] An attempt has been made in the present study to increase awareness of women about cervical cancer and preventive health-seeking behavior, screen all women of the reproductive age group at least once a year and motivate them for annual screening until three negative Pap smears, to provide a screening test with high sensitivity as women have less frequent opportunities for repeated screening and treating women with high-grade dysplasia and cancer. Women continue to ignore symptoms of irregular bleeding, postmenopausal bleeding, and postcoital bleeding. Therefore, in our study, we aimed at educating women about these signs and symptoms and to seek immediate medical care. Thus, an attempt has been made to target the disease before its onset at the level of primary prevention by providing education and counseling and secondary prevention by effective screening and treatment. VIA and VILI have other advantages too like it is very cheap. A study by Mandelblatt *et al*.[29] comparing the cost-effectiveness of VIA, HPV testing, cytology, and a combination of tests show that VIA performed at 5-year intervals in women aged 35–55 years is the least expensive option. The most important advantage, particularly in a population like that seen in our study with a high illiteracy rate and poor follow-up is the immediate availability of the test result. This facilitates diagnosis and treatment to be carried out in the first visit. Hence, the option of VIA and VILI as an alternative to cytology for screening in less developed countries cannot be overlooked. Pap's smear has its own limitations like screening is expensive for low-resource settings, results are not available immediately when compared to VIA and VILI, requires a laboratory setting for the procedure, and also it requires highly trained cytopathologists and staff for large-scale screening so cheaper and easily available visual methods such as VIA and VILI can be a useful alternative. A very recent study by Kaur *et al*. concluded that in low-resource settings, screening by Pap smear has not been successful in reducing the incidence of cervical cancer. VIA and VILI are cheaper and easily available and can be used by medical and paramedical personnel on a large-scale basis.[30] A study by Yagnik Ami and Singh *et al*.[31] also came up with the views that in comparison to a Pap smear, VILI is more sensitive. Specificity is also high for this objective test with good evidence and low cost. The study was better in a way that it also detected the efficacy of Pap smear which other studies have not done.

CONCLUSION

Women who live in poverty, have fewer opportunities for education and awareness and have lower incomes are more likely to develop cervix cancer. When VIA and VILI were compared to Pap smear in our study, their sensitivity was comparable to that of Pap smear. As a result, VIA and VILI can be used instead to screen for carcinoma cervix. In a setting with limited resources like India, VIA, and VILI are appealing tests. The Pap smear has its own limitations, including the difficulty of reaching remote areas, which account for the majority of the Indian population. As a result, the majority of women in India who fall into the low socioeconomic strata of society do not have access to any screening tests. In developing nations, the infrastructure and resources necessary for cytological screening are frequently constrained. Through screening tools such as VIA and VILI, an enormous number of the populace that go undetected can be screened at a reasonable expense with higher sensitivity and specificity.

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