Pap smear cytological findings in women with abnormal visual inspection test results referred to Kenyatta National Hospital

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ABSTRACT

Background: The challenge of cost in establishing cytology and/or Human Papillomavirus (HPV) mass screening for cervical cancer in resource limited countries prompted adoption of visual inspection techniques as alternative tests despite them having low specificity.

Objectives: To determine the pattern of cervical intraepithelial lesions and infections in women with abnormal visual inspection test results referred to Kenyatta National Hospital (KNH).

Methodology: A descriptive cross-sectional study was conducted at KNH where women who were referred to this facility after having abnormal visual inspection test results were recruited.

Results: Of the 232 participants recruited, 57 (24.6%) had a report of atypical squamous cells of undetermined significance (ASCUS) or worse as follows; 5 (2.2%) were ASCUS, 13 (5.6%) were low grade squamous intraepithelial lesions (LSIL), 4 (1.7%) were atypical glandular cells (AGC), 1 (0.4%) was atypical squamous cells cannot exclude high grade (ASC-H), 20 (8.6%) were high grade squamous intraepithelial lesions (HSIL) and 18 (7.8%) were reported as having carcinoma on cytology. Of these abnormal results 3 (1.3%) were from 33 women (14.2%) more than 50 years of age who were also recruited in this study. Infections were detected in 11 (4.7%) of the study participants.

Conclusions and recommendations: Pap smear was useful as follow-up test as it reduced number of referrals for definitive diagnosis to 16.8% while sparing the rest (83.2%) from unnecessary treatment. Pap smear is therefore recommended as follow-up test in women with abnormal visual inspection test results. Increase awareness to service providers and the general public about the Government Policy on the use of visual inspection tests in women more than 50 years of age since 14.2% were inappropriately screened by the visual inspection test.

Key words: Visual inspection techniques, Low cost, Cervical cancer screening, See-and-treat, Pap smear

INTRODUCTION

Invasive carcinoma of the uterine cervix develops over a period of time from precursor lesions or abnormal surface epithelium. This natural history enables detection and treatment of this disease in its early stages thereby preventing its progression to advanced stages and cancer.

The goal of cervical cancer screening is the detection and treatment of pre-malignant lesions before cancer develops. However, cancer of the cervix remains a common disease with a high mortality rate in developing countries including Kenya where resources for conducting Pap smears and related services are limited. In view of this, alternative methods of screening for cervical intraepithelial neoplasia and cancer were developed and recommended for use in these resource limited countries even though they are not perfect. These methods include visual inspection with acetic acid (VIA) and visual inspection with Lugol’s iodine (VILI) which involve application of acetic acid or Lugol’s iodine to the cervix, results reported as negative or positive according to the reaction upon visual inspection of the cervix. Although establishing diagnoses is an imperfect process resulting in a probability rather than a certainty of being right that probability must be acceptable. The World Health Organization recommended use of cytology for large-scale cervical cancer screening programmes, where
sufficient resources exist. At the same time VIA/VILI screening methods were recommended for use only in pilot studies or other closely monitored settings but not recommended for postmenopausal women.

Both Pap smears and these visual inspection tests are screening tests with inherent limitations and the gold standard for evaluation of the abnormal uterine cervical epithelium on screening is biopsy which is often colposcopically directed\textsuperscript{1,5,6}.

In its guidelines, Government of Kenya through the Ministry of Public Health and Sanitation and Ministry of Medical Services recommended that all women who test positive with any of these visual inspection screening tests should have cryotherapy or referred for colposcopy and/or biopsy depending on the set criteria\textsuperscript{7}.

Women with abnormal visual inspection test results who are referred to Kenyatta National Hospital are currently managed by doing Pap smears. This excludes selected cases where colposcopy and/or biopsy is/are done directly. This is because the ‘see-and-treat’ approach is not fully enrolled because of inadequate supplies including cryotherapy equipment. High cost to run the Pap smear screening programme including lack of adequate personnel to interpret the test makes it difficult to establish and/or maintain in resource limited settings. This prompted adoption of low technology, cost effective visual inspection tests, VIA and VILI. The government policy in the National Cervical Cancer Prevention Programme strategic plan 2012-2017 recommended first screening with VIA/VILI and cytology using Pap smear and HPV testing where available\textsuperscript{6,9}.

According to the type and degree of cell abnormality, the Pap smears are reported as atypical cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), Atypical squamous cells cannot exclude high grade (ASC-H), high grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCC), atypical glandular cells (AGC), cervical adenocarcinoma in-situ (AIS) and cervical adenocarcinoma\textsuperscript{1,10}.

Studies have shown that Pap smear is less sensitive but more specific in detection of cervical intraepithelial lesion\textsuperscript{8,11,12}. However the sensitivity is increased by subsequent routine screenings protocols. Visual inspection methods involve application of acetic acid or Lugol's iodine respectively to the cervix and observe colour change of the cervical epithelium after specified time. Reaction of the epithelium depends on amount of protein contained in the epithelium (VIA) or amount of glycogen in the epithelium (VILI) and the reports are given as negative, positive or suspicious for cancer. Sensitivity of visual inspection tests in detection of cervical intraepithelial lesion can be as high as 97\% with specificity as low as 36\%\textsuperscript{12}. However, one of the weaknesses of these visual inspection techniques is the high rate of false positive findings which may lead to unnecessary greater number of colposcopies\textsuperscript{13,14} or in unnecessary cryotherapies in other settings. Immature squamous metaplasia, healing and repair as in inflammatory processes, leukoplakia and condyloma have been cited as culprits in causing false positive results\textsuperscript{13}.

Selection of treatment or management approach for intraepithelial lesion is dependent upon the nature of the lesion including ablative or excisional methods which can be done on an out-patient basis. Treatment for invasive cancer depends on the stage of the tumour and include surgery, radiotherapy, chemotherapy or a combination of these therapies\textsuperscript{7,15}.

**MATERIALS AND METHODS**

In this descriptive cross-sectional study, 232 study participants were recruited from a population of women who were referred to Kenyatta National Hospital (KNH) after having abnormal visual inspection test results. The results were for VIA or VILI or both. A Pap smear was collected from each participant in the Family Planning clinic and processed in KNH Cytology laboratory. On microscopic examination, the investigator evaluated the smears first followed by review together with a supervisor. All ‘abnormal’ and 10\% of ‘normal’ smears were reviewed by a second pathologist and there was high degree of agreement (kappa=0.8).

Any discrepant result was referred to a third pathologist as the tie-breaker. Women who were referred for colposcopy and biopsy were followed up but the study managed to trace only a few with a definitive diagnosis.

**RESULTS**

Results for 232 participants were available at the end of the study after excluding eight where one participant had inadequate squamous cell component while seven had heavy inflammatory cells obscuring cellular details.

The mean age of the study participants was 39.1 years (SD=11.0 years) with the range of 18-74 years. There were 33 women representing 14.2\% of the total number of the study participants who were aged 50 years and above (Table 1).
Table 1: Pattern of menstrual cycles according to participant’s age group (n=227)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Regular No. (%)</th>
<th>Irregular No. (%)</th>
<th>Amenorrhea No. (%)</th>
<th>Postmenopausal No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>20-29</td>
<td>37 (23.9)</td>
<td>6 (35.3)</td>
<td>4 (30.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>30-39</td>
<td>68 (43.9)</td>
<td>8 (47.1)</td>
<td>4 (30.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>40-49</td>
<td>47 (30.3)</td>
<td>3 (17.6)</td>
<td>5 (38.4)</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>50-59</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>60-69</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>70-79</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Total</td>
<td>155 (100)</td>
<td>17 (100)</td>
<td>13 (100)</td>
<td>42 (100)</td>
</tr>
</tbody>
</table>

Duration from VIA/VILI to Pap smear: Time taken (in weeks) from the date VIA/VILI was done to the date Pap smear was done was recorded. Majority of patients (76.2%) came for Pap smear test within 4 weeks after VIA/VILI test was done (Figure 1).

Figure 1: Duration from VIA/VILI test to Pap smear test (n=231)

Proportion of smear positive tests: All participants in this study (n=232) had positive results for visual inspection tests. Of these, 57 (24.6%) had a report of ASCUS or worse while the rest 175 (75.4%) had the report of negative for intraepithelial lesion or malignancy (NILM) (Figure 2).

Figure 2: Proportion of Pap smear positive test results (n=232)

Distribution of cytological findings on Pap smear: Out of the 57 participants with abnormal lesions 5 (2.2%) were reported as ASCUS, 13 (5.6%) were LSILs, 4 (1.7%) were AGCs, 1 (0.4%) was ASC-H, 20 (8.6%) were HSILs and 18 (7.8%) were reported as invasive carcinoma (Figure 3).

Figure 3: Distribution of intraepithelial lesions on Pap smear (n=232)

Infections: Infections which included bacterial vaginosis, candida, Herpes simplex cytopathic changes and Trichomonas vaginalis were reported in 11 (4.7%) of the participants.

DISCUSSION

The mean age of the study participants was 39.1 years (1SD=11.0 years) with the range of 18-74 years. Median age of onset of sexual activity was 19 years. These results were comparable to those found by Jeronimo et al.²

There was particular interest in the number of women aged 50 years and above who were recruited in this study whereby 14.2% of the study population were of this age group. In its recommendations for the use of visual inspection tests in developing countries, the WHO does not recommend screening postmenopausal women using visual inspection tests. This was adopted by Kenyan government where it does not recommend screening women over 50 years of age with visual inspection tests. The inclusion of this age group in this
study may be due to lack of awareness to the service providers or the women themselves. These women should be referred for cytology because the visual inspection tests have low sensitivity to detect lesions because of the shift in position of the transformation zone deep inside the endocervical canal making its visualization difficult. Again, the false positivity rate is likely to be high due to the nature of the epithelium which is prone to inflammation by both infective and non-infective agents which could explain the results found in this study.

Of the 232 participants who met the inclusion criteria, only 57 (24.6%) had a result of ASCUS and above. Of these, 18(7.8%) were ASCUS or LSIL. The rest were AGC, ASC-H/HSIL or invasive carcinoma. Because of the natural history of cervical cancer, cases of ASCUS and LSIL are safely followed up after 6 and 12 months respectively where higher proportion regress while only a small proportion (<1%) will progress to cancer. The rest of the lesions need to be investigated with colposcopy where treatment and biopsy may be indicated.

The proportion of women with high grade lesions and cancer detected by cytology in this study was higher compared to the general population. For example HSIL was (8.6%) in this study population as compared to general population (0.5%-3%) as reported by Koss and Edmund et al. This could be due to the population selected in this study whereby the participants were screen positive by VIA/VILI. In their study, Lewis et al. compared triage methods on Kenyan women who screen positive following visual inspection of the cervix with acetic acid.

With similar cut-off point of ASCUS as abnormal test, the rate of cervical abnormality detection was 54% which is higher than findings in this study (24.6%). Lewis et al. study included women in the 30-39 year age groups while this study included any age starting from 18 years. However this could not explain the difference because similar age group in the present study had lower rate (31.2%) of abnormal results as compared to their counterparts in Lewis et al. study. The difference could be attributed to the fact that this study underwent a rigorous quality control with four levels of sequential specimen evaluation while the study by Lewis et al. evidently had two levels and with poor agreement (kappa=0.08) versus 0.8 in this study.

In a study by Shastri et al. where they compared VIA/VILI, Pap smear and HPV test, the detection rates of LSIL, HSIL and cancer on cytology were 0.2%, 0.8% and 0.5% respectively. This is lower compared to that found in this study i.e. LSIL, HSIL and cancer were 5.6%, 8.6% and 7.8% respectively. This difference could be explained by the fact that Shastri et al. selected asymptomatic, apparently health and previously unscreened women while this study included women who were screen positive for both or either of VIA/VILI; a high risk group. The detection rate of cervical intraepithelial lesions with ASCUS as a threshold was 44% in a study by Mabeya et al. who compared Pap smear with VIA in HIV-infected women. This is higher than that obtained in this study (24.6%) and the difference could be attributed to the fact that HIV-infected women are at higher risk of harboring cervical intraepithelial lesion as found by Muchiri. At LSIL threshold, detection rate of cervical intraepithelial lesions was 2.2% in Sarian et al. study in which they evaluated VIA/VILI, cervical cytology and HPV testing. With similar threshold of LSIL, detection rate in this study was 19% which is higher than Sarian et al. study. This could be due to study population difference where Sarian et al. included apparently healthy women with no previous abnormal test smear results.

In this study the number of women referred for definitive diagnosis and/or therapy was further reduced to 39(16.8%) by cytology. This means that Pap smear has excluded women who most likely do not require any treatment for neoplasia thereby saving them from potential complications associated with particular treatment.

Duration between the date VIA/VILI was done to the date Pap smear was done was recorded. Majority (76.2%) of women came for Pap smear within 4-12 weeks. Although reasons for this turnout within this short period of time in this study have not been explained, anxiety may be suggested as one of them as put down by Marcus that 'the psychological impact of false positives, and the results of cancer screening can wind up being the opposite of what patients seek: Rather than peace of mind, they can come away with more questions, distress... than they bargained for'. Advantages of triaging with Pap smear after screen positive test may be two fold. First the anxiety that the woman has about having cancer reduces or disappears sooner or later if triage test result is negative. Secondly, only women at high risk of having cancer i.e. with HSIL and above may receive more definitive management with or without therapy.

Inflammation has been implicated as a cause of positive visual inspection test results among other causes with infections as one cause of such inflammation. The proportion of infections detected in this study was low (4.7%). This compares well with a similar study by Lewis et al. whose infection detection rate was 6.5%. Detection rate for Candida albicans in Pap smear was 7.6% in a study by Avwioro et al. in which they determined the sensitivity of a Papanicolaou smear in the diagnosis of Candida albicans infection of the cervix which translated to sensitivity of 25.25%. Although sensitivity for infection detection was not calculated in the present study, Avwioro et al. study mentioned above and several other studies have confirmed the low sensitivity of Pap smear in infection detection in general which could explain the results found in this study. Sensitivity of visual inspection tests in detection of cervical intraepithelial lesion can be as high as 97% with specificity as low as 36%. The low specificity for the visual inspection tests could therefore explain the small number of abnormal results on Pap smear found in this study.
CONCLUSIONS

Pap smear was useful as a follow-up test as it reduced the number of referrals for definitive diagnosis to 16.8% while sparing the rest (83.2%) from unnecessary treatment and its potential complications.

RECOMMENDATIONS

(i) Pap smear should be used to triage women with positive visual inspection test results.
(ii) Increase awareness to service providers and the general public about the Government Policy on the use of visual inspection tests in women more than 50 years of age because 14.2% of study participants were inappropriately screened using visual inspection tests.

STUDY LIMITATIONS

All women with normal cytological reports on Pap smear were recommended for routine follow-up as this is the standard practice at the study facility. This might have affected the results as Pap smear might have missed some abnormal cases due to its low sensitivity.

REFERENCES

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