Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Research

Comparison of Papanicolaou Smear Tests Among HIV Negative and HIV Positive Pregnant Women on HAART at a Tertiary Hospital

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Abstract

Background: Cervical cancer is the most common gynaecological cancer worldwide, causing morbidity and mortality, especially in developing countries like Nigeria. It develops from premalignant lesions of the cervix. Human immune deficiency virus (HIV) increases the risk of dysplastic changes in the cervix. Pregnant HIV-positive women may be at a higher risk of having pre-invasive cervical lesions. Pregnancy presents an opportunity to screen women for premalignant lesions of the cervix using a Papanicolaou (Pap) smear, especially in an environment like ours where women of reproductive age have poor health-seeking behaviour. The objective of this study is to compare the cytological patterns of Pap smear of pregnant women who are HIV positive compared to their HIV negative counterparts at the antenatal clinic of Alex Ekwueme Federal University Teaching Hospital Abakaliki (AE-FUTHA).

Methodology: This is a comparative cross-sectional study that involved performing Pap smears on consenting HIV-positive pregnant women on HAART and HIV-negative pregnant women attending the antenatal clinic of AE-FUTHA. One hundred pregnant HIV-positive women on HAART and one hundred pregnant HIV-negative women who met the inclusion criteria and gave consent were recruited into the study by consecutive sampling method. A pretested questionnaire was administered to the women. A pap smear test was carried out on each of the participants. The data was analysed using Epi info version 7.2.1. Continuous variables were presented as mean and standard deviation while categorical variables were presented as numbers and percentages. Categorical variables were analysed using Chi-square (Fisher's exact test was also used), while means were compared using a t-test. A P-value < 0.05 was considered as statistically significant.

Result: The prevalence of abnormal Pap smear among pregnant women in AEFUTHA was 14%. The prevalence among HIV-positive pregnant women was 24% while the prevalence for HIV-negative women was 4%. This difference was statistically significant (P value was <0.001).

Conclusion: This study has demonstrated the presence of premalignant cervical lesions in pregnant women with a significantly higher prevalence among HIV-positive pregnant women. Therefore, there is a need to incorporate Pap smear tests among routine antenatal investigations, especially for HIV-positive pregnant women.

***Keywords*:** *HIV Positive, HIV Negative, Pregnancy, Pap smear, HAART.*

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How to cite: Marcel-Onwudiwe CS, Esike COU, Agwu MU, Adebayo JA, Nweke AN, Uzoigwe JC, Uche-Omovoh IC, Uwakwe EC. Comparison of Papanicolaou Smear Tests Among HIV Negative and HIV Positive Pregnant Women on HAART at a Tertiary Hospital. Niger Med J 2024;65(6):1070-1079.https://doi.org/10.60787/nmj.v65i6.569.

Quick Response Code:

Introduction:

Cervical cancer is the second most common cancer in women worldwide and the leading female genital tract malignancy in Nigeria[1,2]. It is associated with high morbidity and mortality[3,4]. It accounts for 500,000 new cases and 273,000 deaths worldwide every year[5]. Of the new cases, 80% occur in developing countries[6,7]. In Nigeria, about 14,089 women are diagnosed with cancer of the cervix annually with about 8240 deaths occurring yearly[8]. Most of these morbidity and mortality caused by cervical cancer in developing countries are principally due to lack of proper cervical cancer screening programs for women. Awareness and uptake of cervical cancer screening is very low among Nigerian women including health workers[5,9,10,11]. Moreover, there are no established screening programs in our environment especially in rural areas[9,12]. This makes the incidence of cervical cancer in the country to be high.

Cervical cancer develops from premalignant lesion of the cervix. It is a precancerous condition, in which abnormal cell growth occurs on the surface lining of the cervix or endocervical canal[12]. It is also called cervical intraepithelial neoplasia (CIN). There are three types of CIN; CIN I which is mild dysplasia, CIN II which is moderate dysplasia and CIN III which is severe dysplasia[13]. CIN in pregnancy has been examined in several studies. Some studies showed that pregnancy has no effect on cervical neoplasia[12]. The incidence of abnormal Pap smear during pregnancy has been quoted to be from 0.72 to 1.62%[13]. In United States, about 2-3million abnormal Pap smear is diagnosed each year and 5% to 13% of these are detected in pregnancy[1,12]. In northern Nigeria, a prevalence rate of 6% was reported[12]. In Abakaliki, the prevalence of pre-invasive cervical cancer among pregnant women was 6.3%[1]. The peak incidence of CIN is found in women in their third decade which is the time of maximal childbearing capacity[13]. This Cervical dysplasia usually causes no symptoms and is often discovered by routine Pap smear test. The prognosis is excellent for women with cervical dysplasia who are discovered by screening and received appropriate treatment and follow-up. But women who go undiagnosed or who do not receive appropriate care are at higher risk of developing cervical cancer and presenting with advanced disease[13].

Risk factors associated with cervical dysplasia and cervical cancer include human papilloma virus (HPV) infection, early coitarche, multiple sexual partners, having partner with multiple sexual partners, cigarette smoking, Human Immunodeficiency virus (HIV) infection[14,15-19].

Despite having heavy burden of pregnant women who are HIV positive, little is known on how their status could affect the premalignant lesions of the cervix when compared with HIV negative women. This is important because they may be at higher risk of CIN. Preventable strategies like screening using Pap smear during antenatal clinic could be fashioned out for them to protect them against this disease if the prevalence is found to be higher in them.

Studies have shown that abnormal Pap smear and invasive cervical pathology are higher among HIV positive women compared to their HIV negative counterparts[7,14,17,20]. Most HIV positive women are on highly active anti-retroviral therapy (HAART) which will help to improve their life span long enough for cervical cancer precursors to manifest and progress to invasive cancer if nothing is done for them in this regard[2,21] as is presently the case.

There are various methods used in assessing changes in the cervical cells with the most common being Pap smear[21]. Pap smear examination is a simple, cheap and safe diagnostic method for early detection of presence of abnormal, atypical cells which thereby helps to decrease cervical cancer[2]. Pap smear detects 60-70% of cervical cancer[13]. The accuracy of Pap smear in pregnancy is almost similar to that of non-pregnant women[13]. A clinical difficulty is that the physiological changes of the cervix during pregnancy can in many ways mask the premalignant lesions and might be missed if deep smears are not taken[13].

In any case, one will not abandon the window and opportunity to screen women because of the challenges in Pap smear evaluation. Collecting Pap smear in pregnant women has not been shown to pose any risk[13].

Pregnancy presents a unique opportunity to screen women of reproductive age for cervical cancer and premalignant lesions of the cervix, which is relatively common in this age group[22,23]. In Nigeria, routine screening for cervical cancer in pregnancy is not usually practiced even though cancer of the cervix is the commonest genital tract malignancy in Nigeria. This makes it difficult to know the prevalence rate of premalignant disease of the cervix in pregnancy[6,12]. Pregnancy may present a window of opportunity for all pregnant women who have not taken part in cervical cancer screening program before. Pap smear though a standard care is an uncommon practice in our environment. In climes where such screening programs are effective, there has been remarkable reduction in both morbidity and mortality from invasive cancer of the cervix[5-7,12]. However, a high incidence and mortality rates continue in developing countries where resources available for prevention, diagnosis and treatment of cervical cancer are limited[5,10,23]. Since these pre-invasive cervical lesions can be detected by screening and are amenable to treatment before it becomes invasive, pregnancy offers an opportunity to provide screening to women who otherwise might never be screened.

Pregnancy is a period when most young and apparently healthy women commonly seek regular medical attention. It therefore presents an opportunity for us to provide cervical screening, and this should not be missed. This is more imperative for HIV positive pregnant women since previous studies have found HIV infection to be a risk factor for cervical cancer. Non screening of HIV positive pregnant patients may disproportionately predispose them to cancer of the cervix which in addition to their already immune compromised status will compound their health problem and predispose them to preventable deaths. This provides the background and justification for this project. Moreover, such a study is yet to be carried out in our study environment.

Methodology

Study location and duration

The study was carried out at the department of Obstetrics and Gynaecology in conjunction with the histopathology and haematology department of Alex Ekwueme University Teaching Hospital Abakaliki (AEFUTHA), Ebonyi State, Nigeria. The state has several health institutions of different cadres but with mainly primary health care facilities in the rural areas without facilities for screening for cervical cancer. There is also poor road network in the rural areas which may become inaccessible during the rainy season, making accessibility to health care facilities in the urban area with diagnostic tools difficult.

AE-FUTHA is a health institution formerly called Federal Teaching Hospital Abakaliki (FETHA). It is located at the center of the capital territory and receives referrals from all parts of the state and neighbouring states of Abia, Benue, Cross River and Enugu. The hospital has heavy obstetrics patient load as it provides for the primary, secondary and tertiary health needs of the state and surrounding states due mainly to the collapse of these cadre of health facilities. The study lasted for a period of 8 months, 10th February to 14th October 2020.

Study design

The study was a comparative cross-sectional study carried out at the department of Obstetrics and Gynaecology in conjunction with the histopathology and haematology department of AEFUTHA among 100 HIV positive pregnant women on HAART and 100 HIV negative pregnant women attending antenatal clinic.

Study population

All HIV positive pregnant women on HAART and HIV negative pregnant women who were recruited from the antenatal clinics after proper counseling had been given and a written informed consent obtained.

Inclusion criteria: Consenting HIV negative women who are pregnant and consenting HIV positive women who are pregnant and on HAART.

Exclusion criteria: Were Pregnant Women with history of cervical cancer; those previously treated or being treated for premalignant lesion of the cervix; Pregnant women who were screened for cervical cancer in less than one year or those who have received HPV vaccine and age less than 21 years. Other exclusion criteria were women with history of premature rupture of membrane; women with history of antepartum haemorrhage or threatened miscarriage; Pregnant women with abnormal vaginal discharge and pregnant women in their first trimester.

Sample size calculation

The sample size was determined using the following formula[24]

$n = z^2pq/e^2$

Where n = minimum required sample size

z = standard variant (1.96),

P = prevalence of abnormal Pap smear among pregnant women in Abakaliki[1]

= 6.3% = 0.063

q = (1-p), = 0.937

e^2 = Acceptable error at 0.05.

$n = z^2pq/e^2$

$= 1.96^2*0.063*0.937/0.05^2$

$= 3.8416*0.063*0.937/0.0025$

$= 0.2267734896/0.0025$

$= 90.71$

n = 91 (to the nearest whole number)

Ten percent attrition rate was added to the minimum sample size.

10% of 91 = 91 x 10/100

= 9.1

Sample size = 91+ 9 =100

Sample size = 100 for each group

Blood test

All participants had their HIV status determined using the rapid diagnostic HIV test kit (Determine).

Instrument of data collection

A Semi-structured questionnaire that was pretested at Mile 4 Hospital Abakaliki was administered for the study before sample collection. It was an interviewer-administered questionnaire. The questionnaire itself contained questions on sociodemographic data, sexual history, gynaecological history, and obstetrics history, history of prior sexually transmitted infection, knowledge of Pap smear test and cervical cancer and screening and HIV status. The social class of the client was determined using the husband's occupation and the woman's level of education.

Questionnaires were coded with affixed serial numbers of the clients which corresponded with the numbers on the slides and the histopathology request forms; this ensured proper matching of result with the questionnaire. The coded serial number was to ensure confidentiality.

Ethical consideration

The purpose of the Pap smear was explained to the participants and informed consent was obtained. Furthermore, all study participants were told that they had the right to withdraw from the study at any time during the study with no punitive measures. They were informed that all information would be kept strictly confidential. The required approval was obtained from the Ethical and Research Committee of Alex Ekwueme University Teaching Hospital Abakaliki on the 6th of August 2019. (Reference number FETHA/REC/VOL2/2019/262. The participants did not pay for the tests. Those found to be smear positive were referred to the well women centre of AE-FUTHA for further evaluation.

Sampling technique

The recruitment was by a consecutive sampling method among consenting HIV-positive pregnant women on HAART and HIV-negative women that are pregnant. This is continued until a sample size of 100 respondents was obtained in each group (total of 200).

Data collection

Papanicolaou smear

Women were asked to avoid coitus, douching or vaginal insertion that will interfere with the result, 48 hours prior to the day of the test during counseling. The patients were subjected to general and abdominal examinations. Both speculum and pelvic examinations were also done to detect any gross abnormal lesions that would exclude them from the study such as detecting any abnormal vaginal discharge. These were done during booking and regular antenatal visits. Women in their first trimester were excluded because of higher rate of miscarriage in this group.

The participants were placed in the litothomy position, and a sterile disposable Cusco speculum was passed into the vagina to expose the cervix and the cervix was visualized with the aid of an angle poised lamp. The cervix was examined for lesion and women with visible lesion on the cervix were excluded from further participation in the study and were sent to the antenatal clinic for further evaluation and intervention. Ayre's spatula was inserted into the cervix and rotated 360 degrees. All samples were placed on two pre-labeled slides and a smear was made and immediately fixed by dipping the slide inside 95% alcohol and sample was sent to histopathology laboratory for staining with Pap staining technique.

The fixed slides were hydrated in 90% and 70% alcohol each for 1 minute respectively. They were rinsed in water two times, and then stained first in Harris alum haematoxylin for 5 minutes. They were rinsed in water, then decolourized with 1% acid alcohol for 10 seconds and Blue in Scott's tap water for 5 minutes. They were rinsed in 95% alcohol again and then stained in orange G stock solution for 4 minutes. Then rinsed in 95% alcohol and finally stained with Eosin Azure 50 for 4 minutes. The slides were further rinsed with 95% alcohol. Cleared in xylene two times, 3 minutes each and mounted in a neutral synthetic resin medium and cover slip.

The researcher and the cytopathologist prepared and examined the slides. The cytopathologist was blinded to the HIV status of the patients to avoid bias. The Pap smear was reported using Bethesda 2001 system terminology. Women with abnormal smear were referred to the antenatal clinic for further examination. Abnormal Pap smears are atypical cell of undetermined significance (ASCUS), Low grade squamous intraepitelial lesion (LGSIL) and High grade squamous intraepithelial lesion (HGSIL), while the normal Pap smear are the normal smear and the inflammatory cells.

Data Analysis

The data was analyzed using Epi info version 7.2.1 of the Centre for Disease Control, Atlanta, USA, 2011 and MathCAD 14 Professional. The continuous variables were presented as mean and standard deviation while categorical variables were presented as numbers and percentages. Categorical variables were analysed using Chi square and Fisher's exact while means were compared using T-test. A P-value less than 0.05 was considered statistically significant.

Results

Table 1: Sociodemographic Characteristics of study participants

Parameters	**HIVpositive**	%	**HIVnegative**	**%**	**p-value**
Age in years					
21-30	52	52.0	49	49.0	0.752
31-40	44	44.0	51	51.0	
41-50	4	4.0	0	0.0	
Total	100	100.0	100	100.0	
Mean age	29.7±5.5		30.6±4.5		
Religion					
Christianity	100	100.0	100	100.0	>0.999
Islam	0	0.0	0	0.0	
Others	0	0.0	0	0.0	
Total	100	100.0	100	100.0	
Occupation					
Civil servant	37	37.0	42	42.0	0.972
Trading	22	22.0	26	26.0	
Farming	6	6.0	2	2.0	
Artisan	10	10.0	4	4.0	
Student	17	17.0	16	16.0	
Unemployed	8	8.0	10	10.0	
Total	100	100.0	100	100.0	
Educational status					
None	9	9.0	2	2.0	0.08
Primary	9	9.0	7	7.0	
Secondary	27	27.0	31	31.0	
Tertiary	55	55.0	60	60.0	
Total 1	100	100.0	100	100.0	
Parity					
0-1	59	59.0	67	67.0	0.141
2-4	28	28.0	26	26.0	
≥5	13	13.0	7	7.0	
Total	100	100.0	100	100.0	
Marital status					
Married	100	100.0	100	100.0	<0.999
Single	0	0.0	0	0.0	
Divorce	0	0.0	0	0.0	
Widow	0	0.0	0	0.0	
Total.	100	100.0	100	100.0	
Social class					
1	0	0.0	0	0.0	0.399
2	76	76.0	83	83.0	
3	13	13.0	12	12.0	
4	6	6.0	3	3.0	
5	5	5.0	2	2.0	
Total	100	100.0	100	100.0	

The socio-demographic characteristics are shown in table 1. There was no statistical difference in all the sociodemographic variables between the two groups. The mean age of the HIV positive women was 29.7 ± 5.5 years, while the mean age of HIV negative women was 30.6 ±4.5 years, P-value= 0.752. All the respondents were married and were all Christians. The majority of the respondents belonged to social class 2, 70% and 83% for HIV positive and HIV negative respectively. A greater population of the participants were literate with 82.0% and 81.0% having secondary education or higher in HIV positive and HIV negative women respectively.

Table 2: Comparison of Pap smear result in HIV positive and HIV negative pregnant women

Pap smear result	**HIV positive (%)**	**HIV negative (%)**	**X^2**	**p-value**	**Post Hoc Test p-value**
Normal Pap smear	76 (76.0%)	96 (96.0%)	16.611	< 0.001	< 0.001
Abnormal Pap smear	24 (24.0%)	4 (4.0%)			< 0.001
Total	100 (100.0%)	100 (100.0%)			

Table 2 illustrated the comparison of Pap smear result in HIV positive and HIV negative pregnant women. Twenty-eight of the participants had abnormal Pap smear giving a prevalence of 14% (1:7 pregnant women). The prevalence of abnormal Pap smear was higher in HIV positive pregnant women at 24% (1: 4 women). Out of 100 HIV negative women, four had abnormal Pap smear, giving a prevalence of 4% (1:25 HIV negative women). The difference in the two was statistically significant (p< 0.001). Seventy-six (76.0%) of HIV positive women had normal Pap smear and 96 (96.0%) of HIV negative women had normal Pap smear result. The difference in the two was also statistically significant (p< 0.001).

Table 3: Comparison of pattern of Pap smear results in HIV positive and HIV negative pregnant women by Bethsida classification.

Pap smear Result	**HIV positive (%)**	**HIV negative (%)**	**X^2**	**p-value**	**Post Hoc test p-value**
Normal	30 (30.0%)	46 (46.0%)	19.097*	**0.**003	**0.**009
Inflammatory	46 (46.0%)	50 (50.0%)			0.0564
ASCUS	19 (19.0%)	2 (2.0%)			<0.001
LGSIL	4 (4.0%)	1 (1.0%)			0.058
HGSIL	1 (1.0%)	1 (1.0%)			1.000
Total	100 (100.0%)	100 (100.0%)			

* Fishers exact test was used.

Table 3 compared pattern of Pap smear results in HIV positive and HIV negative pregnant women. Nearly one-third 30 (30.0%) of HIV positive women, had normal Pap smear, whereas 46 (46%) of HIV negative women had normal Pap smear. The difference between them was statistically significant with a p-value of

0.009. Forty-six (46.0%) of HIV positive women had inflammatory cells, while 50 (50.0%) of HIV negative women had inflammatory cells. The difference between the two was not statistically significant with a p-value of 0.564. Nineteen (19.0%) of HIV positive women had ASCUS, while 2 of HIV negative women had ASCUS. The difference between the two was statistically significant with a p-value of <0.001. Four (4.0%) of HIV positive women had LGSIL and 1 (1.0%) of HIV negative women had LGSIL. The difference between the two was not statistically significant with a p-value of 0.058. One (1%) from each group was found to have HGSIL. The difference between the two is not statistically significant.

Discussion

The importance of Pap smear in prevention of cervical cancer cannot be over emphasized. This study compared the prevalence and pattern of abnormal Pap smear, association of sociodemographic factors and abnormal Pap smear between HIV positive and HIV negative pregnant women. Index study found that the overall prevalence of abnormal Pap smear in pregnant women was 14%. Abnormal Pap smear results were more prevalent among HIV positive participants than HIV negative women (24% versus 4%). These findings support the relevance of Pap smear test for pregnant women as part of antenatal care especially HIV positive pregnant women.

The overall prevalence of abnormal Pap smear in this study was 14%. The prevalence of 14% is high and unacceptable and all effort should be geared towards reducing it. This is higher than 6% found at Zaria by Bakariet al[12] and Thailand by Jirapon et al[25] respectively. In India, 1% was noted by Priyaet al[13] and 6.3% found in Abakaliki by Ekwedigwe et al[1]. This difference may be because they screened more of HIV negative pregnant women while we screened equal numbers of HIV positive and HIV negative women as studies have shown that the prevalence of abnormal Pap smear is higher in HIV positive women[7,20].

This study found significantly higher prevalence of abnormal Pap smear among HIV positive pregnant women compared to their HIV negative counterpart. HIV is one of the risk factors of cervical intraepithelial lesions, this must have accounted for higher prevalence of abnormal Pap smear among HIV positive women. This finding is like findings 25.2% by Agboeze et al in Abakaliki [14] because it was done in a similar environment. It is also similar to the findings of 26.6% by Lawal et al.[20] Muhammed et al in Kano found a much higher prevalence (32.7%) of abnormal Pap smears in HIV positive women[7].This difference may be due to the fact that most of the participants in Kano were single, divorced or widowed. These groups of women are more likely to have multiple sexual partners which is one of the risk factors of CIN but our respondents were all married.

However, this finding differs from the finding of 12.6% in India by Madanet al[2] and in Enugu by Dim et al[17]. The participants in India and Enugu were non pregnant women[2,17]. This difference may be because abnormal cervical cytology is higher in pregnant women than in non-pregnant women[25].

The prevalence of abnormal Pap smear in HIV negative pregnant women as found in our study was 4% and lower than that in HIV positive women. This is because HIV negative women are more immunocompetent compared to HIV positive women. This was similar to the findings of 4.6% in Enugu by Dim et al[17] but differed from the finding of 8% by Muhammed et al in Kano[7]. The difference may be because some of the participants at Kano smoked cigarette while none of our respondents smoked. Studies have shown a fourfold increase of cervical dysplasia in primary smokers and a 1.4 times higher risk if they were secondary smokers[7]. Dinc et al in Turkey found a much lower prevalence of 0.9% of abnormal smears in HIV negative pregnant women[6]. This difference may be because; Turkey is a developed country where prevalence of cervical intraepithelial lesions is less because of their good health seeking behaviour.

This study noted that ASCUS was significantly higher; 10.5% with a P value of <0.001 in HIV positive women. LGSIL (2.5%) and HGSIL were also higher in HIV positive women, but the finding was not statistically significant. This is similar to that found at Nnewi by Ugboajaet al[3]. Also, a study done at Kolhapur, India found ASCUS as the commonest abnormal Pap smear[2]. This study's findings however differ from the findings at Kano where prevalence of HGSIL was higher[7]. The varying prevalence could be because in some of the respondents at Kano, both HIV positive and HIV negative subjects smoked cigarettes which increases the risk of cervical intraepithelial lesions, while none of our participants smoked cigarette.

This study strengths is in the comparative cross-sectional study design which is stronger than non-comparative cross-sectional studies which was the more common among design in similar works among pregnant women done in the past especially in Nigeria.

The limitations of the study arise from the physiological changes in the cervix during pregnancy which may mask premalignant changes; therefore, some women with premalignant changes may have been missed. In addition, follow-up with biopsy and treatment is a challenge for screening positive women due to increased risk of haemorrhage.

Conclusion

This study has demonstrated the presence of premalignant cervical lesions in pregnant women with a significantly higher prevalence among HIV positive pregnant women. ASCUS has been found to be the commonest premalignant lesion in pregnant women. Due to the poor health seeking behavior of our women, antenatal visits could be used as an opportunity to screen these women.

Funding Information: No external funding was received for this study.

Conflict of Interest Statement: None

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