The Pattern of Cervical Histology among Women with Human Immunodeficiency Virus infection Receiving Care at a Terciary Centre in South-South Nigeria

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DOI: https://dx.doi.org/10.51244/IJRSI.2021.8401

Abstract: Background: **The transitional area of the cervix has variable histological features due to constant changes following irritation by hormones, infection as well as trauma. These changes range from squamous metaplasia to cervical intraepithelial neoplasia and invasive cancers. Women with HIV infection are prone to premalignant and malignant lesions of the cervix due to immunosuppression and persistent co-infection with the highly oncogenic human papilloma virus serotypes. They are therefore thought to be sexually transmitted and they contribute significantly to reproductive ill-health and mortality among women.**

Objective: **This was to determine the actual prevalence of precancerous and cancerous lesions of the cervix using histological assessment among HIV positive women receiving care at the University of Port Harcourt Teaching Hospital (UPTH), Alakahia between August and June 2015.**

Materials and Methods: **One hundred HIV positive women on highly active antiretroviral therapy (HAART) were recruited randomly for the study with an uptake rate of 96%. Informed consent was obtained and data collected using a semi-structured questionnaire. They all had cervical biopsies and the specimens were processed by the histotechnologist and reported by the histopathologist. Data analysis was done using SPSS.**

Results: **The mean age of patients was 37.0 ± 6.6 years and the mean age of those with dysplasia was 38.1 ± 6.6 years. The age range of the patients was 21-56 years with the highest number of respondents (27.1%) in the 30- 34 years group. This was closely followed by 35-39 years with 26.0%. Majority of the patients (49.0%) were married and the others were either single, divorced or widowed. Most of the patients had at least secondary education (38.5% and 37.5% for tertiary and secondary levels of education respectively). The parous women weresixty (62.5%) while the nulliparous women were thirty six(37.5%).Thirty-four (35.4%) of the respondents had their first sexual intercourse before eighteen years of age while fifty-five (57.3%) had it after the age of eighteen. Seven (7.3%) had no idea of their age at first sexual exposure. Nineteen (19.8%) of them had five or more lifetime sexual partners while sixty-six (68.8%) had two to four sexual partners. Six (6.2%) have had one and five (5.2%) did not respond.Seventeen (17.7%) of the respondents had CD4 counts less than 250 cells/mm^3, thirty (31.3%) had values between 250 to 499 cells/mm^3 while forty-nine (51.0%) had 500 cells/mm^3 and above. Thirty-six (37.5%) were normal, twenty (20.8%) had cervicitis, twenty-three (24.0%) had CIN I, ten (10.4%) had CIN II, six (6.3%) had CIN III and one (1.0%) had endocervical polyp.**

Conclusion: **There is need for women with HIV infection to be screened regularly considering the high prevalence of cervical intraepithelial neoplasia among them.**

Key Words: **Cervical, histology, HIV, CIN, malignancy, pattern, South-South, women.**

I. INTRODUCTION

The cervix is the lowermost portion of the uterus whichis composed mainly of fibrous tissues with an average of 10 to 15% of smooth muscle fibers. It is covered by stratified squamous epithelium up to the internal os where it changes abruptly to the columnar type. This transitional area, also known as the transformation zone has variable histological features which change constantly following irritation, hormonal changes as well as infection and trauma. Thus, this zone is predisposed to severe dysplasia, carcinoma in situ and even invasive carcinoma.[1]

Worldwide, cervical cancer is the fourth most common cancer among women with an estimate of approximately 570,000 new cases and 311,000 deaths (in 2018) with a standardized incidence of 13.1 per 100,000 women.[2] More than 85% of the global burden of the disease occur in the low and middle income countries.[3]

Human Immunodeficiency Virus (HIV) infection is a sexually transmitted disease of public health importance. At the end of 2019, 38 million people were living with HIV/AIDS globally, and in the African sub-region nearly 1 in every 25 adults were living with HIV/AIDS accounting for more than two-thirds of the global statistics.[4]

Cervical intraepithelial neoplasia (CIN) is the premalignant transformation and abnormal growth of squamous cells on the surface of the cervix. It is mainly caused by chronic infection of the cervix and eventual integration into the cellular genome by high risk HPV genotypes like 16 or 18. Histologically, it is classified into; CIN 1 which corresponds to low grade

squamous intraepithelial lesion (LSIL), and CIN 2 and 3 which correspond to high grade squamous intraepithelial lesion (HSIL) according to the cytological classification by Bethesda. About 70% of CIN 1 will regress spontaneously within one year and 90% within two years while 50% ofCIN 2 will regress within 2 years. Progression to cervical cancer occurs in about 1% of CIN 1, 5% CIN 2 and at least 12% of CIN 3 and this usually takes about 10-15 years.[5]

Women infected with HIV are at increased risk of cervical intraepithelial neoplasia(CIN) and invasive cancer of the cervix as a result of immunosuppression and opportunistic infection with oncogenic strains of human papilloma virus(HPV).[6,7,8,9]Cervical cancer is an AIDS defining condition, and women who are HIV positive are three to five times more likely to develop cervical cancer.[10,11]Many studies worldwide have shown increase in the prevalence of CIN among HIV-positive women than the negative population. In the HER (HIV Epidemiology Research) study, CIN was found in 19% of HIV-positive women compared to 5% of HIV-negative women.[12] Similar results were found from the Women Interagency HIV Study (WIHS) group[13] and a study done in Abidjan (Ivory Coast).[14] In New York, the incidence of CIN was found to be 8.3% in HIV-positive women and 1.8% of HIV-negative women.[15]

This study was conducted to determine the prevalence of cervical intraepithelial neoplasia and invasive cervical lesions among HIV positive patients receiving care at University of Port Harcourt Teaching Hospital, Port Harcourt using histology since this gives the definitive diagnosis. This was important because it would further express the need to institute adequate and regular screening measures among this population.

II. METHODOLOGY

This was a cross-sectional study conducted at the oncology unit of the Department of Obstetrics and Gynaecology of University of Port Harcourt Teaching Hospital (UPTH) between June and August 2015.

The sample size was calculated using the formula,($N= Z^2 P(1-P)/ d^2$)[16]where,

N- Sample size,Z- Proportion of normal distribution corresponding to the required significance level (5%) which is 1.96,P- Prevalence of abnormal cervical smears among HIV-positive women in University of Port Harcourt Teaching Hospital from a previous study (0.344)[17] and d- Margin of error (0.1)

Thus $n= 1.96^2 \times 0.34 (1-0.34)/ 0.1^2 = 0.862/0.01= 86.2$. An attrition rate of 10% (8.6) was added to the minimum sample size of 86.2, giving a total of 94.8. This was approximated to 100.

One hundred HIV-positive women attending the Sexually Transmitted Disease (STD)/infectious disease clinic who fulfilled the eligibility criteria were recruited by simple random sampling after adequate counselling. Informed consent was obtained from each of them and they were then referred to the oncology unit of the department of obstetrics and gynaecology for the study.

The procedure was again explained to each patient and a written consent obtained. A detailed history was obtained using a pre-structured questionnaire and vital information such as biodata, history of present illness, past medical history, menstrual history, family and social history, husband's HIV status, socioeconomic status, previous sexual relationship, current medications (if on HAART) and duration, and latest $CD4^+$ count (done in the last three months and documented in their case notes) were entered.

A colposcopically directed biopsy was done following the sequential application of 5% acetic acid and Lugol iodine to identify the abnormal areas and then xylocaine spray on the entire cervix for analgesia. Using the Tischler-Morgan cervical punch biopsy forceps, the sample was taken from the abnormal areas with the margin inclusive. In patients whose cervix appeared colposcopically normal, samples were taken from four quadrants. The collected tissues were put into a universal bottle containing 10% formalin immediately for fixationand then labelled appropriately.The cervical tissues werehanded over to the histotechnologist and histopathologist for processing and reporting.

III. RESULTS

Out of one hundred patients that had cervical biopsy, four had unsatisfactory results leaving a total number of ninety six.

The mean age of patients was 37.0 ± 6.6 years and the mean age of those with dysplasia was 38.1 ± 6.6 years. The age range of the patients was 21-56 years with the highest number of respondents (27.1%) in the 30- 34 years group. This was closely followed by 35-39 years with 26.0%. Majority of the patients (49.0%) were married and the others were either single, divorced or widowed. Most of the patients had at least secondary education (38.5% and 37.5% for tertiary and secondary levels of education respectively). The parous women were more than the nulliparous women (62.5% and 37.5% for the parous and nulliparous women respectively). These are shown on Table 1.

Thirty-four (35.4%) of the respondents had their first sexual intercourse before eighteen years of age while fifty-five (57.3%) had it after the age of eighteen, however seven (7.3%) had no idea of their age at first sexual exposure.

Majority of the women have had more than one sexual partners in their lifetime; nineteen (19.8%) of them had five and above while sixty-six (68.8%) had two to four sexual partners. Only six (6.2%) have had one sexual partner in their lifetime, however five (5.2%) did not respond. These frequencies are shown in Table 2 below.

Seventeen (17.7%) of the respondents had CD4 counts less than 250 cells/mm^3, thirty (31.3%) had values between 250 to 499 cells/mm^3 while forty-nine (51.0%) had 500 cells/mm^3 and above.

Table 3 shows the histology findings; thirty-six (37.5%) were normal, twenty (20.8%) had cervicitis, twenty-three (24.0%) had cervical intraepithelial neoplasia I (CIN I), ten (10.4%) had cervical intraepithelial neoplasia II (CIN II), six (6.3%) had cervical intraepithelial neoplasia III (CIN III) and one (1.0%) had endocervical polyp.

Table 1: Socio-Demographic Characteristics of Thepatients (N=96)

Variable	N	Percentage (%)
Age(years)		
20-24	1	1.0
25-29	11	11.5
30-34	26	27.1
35-39	25	26.0
40-44	22	22.9
45-49	6	6.3
>50	5	5.2
Marital Status		
Single	28	29.2
Married	47	49.0
Divorced	5	5.2
Widowed	16	16.6
Educational level		
None	2	2.1
Primary	21	21.9
Secondary	36	37.5
Tertiary	37	38.5
Parity		
0	36	37.5
1-4	51	53.1
≥ 5	9	9.4

Table 2: Sexual Characteristics of the Patients (N=96)

Variable	N	Percentage (%)
Coitarche		
< 18 years	34	35.4
≥ 18 years	55	57.3
Not specified*	7	7.3
Number of sexual partners**		
1	6	6.2
2-4	66	68.8
≥ 5	19	19.8
Not specified*	5	5.2

*Value not given **Lifetime number of sexual partners

Table 3: Histological Diagnosis

Histology findings	N	Percentage (%)
Normal	36	37.5
Inflammatory/Cervicitis	20	20.8
CIN-I	23	24.0
CIN-II	10	10.4
CIN-III	6	6.3
Cervical polyp	1	1.0
Total	96	100.0

Table 4: Analysis for Factors Associated With Dysplasia

Factors	Dysplasia		Total n (%)	Chi Square	P value
	Present n (%)	Absent n (%)			
Parity					
0	11 (30.6)	25 (69.4)	36 (100.0)	3.92*	0.15
1-4	26 (51.0)	25 (49.0)	51 (100.0)		
≥ 5	2 (22.2)	7 (77.8)	9 (100.0)		
Coitarche					
< 18 years	14 (42.4)	19 (57.6)	33 (100.0)	1.84*	0.39
≥ 18 years	21 (37.5)	35 (62.5)	56 (100.0)		
Not specified	5 (66.4)	2 (28.6)	7 (100.0)		
Number of sexual partners					
1	2 (33.3)	4 (66.7)	6 (100.0)	1.00*	0.51
2-4	27 (40.9)	39 (59.1)	66 (100.0)		
>5	7 (36.8)	12 (63.2)	19 (100.0)		
Not specified	3 (60.0)	2 (40.0)	5 (100.0)		
CD4 count (cells/mm^3)					
<250 cells/mm^3	7 (41.2)	10 (58.8)	17 (100.0)	1.00	0.61
250-499 cells/mm^3	10 (33.3)	20 (66.7)	30 (100.0)		
>500 cells/mm^3	22 (44.9)	27 (55.1)	49 (100.0)		

*Fisher exact

Mean CD4 count of those with dysplasia= 612.51, SD-438.05 cells/mm^3

Mean CD4 count of those without dysplasia= 503.97, SD-384.41 cells/mm^3

Mean duration of antiretroviral therapy= 4.85± 3.3 year

IV. DISCUSSION

The histological diagnosis made from the biopsy specimens were: cervical intraepithelial neoplasia graded as I, II and III; inflammatory changes (cervicitis), endocervical polyp and normal cervical epithelium. The prevalence of grade I lesion was 24% which was higher than that of grade II (10.4%) and grade III (6.3%). No case of invasive cancer was detected in this study population.

The histological pattern of the 9cervical biopsy specimens was consistent with cervical intraepithelial neoplasia in 40.7% of cases, that is, nearly one in every two HIV positive patients (40.7%) in this study had cervical intraepithelial neoplasia

(CIN) which was quite significant. The incidence of cervical dysplasia is about 4 to5 times higher among HIV infected women and girls than their HIV negative counterparts.[15] A similar statistics was recorded in Kanu, Nigeria.[18]

The prevalence of cervical dysplasia from this study was comparable to a study conducted in Cameroun which reported a prevalence of 43.5%,[19] although this was determined by cytology rather than histology used in the current study. Other studies conducted in Nigeria and Ethiopia showed lower prevalence rates.[20,21] The difference in the prevalence rates may be due to the use of Pap smear for the diagnosis of cervical dysplasia as opposed to histology used in this study, and this was possibly due to the high false negative rate associated with Pap smear.[22] Histological examination is the gold standard for diagnosis as this is more sensitive than the available screening methods.

In another study conducted by Ononogbu et al in Nigeria using visual inspection with acetic acid (VIA)/ visual inspection with lugol's iodine, the prevalence of pre-cancer and cancer of the cervix was 6% and it was found to be marginally affected by HIV infection since the introduction of anti-retroviral therapy.[23]Although the prevalence of premalignant lesions of the cervix was high in the current study, no invasive lesion was detected probably due to the small sample size.

Some studies in the past have shown that multiparity, early coitarche, multiple sexual partners and low CD4 count have been associated with increased risk of dysplasia among HIV positive women.[24] Parham et al[25] and Atashili[26] et al reported that parity, multiple number of lifetime sexual partners and coitarche showed no statistically significant association with dysplasia, however, low CD4 count was found to be associated with increased risk of development of dysplasia. From this study, dysplasia was commoner among those with lifetime sexual partners of two and above, as well as those with one or more children. On the other hand, dysplasia was more among those with age at first sexual intercourse (coitarche) greater than 18 years and CD4 count greater than 500cells/mm^3. The mean CD4 count of those with dysplasia was 612.51 cell/mm^3 while that of patients without dysplasia was 503.97cells/mm^3 and this may be due to that the patients were on HAART with a mean duration of 4.85 years. These factors when analysed univariately were found not to be statistically significant as s.

This study has shown that the prevalence of premalignant lesions of the cervix is high among women with HIV infection receiving care at UPTH, further expressing the need for establishment of an effective screening protocol in this population. This can be incorporated into the treatment program for wide coverage and acceptance.

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