

High risk human papilloma virus (HPV) common among a cohort of women with female genital mutilation

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Abstract

Background: Nigeria accounts for 25% of cases of Female genital mutilation (FGM) worldwide, with increased incidence of cervical cancer.

Objective: This study was aimed at evaluating the relationship between FGM and HPV in a locality with high prevalence of FGM.

Methods: Papanicolaou test, DNA hybridization using Polymerase Chain Reaction (PCR), and flow-through hybridization was done to determine the genotypic variants of the HPV. Physical examination and questionnaires were also used to ascertain presence of FGM.

Results: FGM was found among 98(49%) subjects, while 23(11.5%) had one or more genotype of HPV. Majority of the cases of HPV (78.3%) occurred in FGM subjects. Seventeen Genotypes of HPV were found among subjects with FGM consisting of 11 high risk (16, 18, 31, 33, 35, 39, 52, 56, 73, 81, 82) and 6 low risk (43, 44, 6, 26, 84, 70). A correlation (p value = 0.0052 at 95% CI) was found between FGM and HPV prevalence with a positive result for post hoc analysis. Results show the first reported case of quintuple HPV infection in a single subject in Nigeria.

Conclusion: FGM needs to be halted as it has no known health benefit yet may increase the risk for cervical cancer.

Keywords: HPV, female genital mutilation.

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Introduction

Human papillomavirus virus (HPV) infection is one of the most common viral sexually transmitted infections in the world.¹ Persistent infection by high risk HPV have been associated with the development of cervical cancer² and more recently oropharyngeal cancer.³ HPV prevalence rate among women with normal cytology ranges from 10%-26%.³ The high prevalence rate of HPV among Nigerian women leads to a corresponding risk in the increase of cervical cancer cases in Nigeria. Currently, cervical cancer is the second highest cause of cancer deaths among Nigerian women², with 8,240 deaths occurring annually in Nigeria accounting for 49.8% and

3.1% of cervical cancer related deaths in West Africa and globally respectively.³

Also, female genital mutilation (FGM) is still a common practice in Nigeria. Nigeria has the highest number of women that has undergone female genital mutilation in the world, accounting for about 25% of all cases of female genital mutilations in the world.⁴ With no health benefit attributed to this practice, various health complications both short term and long term have been the bane of women and children subjected to this ignoble practice.⁵ Some of the short term effects of FGM include severe pain, shock, hemorrhage, urinary tract infection to some long term effect such permanent damage to the female genital tissue, chronic inflammation, long life trauma and permanent damage to the urethra.^{4,5} Various factors such as religion, traditions, beliefs have led to increased practice of FGM. However, younger women tend not to support this harmful practice. It is worthy of note that FGM violates the fundamental human rights of women.^{4,5}

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Various risk factors have been associated with the prevalence of HPV and cervical cancer including smoking, parity,⁶ alcohol, continuous usage of steroid contraceptives.⁷ Generally, the risk factors associated with HPV prevalence is largely attributed to both biological and behavioral factors. However, there are no literature linking the prevalence of HPV to FGM or considering FGM as a probable risk factor in HPV prevalence. However, WHO⁵ indicated that FGM could result in an increased risk of cervical cancer while stating that more research needed to be done.

Hence this study was carried out to determine a significant association between HPV and FGM prevalence in Ilorin, Nigeria.

Materials and method

Sampling

This study was carried out in Ilorin, Kwara state. A consecutive sampling of 200 women determined using Fisher's formula for cross sectional study were surveyed for this study. The subjects also met the inclusion criteria for HPV testing including age, being sexually active, parity and subjects who have not had complete or total hysterectomy. Sampling was carried out in Ilorin in November 2016.

Study population

The study was carried out among consenting women within the ages of 15yrs and 60yrs (note: choice of age range starting from 15yrs was necessitated by the common age of first child birth in the study area which is often at 15yrs), who met the inclusion criteria, attending the Family planning clinics of Sobi Specialist Hospital, Ilorin. A structured close ended questionnaire was administered to these subjects. Informed consent was obtained from all individual participants included in the study.

Data collection

Questionnaires were administered to subjects who met the inclusion criteria. The response to the questionnaire gave information about; Socio-demographic characteristics such as age, sex, and the socioeconomic status such as level of education and occupation. It also gave information about patient's history of disease, awareness, and patient's disposition with respect to various risk factors associated with HPV and cervical cancer.

Sample collection and analysis

Cervical smears were collected using a cytobrush by a Gynecologist and immediately placed in a preservative liquid and transported to the laboratory. FGM was determined through self-report and clinical examination by a gynecologist during pap smear collection. The samples were collected and taken to the laboratory for the following analysis; Papanicolaou test, DNA hybridization using Polymerase Chain Reaction (PCR), and flow through hybridization was done to determine the genotypic variants of the HPV. For Pap test, Lituto (Liquid based cytology) was utilized instead of the conventional cytology to aid proper recovery of HPV DNA present. For Pap smear staining, the conventional staining procedure as described by Papanicolaou⁸ was done with cytology slides classified according to The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnose.

Molecular characterization of HPV genotypes

HPV testing was performed at Nova Diagnostics Nigeria. DNA extraction was done using DNA extraction kits (Integrated technologies, USA) according to the manufacturer's instruction. For the molecular characterization of HPV, The GenoFlow (GF) was used. GenoFlow developed by Diagcor Bioscience Inc., as the capacity of genotyping 33 types of HPV including 17 high risk (genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82) and 16 low risk (genotypes 6, 11, 26, 40, 42, 43, 44, 54, 55, 57, 61, 70, 71, 72, 81 and 84) with a universal probe to determine other variants of HPV not captured among the 33. It uses a modified PGM1 primer, using it for the amplification of HPV L1 region.

PCR was performed in a thermocycler (Thermocell, China), the reaction mixture was utilized as stated by Diagcor. The reaction sequence was as follows; initial incubation at 95°C for 9 min, and then went through 43 cycles of denaturation at 95°C for 20 s, annealing at 55°C for 30 s, elongation at 72°C for 30 s. A final extension was carried out at 72°C for 5 min. After amplification, hybridization was carried using the Genoflow utilizing flowthrough hybridization. This was done after rigorous washing with the hybridized DNA detected using streptavidin-alkaline phosphatase followed by colorimetric development using nitroblue tetrazolium-5-bromo-4-chloro-3-indolyl-phosphate (NBT-BCIP). Relationship between FGM and HPV infection was established using Chi-square test with a value corresponding to $P < 0.05$ regarded as significant.

Using logistic regression confounding variables were equally control in establishing the relationship between FGM and HPV.

Results

The demographic activities of the study population are represented in Table 1. Majority of the women under

study were Muslims, had some form of formal education and married. Results from this study shows that only 2 (1.0%) of the subjects showed one or more form of cervical cytology abnormality. The abnormalities seen among the subjects were Low grade Squamous Intraepithelial Lesions (LSIL). Results also showed that 23 (11.5%) subjects had one or more genotype of HPV.

Table 1: Demographic characters of the study population

Demographic Characteristics		Study Population (%)
Age of subjects	15-20years	12 (6)
	21-30years	128 (64)
	31-40years	56 (28)
	41-50years	4 (2)
	Total	200 (100)
Type of Education	Formal Education	180 (90)
	Informal Education	20 (10)
	Total	200 (100)
Highest level of Education	Primary Education	12 (6)
	Secondary Education	60 (30)
	Tertiary Education	108 (54)
	Informal Education	20 (8)
	Total	200 (100)
Religion	Christian	12 (6)
	Muslims	184 (92)
	Others	4 (2)
	Total	200 (100)
Marital status	Married	196 (98)
	Single	4 (2)
	Widow	0 (0)
	Total	200 (100)

Furthermore, FGM was found among 98 (49%) subjects with majority of the cases of HPV infection (78.3%) found among subjects with FGM (Table 2). Similarly, the two incidence of LSIL were found to be present among subjects with FGM and the smears contained multiple genotypes of HPV. A total of 17 different genotypes of HPV were found in this study consisting of 11 high risk (16, 18, 31, 33, 35, 39, 52, 56, 73, 81, 82) and 6 low risk

(43, 44, 6, 26, 84, 70) genotypes.. Furthermore, the results from Table 2 show that the prevalence of any HPV was higher among women with FGM compared to women without FGM [18 (78.3%) vs. 5 (21.7%), crude Odds Ratio=4.37, 95% Confidence Interval: 1.5520 to 12.2769] as was the prevalence of any HR-HPV [19 (95%) vs. 1 (5%), crude Odds Ratio= 12.67, 95% Confidence Interval: 1.1772 to 13.6].

Table 2: Relationship between female genital mutilation and HPV infection

Risk factors	Subjects with female genital mutilation		X ² (p value)	95 % CI	Odds ratio	
	Yes	No				
HPV Prevalence	Positive	18	5	7.63 (0.01)	1.56 to 12.28	4.37
	Negative	80	97			
HPV Genotypes	High Risk	19	1	5.88 (0.15)	1.18 to 13.60	12.67
	Low Risk	6	4			
Co-infection	Multiple HPV infections	9	2	0.01 (0.67)	0.13 to 9.61	1.11
	Single HPV infection	10	2			

P value <0.005 is statistically significant

Table 3 shows the risk factors that showed positive correlation to HPV prevalence. The relationship between HPV, FGM and these risk factors which are potential confounding variables. Risk factors with the least exposure to HPV infection were chosen as the reference groups (Table 3). Table 4 shows the relationship between FGM, HPV infection and confounding variables.

Table 3: Risk factors associated with HPV infection

		HPV Infection		X ² (P value)	OR (95% CI)
		Yes	No		
Age of subjects	15-20years	2	8	8.3 (0.04)	0.08 (0.03-0.13)
	21-30years	15	73		
	31-40years	6	62		
	41-50years	0	34		
Sex at an Early Age	Yes	17	80	6.72 (0.01)	0.29 (0.11-0.77)
	No	6	97		
Sexual Partner Circumcised?	Yes	15	70	5.49(0.02)	0.3489 (0.14-0.87)
	No	8	107		
Subjects in a polygamous marriage?	Yes	16	62	10.21 (0.00)	0.2359 (0.09-0.60)
	No	7	115		

Table 4: Regression analysis of the relationship between HPV Infection and FGM

Model		Coefficients ^a						
		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.682	0.071		23.849	0.000	1.543	1.821
	Subjects with FGM	0.135	0.044	0.211	3.037	0.003	0.047	0.222
2	(Constant)	1.480	0.098		15.131	0.000	1.287	1.673
	Subjects with FGM	0.134	0.044	0.209	3.068	0.002	0.048	0.219
3	Age of subjects	0.077	0.027	0.199	2.911	0.004	0.025	0.129
	(Constant)	1.506	0.097		15.520	0.000	1.314	1.697
	Subjects with FGM	0.904	0.305	1.417	2.960	0.003	0.302	1.506
	Age of subjects	0.074	0.026	0.189	2.809	0.005	0.022	0.125
4	Sex at an Early Age	-	0.305	-1.220	-2.548	0.012	-1.381	-0.176
	(Constant)	0.778						
	Subjects with FGM	1.377	0.107		12.843	0.000	1.166	1.589
	Age of subjects	0.922	0.301	1.444	3.063	0.003	0.328	1.515
	Sex at an Early Age	0.078	0.026	0.201	3.028	0.003	0.027	0.129
Been Wife in a polygamous marriage	-	0.303	-1.347	-2.842	0.005	-1.456	-0.263	
		0.860						
		0.132	0.050	0.202	2.634	0.009	0.033	0.231

a. Dependent Variable: HPV Infection

Analysis showed a minimal effect in the odds ratio of subjects with FGM in the second model when the predictor age was added. Thus age alone was not a confounding variable. However, in the models 3 and 4 when two additional predictors were added, there was a corresponding positive increase in the odds ratio of the predictors.

Discussion

This study provides a comprehensive reports on the genotypic variants of HPV present in a North Central state of Nigeria with High level prevalence rate of FGM. Majority of the subjects were found between the age of 21-30 years accounting for 128 (64.0%) of the study population. This was not surprising, as sampling was done among women attending family planning clinics of the surveyed hospital. Majority of the women belonged to the child bearing age which forms the fulcrum of this study. Mbamara et al.⁹ Odusolu et al.¹⁰ and Schluterman et al.¹¹, also recorded this age range as been the most prevalent in their study of HPV infection among a cohort of women. They had a prevalence rate of 52%, 66.6%, 80.6% respectively.

Results revealed that out of the 200 women who participated in the study, 198 (99.0%) had normal cytology (they were negative for intraepithelial lesion or malignancy), while 2 (1.0%) women had abnormal cytology (they were positive for intraepithelial lesion or malignancy). The prevalence of 1.0% abnormal cytology in this study is different from that reported by Durowade et al.¹³ in Kwara state, which reported a prevalence rate of 5% for

abnormal cytology. Although the result of 99.0% for normal cytology is higher than those reported by Adekunle and Samaila¹³ who reported 74.5% normal cytology, and Odusolu et al.¹⁰ who reported the prevalence of normal cytology as 83.7% it is worthy of note that majority of these studies were retrospective, and a large section of such patients were not voluntary, but patients who already had gynecological problems and cytology was recommended. This is likely going to result in higher number of abnormal cytology compared to this study which utilized normal women with no related gynecological problems. Thomas .4 reported a prevalence of 9.4% abnormality for a similar study in Ibadan.

A key feature of this study is establishing the relationship between FGM and HPV prevalence. Although no direct relationship has been drawn between HPV prevalence and FGM in the past, a significant difference existed statically (p value =0.0052, 95% CI 1.5520 to 12.2769). Results from the linear regression analysis carried out on Table 4 further establishes this relationship between HPV and FGM. After standardizing for age of the subjects, there was minimal effect on the odds ratio (0.135 to 0.134) of

the subjects with FGM. However, there was a significant positive change of the odds ratio to 0.904 and 0.922 after adjusting for subjects who had sex at an early age and subjects in a polygamous marriage. The high prevalence of FGM (49%) among the subjects shows that FGM is still a common practice in Ilorin, Nigeria. It is worthy of note that this study did not seek out directly subjects with FGM, rather subjects attending family planning clinics were recruited.

It has been noted that FGM has no known health benefits (WHO, 2016) yet the health risk associated with it are numerous. It was clearly noted in this study that High risk HPV was found more commonly in subjects in subjects with FGM. The reason for this is not yet established as there is a dearth of literature focusing on the infection acquisition mechanism of women with FGM, as most studies focuses on epidemiological studies of FGM.¹⁶ The presence of abnormal cytology and higher presence of multiple HPV infections among these women with FGM further shows that FGM could be a potential risk factor in the prevalence of HPV infection and thus cervical cancer.

Results from this study showed that 11.5% of the study population had one or more HPV infection. This is relatively high as majority of these women with HPV infection had normal cytology i.e. were negative for intraepithelial lesions. While Al-Awadhi et al.¹⁷ reported a prevalence of 2.4% among women with normal cervical cytology in Kuwait, Adenis et al.¹⁸ reported a prevalence rate of 27.2% among women with normal cytology in French Guiana. Although Adenis et al.¹⁸ reiterated that the figure stated in their research was among the highest in the world.

A total of 17 different genotypes of HPV were found in this study consisting of 11 high risk (16, 18, 31, 33, 35, 39, 52, 56, 73, 81, 82) and 7 low risk (43, 44, 6, 26, 84, 70) genotypes. The use of flow through hybridization as utilized in this study has been shown to possess the ability to identify 33 different genotypes of HPV.¹⁹ While Nyengidiki et al.²⁰ and Kolawole et al.²¹ obtained 4 genotypes of HPV (16, 18, 31, 35) in studies in Port Harcourt and Lokoja Nigeria respectively.

Furthermore, subjects with abnormal cytology i.e. Low grade Squamous Intraepithelial Lesions (LSIL) found in this study had multiple HPV genotype. This study also reports the presence of quintuple infection of HPV (HPV

70, 33, 73, 81, 82). This was found among subjects with Low grade squamous intraepithelial lesions. This is the first report on quintuple HPV infection in a single subject in Nigeria. Sharifah et al.²² obtained high risk HPV genotypic variants of 16, 18, 31, 51, 52, 56, 58 and 66, from abnormal cervical smears, with the highest frequency of genotypes occurring in LSIL smears. Thomas et al.¹⁴ obtained similar results in Ibadan, Nigeria where the common high risk HPV genotypic variants found among the subjects were 16, 31, 35 and 58. These cases of multiple infections tend to have been more common in subjects FGM. Other factors such as age of the subjects, being in a polygamous marriage and sexual partner circumcision all had a statistical relationship with HPV prevalence. These factors have been previously established as potential risk factors for HPV infection and cervical cancer.² Thus focus was not placed on their individual ability to increase HPV prevalence, but as confounding variables as shown in Table 4.

While the relationship between cervical cancer, FGM and HPV infection is still not well understood. Some studies have also drawn a relationship between FGM and invasive cervical cancer. Osterman²³ reported that in their analysis of Senegalese women with and without cervical abnormalities and invasive cancer, a strong association between FGM and invasive cervical cancer was found. It is not exactly clear while subjects with FGM are more likely to develop cervical cancer but a look at the oncogenic mechanisms of most cancerous cells has shown a direct correlation between inflammation which is a primary defense mechanism by the body against infections and carcinogenesis.²⁴ Sexually transmitted infections such as HPV, herpes simplex type are known to also induce inflammatory response.²⁵ With chronic inflammation one of the prolonged effect of FGM, it thus can be argued that women with FGM especially those with chronic inflammatory responses are more likely to develop cervical cancer. Furthermore, studies have shown that FGM increases the risk of having bacterial vaginosis (BV).²⁶ Morrison et al.²⁶ in their study of the long term effect of FGM among a rural community in Gambia noted that women with FGM had a higher prevalence of BV at an adjusted odds ratio (OR)=1.66; 95% confidence interval (CI) 1.25–2.18. This is important because different studies have shown that the presence of BV among subjects significantly increases their risk of acquiring HPV in-

fection. While the actual mechanism is not known, this strong correlation cannot be overlooked.^{27,28,29} Thus one can imply that FGM which significantly increases the risk of genital inflammation as well as BV, invariably increases the risk of acquiring HPV infection and thus cervical cancer. Also, a link has been established between HPV infection and BV in women. Studies have shown that BV which is characterized by low level of *Lactobacillus* spp, increased prevalence of anaerobes,³⁰ is linked with persistent HPV infection and developing precancerous lesions.^{31,32} Although it was observed in this study that the two subjects already developing cervical neoplasia had high risk HPV, the data is too small to make any conclusion from that.

This study clearly establishes a statistical correlation between HPV and FGM prevalence. However, there is a need to take a further look at the role other risk factors associated with HPV infection play vis-à-vis FGM among a cohort of women with only FGM. Meanwhile there is a need to increase the awareness of Nigerians about the dangers of FGM in order to curb this abuse that is still being perpetuated against women in Nigeria.

Limitation of study

The type of FGM the subjects had were not considered. This could be relevant in understanding cervical cancer pathogenesis.

Conflict of interest

None declared.

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