Infectious Agents and Cancer

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Seroprevalence of human papilloma virus 6, 11, 16 and 18 among pregnant women in Mwanza-Tanzania

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Abstract

Introduction High-risk human-papilloma viruses 16 and 18 (HR-HPV 16 and HR-HPV-18) are well known to be associated with carcinoma of the cervix, head and neck, penis, and anus. Low-risk human papillomaviruses 6 and 11 (LR-HPV 6 and LR 11) infection has been associated with anogenital warts, oral papilloma, and laryngeal papillomatosis in children. HPV infection during pregnancy (HR-HPV and LR-HPV) increases the risk of vertical transmission from infected pregnant women to unborn children. The burden of HR-HPV type 16 and 18 and LR-HPV 6 and 11 is not well documented among pregnant women attending antenatal clinics (ANC). This study determined the seroprevalence and distributions of HR-HPV 16, 18, and LR –HPV 6, 11 antibodies among pregnant women attending ANC at Bugando Medical Centre (BMC) in Mwanza, Tanzania.

Methodology A cross-sectional study involving 255 pregnant women enrolled in obstetrics and gynecology outpatient clinics was conducted between November 2020 and March 2021 at Bugando Medical Centre (BMC) in Mwanza. A structured pre-tested questionnaire was used to obtain patients' information. Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) was used to detect HPV 6, 11, 16 and 18 specific immunoglobulin G (IgG) from sera. Stata version 15v1 was used for the descriptive data analysis.

Results The median age was 27(IQR: 22–31) years. The overall HPV seropositivity for any of the four serotypes was 63.9% (165/255), 95% CI: 58.0-69.7, whereby 37.6%(97/255), 32.2%(83/255), 15.5% (40/255) and 27.1% (70) were positive for HPV 6, 11, 16 and 18 respectively. Eight participants (3.1%) were positive for all 4 genotypes.

Conclusion About two-thirds of pregnant women had antibodies against HPV 6, 11 16, and 18 indicating previous HPV exposure. Vaccination programs should be emphasized to reduce the HPV-related manifestations in this population.

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Introduction

Human papillomavirus (HPV) has been identified as a cause of cervical cancer, other cancers of the anorectal area, and HPV-related diseases like genital warts and respiratory papillomatosis [1, 2]. HPV genotypes have been categorized into low-risk and high-risk. Low-risk genotypes are associated with anogenital warts, oral papilloma, and laryngeal papillomatosis, and high-risk genotypes are associated with cancers of the cervix, anogenital areas, and head and neck [1].

HPV genotypes 16 and 18 account for about 70% of all cervical cancer worldwide [3]. Other high-risk genotypes (HPV 52, 35, 58, 51, 45, 31, 53, and 56) have also been reported to cause cervical cancer [4]. Genotypes 6 and 11 are the low-risk genotype associated with benign lesions; anogenital warts (GWs) and recurrent respiratory papillomatosis (RRP) [1, 2, 5].

The seroprevalence of HPV differs from one population to another, however, sexual behavior increases the exposure of HPV. In Colombia the seropositivity was high among women who had 2 or more sexual partners [6]. The seroprevalence of HPV among pregnant is markedly high; in Brazil the overall seroprevalence rates of four HPV types among primiparous women were HPV16, 9.0%; HPV18, 7.0%; and HPV 6+11, 7.7%. In South Africa, the seroprevalences antibodies to 16, 11 and 18 among pregnant women were 17%, 21% and 16% respectively [7]. Despite the high burden of HPV exposure much has not been documented among pregnant women in Sub–Saharan Africa. In Tanzania, little is known about the magnitude of HPV seropositivity among pregnant women. The determination of HPV current infection by HPV DNA among pregnant women is not routinely done, this may be due to a lot of clinicians avoid to take cervical swabs with a fear of inducing heavy bleeding, infection, and even increase the risk of an iatrogenic miscarriage [8].

Serum antibody to HPV is a useful marker reflecting cumulative HPV exposure hence understanding the burden [9]. Sub-Saharan Africa is reported to have low HPV vaccination coverage and little is known on the seroprevalence of HPV 6, 11, 16, and 18 among pregnant women population. This is the first study in Mwanza, Tanzania to report the seroprevalence of HPV 6, 11, 16, and 18, the information that might be useful in understanding the burden and enforcing the current efforts in controlling the virus due to the fact that about 60% of patient who had anogenital HPV infection within 18months may have detectable antibodies to the specific HPV types [10].

Materials and methods

Study design, study area, and study population

A cross-sectional study involving 258 pregnant women attending the obstetrics and gynecology clinic at Bugando Medical Centre (BMC) was conducted from November 2020 to March 2021. Bugando Medical Centre (BMC) is a zonal hospital in Nyamagana District Mwanza Tanzania with approximately 1000 bed capacity and eleven (11) outpatient clinics. It serves eight regions with an average of over 14 million populations.

Sample size estimation and sampling technique

A minimum sample size of 258 was obtained using the Yamane Taro formula for sample size calculation from a given population [11]. Pregnant women at second and third trimester were recruited. The convenient sampling was used until the desired sample size was reached.

Sample collection and laboratory procedures

A pretested Swahili version of the data collection tool was used to collect data, and a tabular checklist was used to extract information from patient records. Blood samples were collected from consenting pregnant women in plain vacutainer tubes. Sera were extracted and stored at -80^{0}C freezer until processing. Detection of HPV antibodies was done by using a sandwich Enzyme-Linked Immunosorbent assay (ELISA) as per manufacturer instructions (Sunlong Biotech Co.Ltd, China). Sera were retrieved and allowed to attain room temperature before processing. In the microtiter plate, two wells were used as a negative control, two wells as a positive control, and one empty well as a blank. A 50 µl of control solution was added in positive and negative control wells. In the sample well 40 µl of sample dilution buffer and 10 µl sample were added to the bottom without touching the well wall, mixed gently by shaking, then sealed with a closure plate membrane and incubated at 37^{0}C for 30 min. Washing was done using diluted washing buffer by refilling the well with solution and allowed to rest for 30 s before discarding the washing buffer, the washing was repeated 5 times. This was then followed by the addition of 50 µl of Horseradish peroxidase (HRP)-conjugate to each well except the blank. This was followed by incubation at 37^{0}C for 30 min. The substrate was added to each well as 50 µl of solution A and 50 µl of solution B followed by mixing gently by shaking. The mixture was incubated at 37^{0}C for 15 min and then a stop solution was added to terminate the reaction. The absorbance was read at 450 nm using ELISA plate reader. The sample was regarded as positive for HPV antibodies if the optical density was equal to or above the cutoff value and negative for HPV antibodies if the optical density was less than the cutoff value. Positive and Negative controls were run to monitor the performance procedure's accuracy and a comparative pattern for a better result interpretation.

Data management and analysis

A structured pre-tested questionnaire was used to collect information from pregnant women. Laboratory results were recorded into laboratory worksheets, sorted, and sent into a Microsoft Excel sheet for cleaning and coding. Statistical data analysis was performed using STATA version 15v1. Data were summarized in proportions and frequency tables for categorical variables. For continuous variables, data were reported as mean ± standard deviation (SD) or IQR. Univariate logistic regression was done to establish associated factors. A p value of less than 0.05 was considered significant.

Table 1 Social demographic characteristics of participants (*N* = 258)

Maternal characteristics		Frequency	Percentage
Age (years)	18–30	205	79.45
	31–40	53	20.55
Gestation age (weeks)	10–20	27	10.47
	21–30	159	61.63
	31–40	99	38.37
Parity	0–2	172	66.67
	> 2	86	33.33
Location	Rural	18	6.98
	Urban	215	83.33
	Periurban	25	9.69
Religion	Christian	185	71.71
	Muslim	73	28.29
Marital status	Monogamy	207	80.23
	Polygamy	15	5.81
	Separated	26	10.08
	Co-habiting	7	2.71
	Single	3	1.16
Education level	Never attended	25	9.7
	Primary school	170	65.9
	Secondary	55	21.3
	Tertiary	4	3.1
Occupation	Government employment	4	1.6
	Self-employment	100	38.7
	Unemployment	89	34.5
	Housewife	37	14.3
	Petty trader	28	10.8
Water source	Lake or Pond	30	11.63
	Tape water	228	88.37
House type	Local house	37	14.34
	Modern house	221	85.66
Toilet type	Pit latrine	46	17.83
	Modern	212	82.17
HIV Status	Negative	177	68.60
	Positive	81	31.40

Ethical considerations

The ethical clearance was sought from the joint CUHAS/BMC Research Ethics and Review Committee (CREC) and given certificate number CREC/385/2019. Permission to collect data was sought from the Director General of BMC and the head of the department (Obstetrics and Gynecology). Written informed consent was requested from participants after explaining the aim and importance of the study. All procedures and anticipated risks or benefits related to their participation were well explained to them. Participants were asked to participate in the study voluntarily by signing the consent forms. Confidentiality was maintained throughout the study.

Results

Socio-demographic characteristics

The median age of enrolled women was 27(IQR: 22–31) years. More than three-quarters 222 (86%) of enrolled women were married and the majority 215(83.33%) were residing in urban areas. About two-thirds 173(67.8%) of the women had a primary school level of education while more than half 135(52.9%) were not employed. Eighty-one (31.4%) were HIV seropositive (Table 1).

Obstetrics, gynecology, and sexual characteristics

About 156(61%) of enrolled participants had 1st sex before the age of 18 and 203(78.7%) of participants had delivered their first child at the age above 18 years. A total of 121(46.9%) had more than one lifetime sexual partner and 74 (28.7%) of participants had more than one sexual partner at the time of enrollment. Regarding the history of sexually transmitted infections (STI), 48 (18.6%) of the participants had a prior history of STI and only 15(5.8%) had a history of genital ulcer (Table 2).

HPV seroprevalence among pregnant women in Mwanza

Among 258 enrolled women, 165(63.9%)95% CI: 58.0-69.7 were positive for at least one serotype. And the overall seroprevalence for HPV 6,11,16 and 18 was 37.6%, 32.6%, 27.6%, and 15.5% respectively. (Fig. 1). Some participants were positive for multiple HPV serotypes; 36 (13.9%) were positive for both low-risk HPV 6 and 11, and 23(8.9%) were positive for high-risk serotypes 16 and 18. Only 8 (3.1%) participants were positive for all four genotypes (Table 3). Among HPV seropositive patients, 76(46%) participants were aged 15–25 years, 62(37.6%) were aged 26–35 years and 27 (16.3%) were aged 36–45 years (Table 4).

The risk of having HPV IgG positive was more in participants who were living in peri-urban (OR 4.000; 95% CI 1.040-15.381, $P=0.044$).

HPV IgG seropositivity was also significantly associated with having older partners of more than five years (OR 0.976; 95% CI:0.96-1.00, $P=0.049$) (Table 2).

Table 2 Sociodemographic, Obstetrical, gynecological, and sexual characteristics and factors associated with HPV seroprevalence

Characteristics/variables		Positive *n*% Median (IQR)	Univariate (OR, 95%CI)	*p*-value
Age (years)		27(22–31)	1.010(0.974-1.055)	0.482
Gestation age (weeks)		27(22–34)	0.990(0.965-1.240)	0.727
Median (IQR) Parity		2(0–3)	1.103(0.932-1.305)	0.253
Location	Rural	9(50.0)	1	
	Urban	136(63.0)	1.721(0.656–4.512)	0.270
	Periurban	**20(80.0)**	**4.000(1.040-15.381)**	**0.044**
Religion	Christian	185(71.71)		
	Muslim	73(28.29)		
Marital status	Monogamy	130(62.8)	1	
	Polygamy	10(66.7)	1.332(0.553–3.210)	0.522
	Separated	18(69.2)	0.592(0.036–9.023)	0.713
	Co-habiting	6(85.7)	1.185(0.390–3.594)	0.765
	Single	1(33.3)	1.777(0.350–9.023)	0.488
Education level	Never attended	16(64.0)	1	
	Primary school	111(65.3)	1.05(0.446-2.504).	0.899
	Secondary	34(61.8)	0.91(0.341-2.429)	0.852
	Tertiary	4(50.0)	0.562(0.112-2.810)	0.483
Occupation	Government employment	2(50.0)	1	
	Self-employment	63(63.0)	1.703(0.230-12.601)	0.602
	Unemployment	58(65.1)	2.667(0.250-28.438)	0.417
	Housewife	24(64.9)	1.871(0.251–13.934)	0.541
	Petty trader	(64.3)	1.846(0.232–14.673)	0.562
Water source	Lake or Pond	16(53.3)	1	
	Tape water	149(65.3)	1.53(0.769-3.57)	0.210
House type	Local house	23(67.6)	1.09(0.753-1.580)	0.645
	Modern house	140(63.6)	1	
Toilet type	Pit latrine	31(67.4)	1	
	Modern	134(63.2)	0.907(0.485–1.691)	0.756
HIV Status	Negative	112(63.6)	1	
	Positive	53(64.6)	1.044(0.66-1.81)	0.876
Age at first intercourse	Below ≤18	100(60.47)	14.1(0.81–111)	0.306
	Above 18	65 (39.53)	1	
Age at first delivery	Below ≤18	35(21.32)	0.868(0.455-1.68)	0.649
	Above 18	130(78.68)	1	
Number of sexual partners	1 partner	84(61.8)	1.147(0.915-1.436)	0.234
	2 and above	51(41.8)	1	
Partner outside the current relationship	No	115(63.2)	1	
	Yes	50(65.8)	1.120(0.639–1.964)	0.692
How older is sexual partner (Years)		**6 IQR(3-10)**	**0.97655(0.955-0.999)**	**0.049**
Contraceptive use	No	9964.7)	1	
	Yes	66(62.8)	0.923(0.550–1.540)	0.761
History of STI	No	135(64.3)	1	
	Yes	30(62.5)	0.925(0.483–1.771)	0.816
History of genital ulcer	No	155(64.5)	1	
	Yes	9 (60.0)	0.842(0.587–2.147)	0.727

Among recruited women, 81 participants were HIV positive, of these 56 (69%) participants were HPV seropositive. The genotypes were HPV 6, 23(28%), HPV 11; 20(25%), HPV 16; 14(17%) and HPV 18; 19 (23%). About 13(16%) were positive for multiple HPV genotypes and 4 (4.9%) individuals were found to be infected with three different serotypes (Table 5).

Discussion

This is the first report of HPV antibodies for genotypes 6, 11, 16, and 18 in Africa. In this study, the overall HPV seroprevalence among pregnant women was 63.9%. This high seroprevalence shows the increased exposure to HPV, and increase the burden of the disease among pregnant women. The majority of participants who had HPV

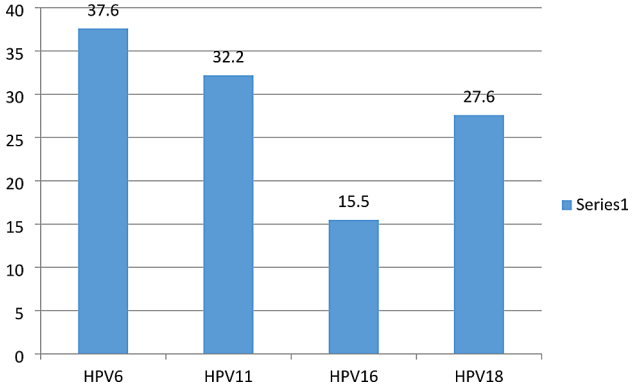

Fig. 1 Genotypes distribution (%)

Table 3 HPV serotype distribution on the study population *N* = 165 participants

Genotypes	No	%
HPV 6	97	37.6
HPV 11	83	32.2
HPV 16	40	15.5
HPV 18	70	27.1
HPV 6_HPV 11	36	13.9
HPV 6_HPV 16	18	6.8
HPV 6_HPV 18	32	12.5
HPV 11_HPV16	25	9.7
HPV11_HPV 18	40	15.5
HPV16_HPV18	23	8.9
HPV6_HPV11_HPV16_HPV18	8	3.1
At least one Genotype	165	63.9

Table 4 Age distribution among participants with HPV seropositive

Age	No	%
15–25	76	46.1
26–35	62	37.6
36–45	27	16.3
	165	100

Table 5 HPV genotypes distribution among HIV Subgroup *N* = 81 participants

Genotypes	No	%
HPV 6	23	28.3
HPV 11	20	24.7
HPV 16	14	17.2
HPV 18	19	23.5
HPV 6 and HPV 11	3	3.7
HPV 6 and HPV 16	2	2.5
HPV 6 and HPV 18	2	2.5
HPV 11 and HPV 16	3	3.7
HPV 11 and HPV 18	0	0
HPV 16 and HPV 18	3	3.7
HPV 11,16,18	3	3.7
HPV 6,11, 18	1	1.2
At least one Genotype	56	69.1

antibodies aged between 15 and 25 years, indicating that the infection may be attributed to early sex debut, multiple sexual partners, and likely might have conceived before the body's immune cleared the infection. Considering the majority of women recruited were in this age group, this might be another reason for high seroprevalence. The seroprevalence in the current study was high in comparison to a previous report in Brazil among pregnant woman which documented the seroprevalence of 19.3% [12] indicating epidemiological variation of the infection. Significant proportions of tested women were positive for all HPV 6, 11, 16, and 18, these genotypes are commonly vertically transmitted from the mother to the child [7]. This necessitates the need to emphasize vaccinating girls to prevent future consequences including cervical cancer and adverse pregnancy outcomes.

About one-third of our study population was HIV positive, 69.1% of the HIV-positive population had HPV antibodies and one-third of the population was positive with more than one HPV genotype. HPV infection has been reported to be higher among HIV-infected pregnant women than non-HIV-infected pregnant women [13, 14]. Immunodeficiency caused by HIV increases HPV persistence and hence the risk of HPV-related manifestations [14, 15]. All of the participants in the HIV population were on antiretroviral therapy with some having significant viral load suppression. However, they had significant exposure to HPV. These findings are consistent with different reports worldwide where there was an increased seroprevalence of HPV among the HIV seropositive population than the HIV seronegative population [16, 17].

In this study participants enrolled from peri-urban areas had an increased risk of HPV seropositivity. People in the peri-urban and urban areas may have an increased risk of HPV exposure due to their lifestyle, and increased risk of early sexual activities. This seroprevalence is similar to one of the study done in China; where the seroprevalence was higher among participants from urban provinces than rural provinces [18].

Participants who had older partners more than five years in this report had an increased risk of HPV seropositivity. Previous studies documented that HPV prevalence among males peaks at an older age compared to female counterparts. Lu et al. showed HPV seroprevalence to increase as the age increases with the peak age in all serotypes 6, 11, 16, and 18 being between 35 and 45 years [19]. The prevalence of HPV was found to increase with later age among males than females when the two populations were compared [20]. This may explain the reason why in the report the participants who had older partners had an increased risk of having HPV seropositive.

Conclusion

High seroprevalence of HPV antibodies among pregnant women in the current study shows that the HPV infection is endemic in the putting women at increased risk for cervical cancer and risk of vertical transmission from a mother to the baby considering the majority of HPV seropositive women were in the reproductive age.

Limitations of the study

- This study determined only seroprevalence of HPV and cervical cells were not taken to determine the HPV current infection.
- Only pregnant women were enrolled in this study, seroprevalence of non-pregnant woman was not determined.
- Study was only done at Bugando Medical Centre Tanzania; the findings may not be generalized.

Abbreviations

BMC	Bugando Medical Centre
CUHAS	Catholic University of Health and Allied Sciences
ELISA	Enzyme-Linked Immunosorbent assay
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	High Risk
LR	Low Risk

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Author contributions

F.M., M.M.M., and S.E.M. participated in the design of the work. F.M. participated in collecting specimens and clinical data. F.M., B.M., V.E.F, and VS performed laboratory analysis of the specimen. F.M., S.E.M., and M.M.M. analyzed and interpreted the data. F.M. prepared the first and second drafts of the manuscript. S.E.M, B.G, and M.M.M did the critical revision of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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