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Pap smear screening for a sample of female patients with anogenital warts in Erbil city

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Abstract

Background and objective: Genital human papillomavirus (HPV) infection is closely linked to cancer of the cervix. The Papanicolaou-stained smear is the primary method for detection of high-risk HPV. This study aimed to identify women at risk of developing cervical precancerous lesions.

Methods: This cross-sectional study involved 75 married, non-pregnant women with anogenital warts. Sociodemographic, fertility history, and details of the anogenital wart infection were obtained from all patients through a questionnaire. Pap smear was performed for all patients, and histopathological assessment was done.

Results: The age of the patients ranged from 18 to 55 years. The mean (± SD) age of marriage was 22.2 (± 5.77) years, 12 (16%) women gave birth to a child before the age of 18 years. Filiform warts were identified in 33 (44%) patients, while the acuminate type was found in 24 (32%) patients. Flat warts were seen in nine (12%) patients. There was a significant association between the type of wart and recurrence. Severe erosive cervicitis was found in 45 (60%) smears. Moderate cervicitis was observed in 24 (32%) smears, and six (8%) had mild cervicitis. A significant association was found between duration of the genital wart and cervicitis. Twenty percent had atypical squamous cells of undetermined significance. No malignant changes and no koilocytes were identified.

Conclusion: Early marriage, unawareness of the risk of anogenital warts, and neglecting regular Pap smears are risk factors for developing cervical cancer.

Keywords: Human papillomavirus; Anogenital warts; Pap smear; High-risk female for cervical cancer.

Introduction

Genital warts are the most common sexually transmitted diseases. Genital human papillomavirus (HPV) infection is closely linked to cancer of the cervix, glans penis, anus, vulvovaginal area, and periungual skin. Cancer occurs when there is an integration of the HPVgenome into the host DNA.[1] Papillomaviruses infect and replicate in the squamous epi-thelium of skin (warts) and mucous membranes (genital, oral, and conjunctival papillomas) to induce epithelial pro-liferation. The HPV types are very tissue-specific, causing different disease presentations. The wart develops because of virus stimulation of cell growth and thickening of the basal and prickle layers (stratum spinosum), as well as the stratum granulosum. The viral infection remains local and generally regresses spontaneously but can recur.[2] HPV can reside in basal epithelial cells and lead to subclinical or latent infection. Most cervical dysplasias and cancers are related to oncogenic HPV types.[3] Robust epidemiologic and molecular studies confirm that infection with high-risk HPV is the cause of almost all cases of cervical cancer. Even with high-risk HPVs, the most cervical infection has a benign outcome. Persistent infection with high-risk or other HPV types is a major risk factor. The critical determinants of whether HPV infection of the cervix is transient or persistent and thus at high-risk for malignant progression are not known.[4]

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Women with anogenital warts, or who are the partners of men with anogenital warts, should have their cervical cytology checked regularly.[5] Carcinoma of the cervix is the second commonest cancer among women worldwide, with only breast cancer occurring more commonly. Worldwide, cervical cancer accounts for about 500 000 new diagnoses and 273 000 deaths every year. Of the new cases, 80% occur in the underdeveloped countries, and in some of these countries, cervical cancer is the commonest cancer in women. Cervical cancer is a preventable condition, and considerable effort goes into detecting and treating the pre-invasive disease, primarily in developed countries.[6] The primary method for the detection of high-risk HPV is still the Papanicolaou-stained (Pap) smear. The Pap test is considered by many to be the most cost-effective cancer reduction program ever devised. Several pieces of evidence link it to the prevention of cervical cancer. First, the mortality rate from cervical cancer fell dramatically after the screening was introduced. Second, there was a direct correlation between the intensity of screening and the decrease in mortality. Finally, women in whom invasive cancer does not develop are more likely to have had a Pap test than women with cancer. Screening guidelines differ around the world.[7] As anogenital wart is an increasing venereal disease among our population and to the best of our knowledge, no similar study has been performed in Erbil city. This study aimed to evaluate the cervical cytology abnormalities in women with anogenital human papilloma virus infections to identify those women at increased risk of developing a significant cervical intraepithelial lesion.

Methods

The current study involved 75 married, non-pregnant women with lesions clinically diagnosed as anogenital warts, attending a dermatology clinic in Erbil city. The study was a cross-sectional one, conducted from March 1st, to December 1st, 2017. Each patient with anogenital warts was given a number. Sociodemographic and fertility details including age, age at menarche, age at marriage, number of children, age at first childbirth, past medical history, history of other sexually transmitted diseases, smoking history, type of contraception used, duration of having the wart, initial appearance or recurrent, and screening history were obtained from the participants using a structured questionnaire through a direct interview. Physical examination was performed, and on visual inspection, anogenital warts were classified based on morphology. The following clinical types were recognized: acuminate, hyperplastic, filiform andflat.[8] A Pap test was performed during the second half of the menstrual cycle. Appropriate instructions were given to the patients. The patient must abstain from sexual intercourse and avoid using any vaginal medication or contraceptives 48 hours before sample collection. Patients were sent to the laboratory for Pap smear examination. Smears were taken by a trained technician and prepared for cytological examination. Cervical smear sample is taken with a spatula; turning the brush at a 360° angle. Both ectocervix and endocervix were sampled. Slides were prepared and labeled. The specimen was spread on the microscopic slide, fixed in 95% ethyl alcohol immediately and subsequently stained by Pap stain. After staining, slides were mounted with DPX (distrenedibutyl phthalate xylene) and sent for histopathological assessment. All smears were reviewed by the same pathologist. Smears were reported according to the 2001 Bethesda system. The system classifies squamous cell abnormalities into four categories: (i) ASC (atypical squamous cells), (ii) LSIL (low-grade squamous intraepithelial lesions), (iii) HSIL (high-grade squamous intraepithelial lesions), and (iv) Squamous cell carcinoma.[9] The research was approved by the Research Ethics Committee of the College of Medicine,

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Hawler Medical University. The study was explained in detail for the patients, and informed verbal consent was provided by all study participant. The statistical package for the social sciences (version 23) was used for data analysis. Characteristics of study participants were presented as numbers and percentages. Numerical variables were summarized as means and standard deviations. Frequency distributions, descriptive statistics, and Pearson's Chi-squared and Fisher's exact tests were calculated. Statistical significance was set at P <0.05.

Results

The youngest patient in the study was 18 years, and the oldest was 55 years (mean = 35.5 ± 9.7 years). The mean age of menarche was 13.3 ± 1.0 years. The mean age of marriage was 22.2 ± 5.7 years, 12 (16%) women gave birth to a child before the age of 18 years. Twelve (16%) patients had no children, and the rest had a mean of 2.5 ± 1.6 children. The vast majority (96%)were nonsmokers as shown in Table 1.

Table 1: Sociodemographic and fertility characteristics of patients.

Variable	Frequency	(%)
Age (years)		
≤20	6	(8.0)
21-30	18	(24.0)
31-40	30	(40.0)
41-50	15	(20.0)
>50	6	(8.0)
Age at first child		
<18	12	(16.0)
≥18	63	(84.0)
No of children		
0	12	(16.0)
1	12	(16.0)
2-3	27	(36.0)
≥4	24	(32.0)
Ever screened		
Yes	12	(16.0)
No	63	(84.0)
Smoking		
Smokers	3	(4.0)
Non-smokers	72	(96.0)
Total	75	(100.0)

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No significant association was found between smoking and recurrence of the wart (P >0.05). A significant association was detected between the duration of having genital warts and smoking (P = 0.036), as shown in Table 2. Less than a quarter (16%) have had a pap Smear previously. Filiform wart was the most common type, being identified in 33 (44%) patients. Fifty-seven (76%) patients had their warts for the first time while 18 (24%) patients presented with recurrent warts, as shown in Table 3.

Table 2: The relationship between recurrence and duration of warts with smoking.

	Smokers		Non-smokers		Total		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	***P* value**
Recurrence							
Non-recurrent	3	(5.3)	54	(94.7)	57	(100)	0.321
Recurrent	0	(0)	18	(100)	18	(100)	
Duration							
Weeks	0	(0)	9	(100)	9	(100)	0.036
Months	0	(0)	42	(100)	42	(100)	
Years	3	(12.5)	21	(87.5)	24	(100)	

Table 3: Types and characteristics of anogenital warts.

Character	**Frequency**	**(%)**
Type		
Filiform	33	(44.0)
Acuminate	24	(32.0)
Flat	9	(12.0)
Filiform and flat	9	(12.0)
Recurrence		
Not recurrent	57	(76.0)
Recurrent	18	(24.0)
Duration		
Weeks	9	(12.0)
Months	42	(56.0)
Years	24	(32.0)
Total	75	(100.0)

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Table 4 outlines a significant association between the type of wart and recurrence (*P* = 0.003) and a non-significant association between the type of contraception and recurrence of anogenital warts (*P* = 0.101). All the patients were HIV and hepatitis B and C negative. The most common concomitant sexually transmitted diseases were molluscum contagiosum and herpes simplex virus infection (12 (16%) patients and 6 (8%) patients, respectively). No any method of contraception was used by 27 (36%) patients, natural methods of contraception were used by 24 (32%) patients, and oral contraceptive pills (OCP) were used by nine (12%) patients. Six (8%) patients had an intrauterine contraceptive device (IUCD), and another six were using condoms, while three (4%) patients had a tubal ligation. A significant association was found between the type of contraception and the severity of cervicitis (*P* = 0.001), as shown in Table 5.

Table 4: The relationship between the type of anogenital warts and the method of contraception with the recurrence of warts.

	Nonrecurrent		Recurrent		Total		
	No.	(%)	No.	(%)	No.	(%)	*P* value
Type							
Filiform	24	(72.7)	9	(27.3)	33	(100)	
Acuminate	21	(87.5)	3	(12.5)	24	(100)	0.003
Flat	9	(100)	0	(0)	9	(100)	
Flat &filiform	3	(33.3)	6	(66.7)	9	(100)	
Contraception							
OCP	9	(100)	0	(0)	9	(100)	
Natural methods	18	(75)	6	(25)	24	(100)	
IUCD	6	(100)	0	(0)	6	(100)	0.101
Tubal ligation	3	(100)	0	(0)	3	(100)	
Condoms	3	(50)	3	(50)	6	(100)	
No contraception	18	(66.7)	9	(33.3)	27	(100)	

Table 5: The relationship between Pap smear results and the method of contraception.

Type of contraception	Pap smear results								
	Mild Cervicitis		Moderate Cervicitis		Severe Erosive Cervicitis		Total		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	*P* value
OCP	0	(0)	0	(0)	9	(100)	9	(100)	
Natural methods	6	(25)	9	(37.5)	9	(37.5)	24	(100)	
IUCD	0	(0)	3	(50)	3	(50)	6	(100)	
Tubal ligation	0	(0)	3	(100)	0	(0)	3	(100)	0.001
Condoms	0	(0)	3	(50)	3	(50)	6	(100)	
No contraception	0	(0)	6	(22.2)	21	(77.8)	27	(100)	
Total	6	(8)	24	(32)	45	(60)	75	(100)	

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The commonest organism found on Pap smear was candida (28%), while bacteria were recognized in nine (12%) smears and lactobacilli were found in 3 (4%) smears. The rest were organism-free. Severe erosive cervicitis was found in 45 (60%) smears, moderate cervicitis was observed in 24 (32%) smears and six (8%) had mild cervicitis. A significant association was found between duration of the venereal wart and cervicitis (P <0.001). Mixed inflammatory cells infiltration was found in 42 (56%), while metaplasia and repair changes were detected in 18 (24%). Fifteen (20%) had atypical squamous cells of undetermined significance (ASCUS) changes. There was a significant association between the duration of the wart and the degree of severity of the inflammatory cells infiltration, including ASCUS (*P* = 0.002), as shown in Table 6. None of the smears showed malignant changes, and no koilocytes were found in any of the smears.

Discussion

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Most sexually active women and men will be infected at some point in their lives, and some may be repeatedly infected. Many HPV strains are asymptomatic and clear up quickly, but a few infect the cervix and cause pre-cancerous lesions that can advance to cancer.[10] Our patient's ages ranged from 18-55 years, with the majority being in the age group 31-40 years (40%). In an Iranian study, the highest incidence was also among the age group 30- 40 years (24.7 %).[11] In a Turkish study, the mean age of the women was 34.9.[12] Another study found the peaked in 20-39-year old, with more than 70% of patients in this age category.[13] Others found the highest incidence in young adults aged 16–24 years.[8] In this study, only 32% were below 30 years of age. These differences c0ould be due to the difference in the age of beginning of sexual activity among different communities. The typical anogenital wart is soft, pink, elongated, and sometimes filiform or pedunculated. The classical 'acuminate' (sometimes called papillomatous, or hyperplastic) form constitutes about two-thirds of anogenital warts. Most other lesions are flat, though more conspicuous than plane warts elsewhere. Both acuminate and flat types may coexist.[8] Three clinical types of warts were seen in our patients. This indicates that different types of HPV exist in our locality, which could be due to different sources of infection. The majority (76%) of our patients presented with warts for the first time in their life making anogenital warts a recent sexually transmitted disease

Table 6: The association between Pap smear findings and the duration of anogenital warts.

Duration	Pap smear findings								*P* value
	Mixed inflammatory cells infiltration		Metaplastic and repair changes		ASCUS		Total		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Weeks	3	(33.3)	0	(0)	6	(66.7)	9	(100)	0.002
Months	27	(64.3)	9	(21.4)	6	(14.3)	42	(100)	
Years	12	(50)	9	(37.5)	3	(12.5)	24	(100)	
Total	42	(56)	18	(24)	15	(20)	75	(100)	

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being introduced to our locality. A large portion of genital HPV infection is either subclinical or latent. Unfortunately, the infectivity of subclinical and latent infection is unknown. Subclinical and latent infection is probably responsible for most "recurrences" after treatment of genital warts.[1]Asignificant association was found between the type of wart and recurrence. Filiform warts were more liable for recurrence. This could be due to the fact that filiform warts have a digitate appearance making them more liable for trauma and manipulation by the patient, which increases the risk of dissemination and recurrence. The duration of having anogenital warts varied from three weeks to five years. The behavior of HPV lesions is influenced by immunologic factors. Nearly all HPV infections are cleared and become undetectable within 2–3 years.[14] Other concomitant sexually transmitted diseases are found in about 15% of patients with genital warts.[15] We diagnosed molluscum contagiosum and genital herpes simplex virus in 16% and 8% of our patients respectively. Only 16% of our patients have had a Pap smear previously, the rest had never performed it and did not have any idea about Pap smear. Our results are consistent with a Turkish study in which over ninety percent of the study group had never heard of and had not undergone Pap smear screening before,[16] while others reported that 95.3% of women had prior screening with Pap smear.[17] This lack of screening in our area will increase the risk of late diagnosis and invasive cervical cancer. Pap smears taken in the mass-screening program have a larger effect on invasive cervical carcinoma.[18] The majority (96%) of our patients had never smoked. Other investigators reported nonsmoking in 73.5%.[16] No significant association was found between smoking and recurrence of the viral infection. While a significant association was detected between the duration of having genital warts and smoking, smokers had warts for a longer duration than nonsmokers. This was concordant with other investigators in which they found that the duration of smoking and the duration of anogenital warts were correlated.[19] The increased rate of progression of anogenital warts in smokers may reflect immune modulation effects induced by cigarettes.[3] Oral contraceptive pills were used by 12% of our patients. In a prospective study, 57.4% of patients with anogenital HPV were found to beoral contraceptive pills user.[20] Smoking, multiparity, and long-term oral contraceptive use can double or triple the risk of viral persistence and progression to precancer and cancer in women with oncogenic types of infection.[21] A significant association was found between the type of contraception and the severity of cervicitis. Severe erosive cervicitis was more among those who did not use any sort of contraception. A non-significant association was found between the type of contraception and recurrence of warts. There is no consistent evidence that condom use reduces the risk of becoming HPV DNA-positive.[22] The mean age of menarche and the mean number of children were 13.3 ± 1.0 years and 2.5 ± 1.6 children respectively. These were comparable to another study in which the mean menarche age was 13.2 (±1.4) years, and the mean number of births was two.[12] As a tradition in our area, girls are usually married after menarche, and they get their first child early in their life. Only smoking and multiple pregnancies appeared to be important risk factors among women found to have HPV associated changes in the biopsy specimen as compared with women who did not have any significant abnormalities in the biopsy specimen.[23] On Pap smear evaluation, infections were found in 40% of our smears, and the infecting organism was candida in 28% and bacteria in 12%. While 17.7% were evaluated for infection in a similar study.[16] *Candida albicans* and *Candida glabrata* are fungal species that infect the vulva, vagina, and cervix.

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These fungi are eosinophilic and often interspersed among squamous cells. The vagina is colonized by gram-positive, rod-shaped bacteria of the genus Lactobacillus. A steep reduction in the proportion of lactobacilli, with a concomitant predominance of coccobacilli, is associated with bacterial vaginosis.[7] Cervicitis is an infection of the endocervix, including the glands and the stroma. Severe erosive cervicitis was seen in 60% of our smears. We also found that those having warts for long durations were prone to have the severest form of cervicitis. Our results are consistent with the literature as chronic cervicitis is the commonest pathology found in women attending gynecology outpatient.[24] In 56% of our, Pap smears only a benign mixed inflammatory cells infiltration was found, while 24% showed heavy mixed inflammatory cells infiltration with metaplasia and repair changes. All types of cervicitis were more common among those having the condition for months. The more severe inflammatory reaction was in those patients having warts for months. Approximately 5% of all Pap smears contain HPV-infected cells, and 10% of women infected with the high-risk HPV types will develop cervical dysplasia, a precancerous state. The first neoplastic changes noted on light microscopy are termed dysplasia. Approximately 40% to 70% of the mild dysplasias spontaneously regress. Cervical cancer is thought to develop through a continuum of progressive cellular changes from mild cervical intraepithelial neoplasia (CIN I) to moderate neoplasia (CIN II) to severe neoplasia or carcinoma in situ. This sequence of events can occur over one to four years. Routine and regular Pap smears can promote early detection, treatment, and cure of cervical cancer.[2] Atypical squamous cells of undetermined significance (ASCUS) changes were seen in 20% of our smears. ASCU means abnormal squamous cells but do not meet the criteria for a squamous intraepithelial lesion.[25] In a retrospective study, 57.4% showed an inflammatory lesion, 4.1% showed ASCUS, and 2.8% showed metaplasia.[26] Another investigator found only 0.4% of women to be ASCUS positive on Pap smear.[17] There was a significant association between the duration of having anogenital warts and the inflammatory cells infiltration and ASCUS. The more severe inflammatory reaction was in those patients having warts for months. Cytologic changes indicating HPV infection are the koilocytotic cells; they are detected in Pap smears. Akoilocyte is a vacuolated squamous cell with a basophilic and pyknotic nucleus in the upper part of the epidermis.[8] No koilocytotic cells were seen, and none of our smears showed malignant cell as well. The HPV infection is usually transient and of no clinical consequence, but a minority of patients retain the oncogenic viruses within their genital epithelium, which can lead to the development of CIN and possible cancer. The HPV infection can persist in certain individuals, and for reasons unknown, an oncogenic process can be triggered in the region of the transformation zone where metaplasia occurs. Integration of the viral DNA into the basal cells of the cervical epithelium in the transformation zone can lead to immortalization of the basal cells and rapid turnover of the basal cells within the epithelium.[27] All of our patients with smears showing ASCUS were followed up and asked to repeat the Pap smear after six months, if a lesion is missed then this should be picked up on a subsequent smear. Spontaneous regression of low-grade disease is not uncommon and is likely to occur through the patient's own cell-mediated immunity.[27] Although the development of HPV vaccines shows promise in reducing HPV-induced neoplasia burden, a high proportion of the general population will continue to require routine cervical cancer screening and therapeutic intervention, and it appears unlikely that HPV vaccination will ever completely abrogate the need for other preventative measures.[28] It is estimated

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that at any given point in time more than 75% of women in the developed world have had some sort of screening undertaken in the previous five years compared to less than 5% of women in the developing world.[29]

Conclusion

Early marriage, having anogenital warts for a long duration due to lack of awareness about anogenital warts and its risk as a cause of cervical cancer and lack of knowledge about the importance of screening Pap test are risk factors for cervical cancer incidence and mortality in our society.

Competing interests

The author declares no competing interests.

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