International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 06 (November-December)|2023 Page: 1081-1088
Original Research Paper

Cervical Dysplasia In Patients With Genital Warts. A Cross Sectional Study

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Article Received: 26-October-2023, Revised: 16-November-2023, Accepted: 06-December-2023

ABSTRACT:
Background: Genital Warts are sexually transmitted infection caused by certain types of human papillomavirus (HPV). **Aim of Study**: To study prevalence of cervical dysplasia in patients with genital warts. **Patients and Method**: A cross-sectional study conducted in Department of Dermatology and Venereology in Al-Yarmouk Teaching Hospital, Baghdad, Iraq from April 2022- April 2023 October. One hundred forty-eight female patients diagnosed with genital warts were enrolled in our study. Pap smear and PCR were done for all patients. Patient ages < 12 years, Pregnant, singles, patients who had total hysterectomy and patients with history of or sexually transmitted infections were excluded from our study. **Result**: highest proportion of study patients was between 30-39 years (50%). Pap Smear was positive in 36.5% of study patients, from those with positive results, 37% diagnosed with CIN1. PCR was positive in 6.8% of study patients, HPV 16 was most prevalent, being positive in 80.0% of them. highest prevalence of cervical dysplasia was found in patients who had warts in both of cervix and anus (88.9%). We noticed that 50% of patients who had two marriages, 32.4% of those who were living in rural areas, 50% of those who had > 4 children, 61.1% of current smokers, and 31.6% of those who were currently using OCP were significantly diagnosed with cervical dysplasia. **Conclusion**: There is significant association between cervical dysplasia and site of genital wart (patients who had warts in both cervix and anus), patient who had two marriages, parity (> 4 children), OCPs using, Smoking, and living in rural areas.

Keywords: genital warts, human papillomavirus, Cervical Dysplasia

INTRODUCTION:

Genital Warts are sexually transmitted infection caused by certain types of human papillomavirus (HPV), mainly types 6 and 11 which are account for 90% of genital warts, the virus can affect the vulva, vagina, cervix, penis, scrotum, perianal skin, and anal canal (1). The most consistent histologic features seen in condylomata include epidermal hyperplasia, parakeratosis, koilocytosis, and papillomatosis. The papillomatosis is more gently rounded than is seen in common warts. The upper portions of the epithelia of mucosal surfaces normally have some degree of cytoplasmic vacuolization, so its detection is specific for condylomata acuminate only if present within the deeper portions of the spinous layer. Mitotic figures may be evident. Usually, invasive squamous cell carcinoma can be ruled out because the epithelial cells show an orderly arrangement and the border between the epithelial proliferation and the dermis is sharp (2). Cervical intraepithelial neoplasia :(CIN), or cervical dysplasia is a precancerous condition that result from abnormal growth of cells on the surface of the cervix that lead to cervical cancer. Another definition, CIN refers to the potentially precancerous transformation of cells of the cervix. Cervical dysplasia commonly occurs at the squamocolumnar junction of the cervix, which is a transitional zone between the squamous epithelium of the vagina and the columnar epithelium of the endocervix (3). Genital warts (GW) and cervical cancer represent a significant financial burden for the health systems worldwide (4). Cervical cancer was one of the leading causes of mortality worldwide, and it is the second most common cancer in women, with an incidence of 470,000 (5). Relatively 230,000 women die every year from cervical cancer; Approximately 190,000 of them are from developing countries in South America, sub-Saharan Africa, and the Far East. In the United States, The incidence of invasive cervical cancer, is much lower; the American Cancer Society predicted that in 2010, there were relatively 12,200 new cases, with total number of deaths at 4,210 , which was due to the use of cytological screening in

these countries (6). In fact, the invasive cervical cancer results from the progression of pre-invasive precursor lesions named cervical intraepithelial neoplasia (CIN), or dysplasia. Despite women's frequent exposure to HPV, development of cervical neoplasia is uncommon. Most cervical abnormalities caused by HPV infection are unlikely to progress to high-grade CIN or cervical cancer, as most of them regress by themselves (7). The long time frame between initial infection and overt disease indicates that several cofactors (e.g., genetic differences, hormonal effects, micronutrient deficiencies, smoking, or chronic inflammation) may be necessary for disease progression (8, 9).

AIM OF SDTUDY:

To study the prevalence of cervical dysplasia in patients with genital warts.

PATIENTS AND METHODS:

This was a cross-sectional study conducted in the Department of Dermatology and Venereology in Al-Yarmouk Teaching Hospital, Baghdad, Iraq during the period from April 2022- April 2023.

Ethical and Official approvals: All patients were verbally informed about the study and they were asked the permission to be part of the study. All personal information was kept anonymous. Data were exclusively used for the sake of this study.

Administrative Approvals were Granted from the Following:

1. The Council of Arab Board of Dermatology and Venereology.
2. Approval from Dermatology and Venereology Department of Al-Yarmouk Teaching Hospital.

Exclusion Criteria:

Age < 12 years, Pregnant and single women, patients who had total, hysterectomy, Patients with history of other sexually transmitted infections.

A questionnaire had been applied to all patients to collect needed information; the questionnaire was filled by the researcher through direct interview with the study patients. It was used to gather the necessary information as the following:

Certain socio-demographic variables: age, no. of previous marriages, residence (rural or urban), occupation (housewife or employee), educational level (illiterate, primary or secondary school, and higher education). Social history (smoking history: weather current or passive smoker). Past medical and surgical history: drug history: including oral contraceptive pills, immunosuppressive drugs or other medication, family history, menstrual and gynecological history, site of warts (anal, vulvar, vaginal, cervix, or perineal), other sites (oral mucosa or others), associated symptoms (itching, bleeding, discharge, or pain), duration of disease (wart).

Study patients and Sample size: One hundred forty-eight female patients who attended outpatient clinic of Dermatology and Venereology in Al-Yarmouk Teaching Hospital and diagnosed with genital warts were enrolled. The patients were examined carefully to confirm the diagnosis of genital warts clinically which was based on visual inspection as flesh-colored, exophytic lesions (small bumps, flat, verrucous, pedunculated, raised papules or dome-shaped lesions on keratinized skin) on the external genitalia, including vulva, perineum, and perianal skin, cervical smear of the patients applied to Al Elwea maternity hospital for Pap smear, then cervical smear samples were transferred to Central Public Health Laboratory in sterile tubes for PCR assay in order to detect HPV-DNA, using Biosystem 7500/USA for the following HPV types detection: 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59 and 66 using Real time PCR Kits (Sacae/Italy) .

Statistical Analysis:

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Chi square test was used to assess the association between cervical dysplasia and certain characteristics. A level of P – value less than 0.05 was considered significant.

RESULTS:

The total number of study patients was 148. All of them were diagnosed with genital warts. The distribution of study patients by general characteristics is shown in figure (1 and 2) and table (1). Study patient's age was ranging from 15 to 56 years with a mean of 31.68 years and standard deviation (SD) of ± 7.4 years. The highest proportion of study patients was aged between 30 - 39 years (50%). Regarding occupation, housewives were representing the majority of study patients (74.3%), while 25.7% were employee. Concerning marital status, the highest proportion of study patients was married 126 (85.1%) and 132(89.2%) were married once. About residence, half of study patients were living in urban areas and the other half were living in rural areas. Current smokers were 18(12.2%) of study patients. Regarding parity, 88(59.5%) of study patients had 3 – 4 children.

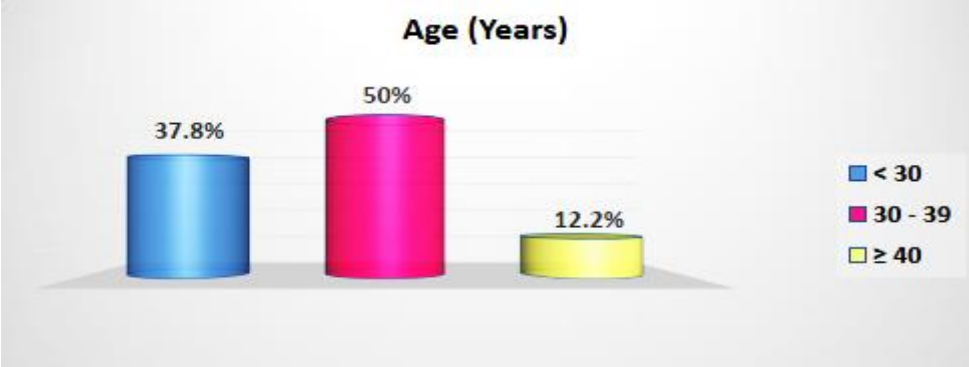

Figure 1: Distribution of study patients by age

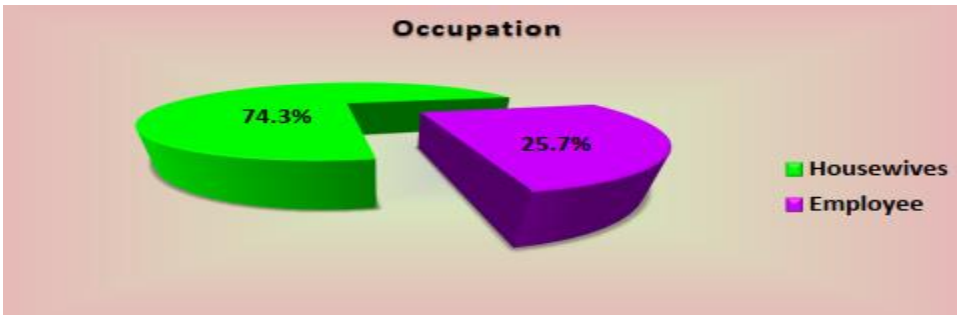

Figure 2: Distribution of study patients by occupation

Table 1: Distribution of study patients by general characteristics

Variable	No. (n= 148)	Percentage (%)
Marital Status		
Married	126	85.1
Divorced	10	6.8
Widowed	12	8.1
Number of Marriages		
1	132	89.2
2	16	10.8
Residence		
Rural	74	50.0
Urban	74	50.0
Parity		
< 3	52	35.1
3 - 4	88	59.5
> 4	8	5.4
Smoking status		
Current smoker	18	12.2
Non-smoker	130	87.8

The distribution of study patients by clinical information is shown in table 2. In this study, 94 (63.5%) of study patients had warts in vulva and 101 (68.2%) had warts for ≥ six months. We noticed that 76(51.4%) of study patients were currently using OCP and 44 (29.6%) of study patients complained from itching.

Table 2: Distribution of study patients by clinical information

Variable	No. (n= 148)	Percentage (%)
Site of warts *		
Vulva	94	63.5
Cervix	42	28.4
Anus	30	20.3
Vagina	4	2.7
Oral Mucosa	2	1.4
Duration of warts (Months)		
< 6	47	31.8
≥ 6	101	68.2
Current OCP intake		
Yes	76	51.4
No	72	48.6
Associated Symptoms		
No	60	40.5
Itching	44	29.6
Bleeding	14	9.5
Discharge	10	6.8
Itching and Discharge	20	13.6

* Some of patients complained from warts in multiple sites, so the total percentage may exceed 100%

The distribution of study patients by investigation results is shown in table (3). In this study, PCR was positive in 10(6.8%) of study patients, and 8(80%) of them were HPV 16. Regarding Pap Smear result, it was positive for cervical dysplasia in 34 (36.5%) from those patients with positive pap smear results, excluding patients with cervicitis from positive results.

Table 3: Distribution of study patients by investigation results

Variable	No. (n= 148)	Percentage (%)
PCR		
Positive	10	6.8
Negative	138	93.2
Type of HPV	**n= 10**	
HPV 16	8	80.0
HPV 18	2	20.0
PAP Smear		
Positive	54	36.5
Negative	94	63.5
PAP smear type	**n= 54**	
CIN1	20	37.0
Chronic Cervicitis	12	22.3
Acute Cervicitis	8	14.8
ASCUS	10	18.5
CIN2	4	7.4

Cervical dysplasia was found in 34(36.5%) patients, 20(37%) diagnosed with CIN1, 10(18.5) with ASCUS, and 4(7.4%) with CIN2. Regarding PCR results it was positive in 10(6.8%), HPV 16 was positive in 8(80%) of them. Table 4 shows the association between cervical dysplasia and positive HPV types.

Table 4 Association between cervical dysplasia and positive HPV types

Cervical dysplasia	HPV 16	HPV 18	Percentage(%)
ASCUS	2		20%
CIN 1	2		20%
CIN 2	4	2	60%

Table 5 shows the association between cervical dysplasia and certain characteristics. In this study, the highest prevalence of cervical dysplasia was found in patients who had warts in both of cervix and anus 16(88.9%) with a significant association between cervical dysplasia and site of warts (P= 0.001). We noticed that 8(50%) of patients who had two marriages, 24(32.4%) of those who were living in rural areas, 4(50%) who had > 4 children, 11(61.1%) of current smokers, and 24(31.6%) of those who were currently using OCP were significantly (P < 0.05) diagnosed with cervical dysplasia. There were no statistically significant associations (P ≥ 0.05) between cervical dysplasia and all other characteristics.

Table 5: Association between cervical dysplasia and certain characteristics

Variable	Cervical dysplasia		Total (%) n= 148	P – Value
	Yes (%) n= 34	No (%) n= 114		
Age (Year)				
< 30	10 (17.9)	46 (82.1)	56 (37.8)	0.368
30 - 39	18 (24.3)	56 (75.7)	74 (50.0)	
≥ 40	6 (33.3)	12 (66.7)	18 (12.2)	
Marital status				
Currently married	32 (25.4)	94 (74.6)	126 (85.1)	0.093
Not married	2 (9.1)	20 (90.9)	22 (14.9)	
Number of marriages				
1	26 (19.7)	106 (80.3)	132 (89.2)	0.006
2	8 (50.0)	8 (50.0)	16 (10.8)	
Occupation				
Housewives	26 (23.6)	84 (76.4)	110 (74.3)	0.744
Employee	8 (21.1)	30 (78.9)	38 (25.7)	
Residence				
Rural	24 (32.4)	50 (67.6)	74 (50.0)	0.006
Urban	10 (13.5)	64 (86.5)	74 (50.0)	
Smoking status				
Smoker	11 (61.1)	7 (38.9)	18	0.001
Non-smoker	23 (17.7)	107 (82.3)	130	
Parity				
< 3	6 (11.5)	46 (88.5)	52 (35.1)	0.017
3 - 4	24 (27.3)	64 (72.7)	88 (59.5)	
> 4	4 (50.0)	4 (50.0)	8 (5.4)	
Current OCP intake				
Yes	24 (31.6)	52 (68.4)	76 (51.4)	0.01
No	10 (13.9)	62 (86.1)	72 (48.6)	
Site of warts				
Vulva	10 (11.4)	78 (88.6)	88 (59.5)	0.001
Cervix	3 (16.7)	15 (83.3)	18 (12.2)	
Vagina	2 (50.0)	2 (50.0)	4 (2.7)	
Anus	3 (25.0)	9 (75.0)	12 (8.1)	
Oral Mucosa	0 (0)	2 (100.0)	2 (1.4)	
Anus and Cervix	16 (88.9)	2 (11.1)	18 (12.2)	
Vulva and Cervix	0 (0)	6 (100.0)	6 (4.1)	
Duration of warts (Months)				
< 6	18 (17.0)	39 (83.0)	47 (31.8)	0.24
≥ 6	26 (25.7)	75 (74.3)	101 (68.2)	

DISCUSSION:

The human papillomavirus is the most common sexually transmitted viral infection that affects most of the sexually active women throughout their lives. Cervical dysplasia is the precursor to cervical cancer. It is caused by the persistent infection of the HPV into the cervical tissue. In our study, patient's age was ranging from 15 to 56 years with a mean of 31.68 years and standard deviation (SD) of ± 7.4 years, The highest proportion of study patients was aged between 30 - 39 years (50%). Pap smear was positive in 34 (36.5%) patients, 20(37%) diagnosed with CIN1, 10(18.5) with ASCUS, and 4(7.4%) with CIN2. Cervicitis was ranging from acute in 8(14.8%) to chronic in 12 (22.3%). In comparison to other studies, Suleiman study in 2019, on 75 married, non-pregnant

women with anogenital warts, also the highest occurrence was found in the age group 31-40 years (40%), different from our study in which Pap smear results as following: ASCUS was found in 15(20%), metaplasia and repair changes in 18(24%), cervicitis in 42(56%) and no malignant changes were identified (10) . Another different results were observed by Babu study in 2017, on 26 women diagnosed with genital warts, in which observed that Pap smears were normal in 10(38.5%), only inflammatory changes were found in 5(19.2%), cellular changes consistent with HPV infection including koilocyte were found in 11(42.2%) (11) . Final different results were observed by Flores and colleagues in their study in 2008, in which observed that high grade CIN and cervical cancer was commonly associated with low socio-economic status ,increased age, high viral load, young age of first sexual intercourse, and, while less commonly association with parity, number of sexual partners, and oral or injectable contraception (12) . In comparison to PCR results of other studies, different results were observed in Ribeiro et al study in 2015, which found that 87% of the referred women with abnormal cervical cytology had an HPV infection, and similar to our study, they found that HPV types 16 and 18 are the most prevalent types being positive in 42.4% of them (13) .

Boda et al study in 2016 observed that PCR for HPV strains from cervical swab was negative in 48.56% of study patients and positive in 51.44% of study patients, and Similar to our study results, HPV 16 and 18 are the predominant genotypes which involved in 70% of cervical cancer cases (14). Other results were observed by Brown, C.R.et al study in 2009, as found that of total 302 participants, regarding cervical swab, 73 (24.2%) were positive for HPV, High risk HPV types were detected in 44 women (14.6%). The most commonly detected high risk HPV types were HPV 16, 52, 58 and 59 (15). Regarding PCR result, as in our study it was positive in only 6.8% of study patient, and there was a low substantial rate of cervical smears for predicting cervical intraepithelial neoplasia, due to recurrent nature of most cervical HPV infection, so there was incidental fluctuation in viral load measurements including beneath the detection border for HPV assays, and HPV infection may pass through a latency period in the basal layer of cervical epithelium at which time that HPV may be undetectable.

In this study, the highest prevalence of cervical dysplasia existed in patients who had warts in both cervix and anus (88.9%) with a significant association between cervical dysplasia and site of lesion (P= 0.001) which may due to the oncogenic nature of HPV, regarding our study around 8 of 10 patients with positive PCR was high risk type (HPV 16) which was the aggressive type that found in 90% of cervical carcinoma (16, 17). Another significant association was observed between cervical dysplasia and 50% of patients with two marriages, which was explained by the fact that increased numbers of sexual partners will lead to exposure to new HPV types from the new partners (18). Increased parity (50% of those who had > 4 children) was another risk factors for cervical dysplasia which was due to increased HPV exposure with sexual activity, also attributed to hormonal changes and depressed immunity of pregnant women that made her susceptible to HPV infection (19). OCP usage was also significantly associated with cervical dysplasia because the use of OCP associated with lower use of barrier methods which lead to other infections during sexual contact and due to direct trophic effect of estrogen on the cervical mucosa especially if higher level or long duration, also high estrogen receptors transcripts level was most likely to have infection (20). Smoking also has been appeared to waned the immune response against viral infections, thus, the smokers have been presented to be HPV-positive than non-smokers (21). Moreover, nicotinic metabolite has been established on the mucosal surface of the cervix of smokers, leading to a direct carcinogenic action of cigarette smoking (22). The last significant association with cervical dysplasia in our study was living in rural areas (32.4%), which due to low access to the medical care, low level of education and awareness of cervical cancers of the women living in rural areas, also women in these areas are exposed to excessive workload and multiple pregnancies added to poor prenatal and birth care (23).

The precise mechanism by which patients with genital warts have an increased risk of cancer is not well established. The oncogenic process for the virus penetrating a lesion, changing the epithelium characteristics, and depressing local immunity, thus resulting in raised the likelihood of harboring oncogenic HPV types that cause cancer (24). Cervical cancer in general develops slowly over a period of years. It is preceded by precursor conditions in which the cells in the cervix develop abnormal characteristics, but not cancerous. The introduction of well-organized screening program with the Papanicolaou test to discover the early-stage cancer leads to great reduction in cervical cancer mortality rate because the majority of CIN 1 and CIN 2 are transient (25).

CONCLUSION:

There is a significant association between cervical dysplasia and site of genital wart (increased in patients who had warts in both cervix and anus). Cervical dysplasia is significantly higher in patients who had two marriages. Cervical dysplasia is significantly associated with increase parity (more than four children). Cervical dysplasia is higher in patients who were currently using OCPs. Cervical dysplasia is significantly associated with smoking. Cervical dysplasia is higher in patients who were living in rural areas.

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