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Clinical correlation of cervical cancer screening using Pap smear test

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ABSTRACT

Background and objectives: Cervical cancer (CC) has a long preinvasive stage, which allows for preventive detection and possible cure. In this study, this stage was a target stage to investigate women with precancerous lesions by applying the Papanicolaou (Pap) smear test and comduct performing a correlation study.s

Patients and methods: A 2-year cross-sectional study was conducted, in which 200 married women (21–60 years old) participated in the investigation, which included women with Pap test abnormal results (atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSILs), and high-grade squamous intraepithelial lesions (HSILs)). These results were used to perform a polymerase chain reaction (PCR) test to detect the presence of human papillomavirus (HPV) of (6 and 11), a low-risk type, and (16 and 18), a high-risk type with colposcopy examination and colposcopy-guided biopsy, if needed for women with abnormal colposcopy outcomes. The treatment, per severity and disease stage, was applied.

Results: The clinical presentation and Pap smear results of women enrolled in the study were as follows: 82.5% women were asymptomatic, postcoital bleeding (PCB) was seen in 17.0%, and intermenstrual bleeding was seen in a single case (0.5%). The history of sexually transmitted diseases was seen in 2.5% of the subjects. Pap smear results were as follows: no remarkable pathology was seen in 36.0%, inflammatory evidence was seen in 32.0%, ASCUS was seen in 19.0%, LSIL was seen in 7.5%, and HSIL was seen in 5.5% of the subjects. Regarding the HPV, the infection was negative in 95.0%, low-risk virus strains were seen in 1.5%, and high-risk viruses were seen in 3.5%. Low-risk HPV included 6, 11, and 42, whereas the high-risk group included five cases of HPV16 and two cases of HPV 18.

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Conclusions: The present work presents the Pap smear test as a highly useful, easy, technically safe, and cost-effective tool for detecting cervical epithelial precancerous lesions, which can be used as a routine screening technique for better treatment outcomes and reducing mortality rates. The power of detection of these lesions can be potentiated when using the Pap test and HPV-PCR test together.

Keywords: *Abnormal smear, Cervical Pap smear, Human papilloma virus, PCR*

INTRODUCTION

Increasingly, cervical cancer (CC) (invasive squamous cell carcinoma) is a leading cause of death for women throughout the globe.[1] It is the most frequent malignant tumor of the woman genital tract throughout many countries.[2] Eighty-six percent of all fatalities from CC occur in developing nations and low- and middle-income economies. This is an indication of health inequality.[3] No exact statistics on the cancer incidence rates can be found in Iraq due to the absence of a population-based national cancer registry center, but based on the World Health Organization (WHO), the Iraq occurrence rate of this cancer is 2.1 per 100,000 women (for all ages).[4] There is a prolonged preinvasive stage, which makes the screening programs for cervical cytology beneficial, and the therapy for preinvasive lesions is successful; therefore, invasive CC has been regarded as a preventable malignancy.[5] A comprehensive screening program may help identify the cancer lesions at an early stage, allowing for patients to get appropriate treatment.[6] As the main screening test for precancerous CIN and the early stages of invasive CC, the Papanicolaou (Pap) smear test is a feasible technique, which can help identify early cervical epithelial alterations. CC fatality in developed countries has decreased significantly as a result of widespread screening programs.[7]

Although invasive CC is avoidable, roughly 12,710 new cases and 4,290 fatalities were reported in the United States in 2011 despite the disease's preventability.[8] Although novel treatment techniques exist, up to 35% of women who are recognized with CC go on to develop metastasis.[9] George Papanicolaou, a gynecologist, first used the cervical Pap smear procedure in 1943. Every-3-year cervical smears, which identify preinvasive lesions in sexually active women between the ages 20 and 60, are suggested for all of these women.[10]

A 0.1% probability of CIN I or II exists when the smear is normal. For CIN II–III, the risk of cancer is 6% with the presence of an inflammatory smear picture, 20–37% with borderline nuclear alterations, 50–75% with the occurrence of mild-to-moderate dyskaryosis, and 80–90% with the existence of extreme dyskaryosis, indicating the presence of the invasive stage at a 50% rate.[11] In addition to HPV, smoking, oral contraceptive use, and the presence of multiple male partners are considered risk factors for CC. A large number (46–63%) of cases of CC are caused by HPV-16, whereas 10–14% of cases are caused by HPV-18.[12]

Aim of the study

CC has a long preinvasive stage, which allows for preventive detection and possible cure. In this study, this stage was a target stage to investigate women with precancerous lesions by applying the Pap smear test and performing a correlation study.

PATIENTS AND METHODS

A 2-year cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Colposcopy Unit, Al-Diwaniyah Maternity and Pediatrics Teaching Hospital, Al-Diwaniyah City, Iraq, in the period between January 2018 and January 2020, in which 200 married women (21–60 years old) participated in the investigation, which included women with Pap test abnormal results,

ASCUS, LSIL, and HSIL. These results were used to perform a polymerase chain reaction (PCR) test to detect the presence of HPV of (6 and 11), a low-risk type, and (16 and 18), a high-risk type with colposcopy examination and colposcopy-guided biopsy, if needed for women with abnormal colposcopy outcomes. The treatment, per severity and disease stage, was applied.

The criteria for the inclusion of the study subjects were the presence of vaginal discharge (bloody or mixed), postcoital bleeding (PCB), intermenstrual bleeding (IMB), and postmenopausal bleeding. The criteria for the exclusion of the study subjects were women with a obvious growth, women with a history of CC treatment, women with a visible cervical lesion/ulcer, women with active bleeding, and women with pregnancy.

The patient's consent (written form) was collected from all subjects who enrolled in the current study, and the study protocol was approved by the Iraqi Ethical Committee. The subject's history data were recorded, which included age, equality, social information, menstrual details, cancer-related family history, smoking, and methods for contraception.

The lithotomy position for each patient was followed. Using a sterile bivalve speculum, posterior- and anterior-directed retractions of the posterior and anterior vaginal walls were performed for visualizing the cervix and vaginal wall properly. Using a wooden Aryes spatula 360°-rotated around the circumferences of the cervical os, the samples were collected from the ectocervix, immediately smeared onto a labeled glass slide, and fixed for 30 seconds with 95% ethanol in a Coplin jar. For endocervical cytology, an endocervical brush was endocervix-inserted until the bristle junction-handle end borderline of the brush approximated the external OS. Then, by 180°-rotation of the brush in the endocervical canal, the samples were taken, rolled on a glass slide, and immediately 95%-ethanol-fixed. The glass slides were sent to a cytopathological laboratory, and the findings were reported using the criteria of the new Bethesda System for reporting cervical cytology 2014, which divides the lesions broadly into intraepithelial-neoplasia negative lesions and abnormalities in the epithelial cells (squamous and glandular cells).[13]

Pap test abnormal results, ASCUS, LSIL, and HSIL of women were used to perform a PCR test to detect the presence of HPV of (6 and 11), a low-risk type, and (16 and 18), a high-risk type with colposcopy examination and colposcopy-guided biopsy, if needed for women with abnormal colposcopy outcomes. The treatment, per severity and disease stage, was applied.

RESULTS

The general characteristics of women enrolled in this study are shown in Table 1. The study included 200 women (31.55 ± 6.66 years old). Parity was in the range of 1–5 with a mean of 2.38 ±1.12. Only three women admitted to be active smokers, and only a single woman was married two times. The methods of contraception are also shown Table 1.

The clinical presentation and Pap smear results of women enrolled in the current study are shown in Table 2. Most patients were asymptomatic (82.5%), PCB was seen in 34 (17.0%), and IMB was seen in a single case (0.5%). The history of sexually transmitted disease (STD) was seen in five cases (2.5%). Pap smear results were as follows: no remarkable pathology was seen in 72 (36.0%), inflammation was seen in 64 (32.0%), ASCUS was seen in 38 (19.0%), LSIL was seen in 15 (7.5%), and HSIL was seen in 11 (5.5%). Regarding human papilloma virus (HPV), infection was negative in 190 (95.0%), low-risk virus strains were seen in 3 (1.5%), and high-risk viruses were seen in 7 (3.5%). Low-risk HPV included 6, 11, and 42, whereas high-risk group included five cases of HPV16 and two cases of HPV18.

Comparison of mean age, BMI, and parity among patients with high-risk HPV, low-risk HPV, and women with no HPV infection was made (Table 3), and all these variables were not

significantly correlated with this infection (P > 0.05). The correlation status between HPV infection and the remaining variables included in the study is shown in Table 4, and the P-value was not calculated as chi-square was not valid because of the small sample size of patients with HPV infection.

TABLE 1. Details of the Study Participants.

Characteristics	Results
Number of cases	200
Age (years)	
Range	21–60
Mean ±SD	31.55 ± 6.66
Parity	
Range	1–5
Mean ±SD	2.38 ±1.12
BMI (kg/m^2)	
Range	17–22
Mean ±SD	19.80 ±0.94
Smoking	
n (%)	3 (1.5%)
Partners	
Two, *n* (%)	1 (0.5%)
Single, *n* (%)	199 (99.5%)
Contraception	
No contraception, *n* (%)	79 (39.5%)
Hormonal, *n* (%)	61 (30.5%)
Condom, *n* (%)	37 (18.5%)
IUCD, *n* (%)	11 (5.5%)
Natural method, *n* (%)	6 (3.0%)
Tubal ligation, *n* (%)	6 (3.0%)

N, number of cases; SD, standard deviation; IUCD, intrauterine contraceptive device.

Statistical analysis

SPSS version 16 and Microsoft Excel 2007 were used to analyze the dataset. Numeric data were stated as range, mean, and standard deviation (SD),

TABLE 2. Clinical Presentation and Pap Smear Results of Women Enrolled in the Current Study.

	n	%
Clinical presentation		
Asymptomatic, *n* (%)	165	82.5
PCB, *n* (%)	34	17
IMB, *n* (%)	1	0.5
History of STD		
n (%)	5	2.5
Pap results		
No remarkable pathology, *n* (%)	72	36
Inflammatory, *n* (%)	64	32
ASCUS, *n* (%)	38	19
LSIL, *n* (%)	15	7.5
HSIL, *n* (%)	11	5.5
HPV		
Negative, *n* (%)	191	95.5
Low risk, *n* (%)	2	1
High risk, *n* (%)	7	3.5

IMB, intermenstrual bleeding ; STD, sexually transmitted disease; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus.

TABLE 3. Comparison of Mean Age, BMI, and Parity Among Patients with High-risk Human Papilloma Viruses, Low-risk Human Papilloma Viruses, and Women with no HPV Infection.

Characteristics	High risk *n* = 7	Low risk *n* = 2	Negative *n* = 191	P
Age (years)	35.14 ± 4.91	33.50 ± 9.19	31.40 ±6.69	>0.05 K NS
Parity	3.29 ± 1.25	3.00 ± 1.41	2.34 ± 1.11	>0.05 K NS
BMI (kg/m^2)	19.86 ± 1.46	19.00 ± 0.00	19.79 ± 0.92	>0.05 K NS

Data are displayed as mean ±standard deviation (SD).
BMI, body mass index; K, Kruskall Wallis test; NS, not significant at P > 0.05

TABLE 4. The Correlation Status Between Human Papilloma Viral Infection and the Remaining Study Variables.

Characteristics	High risk *n* = 7	Low risk *n* = 2	Negative *n* = 191
Smoking			
Yes	1	0	2
No	6	2	189
Partners			
Single	6	2	191
Two	1	0	0
Contraception			
No contraception	1	1	77
Hormonal	3	1	57
Condom	0	0	37
IUCD	2	0	9
Natural method	0	0	6
Tubal ligation	1	0	5
Pap Result			
Unremarkable pathology	0	1	71
Inflammatory	1	1	62
ASCUS	4	0	34
LSIL	1	0	14
HSIL	1	0	10
Presentation			
Asymptomatic	7	1	157
PCB	0	1	33
IMB	0	0	1
History of STD			
Positive	0	1	4
Negative	7	1	187

IUCD, intrauterine contraceptive device; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; PCB, postcoital bleeding; IMB, intermenstrual bleeding; STD, sexually transmitted disease.

whereas the categorical data were given as numerical values and percentages. For the purpose of comparing the means of numerical data across participants with the presence of HPV infection, the Kruskal–Wallis test was utilized. The significance level was adjusted equal to or less than 0.05.

DISCUSSION

CC is more common than it should be due to a lack of or inadequate preventative strategies. Unfortunately, low recognition of the Pap smear test as a CC screening technique, which is an effective strategy of preventing CC from developing, makes

the CC mortality rates to be high in some populations. In developed countries, community-based CC screening strategies that include every three-to-four-year Pap smear test induction have decreased the mortality and occurrence of CC by up to 80% over the last five decades.[14]

There was a mean age of (31.55 ± 6.66 years old) for the females in this research who were married; this is an adequate average age given the fact that CC often occurs between the ages of 40 and 50.[15]

In this research, the women ranged from one to five of parity, and a mean of 3.29 ± 1.25 and was shown to be related with an increased risk of HPV infection. High parity has been linked to an increased risk of cervical neoplasia in previous research.[16] In the present work, 82.5% of subjects were asymptomatic, PCB was found in 17%, and IMB was found in 0.5%. In 36.0% of patients, the Pap smear showed no abnormal pathology; in 32.0%, inflammatory alterations were detected; in 19.0%, ASCUS; in 7.5%, LSIL; and in 5.5%, HSIL.

Previously, 95% and 74.5% of female participants, respectively, were found to have inflammatory alterations detected by a Pap smear test, according to two separate studies.[17,18] Pap smears should be repeated following antibiotic therapy in women with chronic inflammation, according to previous research, otherwise the risk of developing cervical intraepithelial lesions increases.[19,20]

According to Verma et al. (2017), ASCUS, LSIL, and HSIL were discovered in 1%, 5.5%, and 5.5%, respectively, of the study community.[21] Moreover, ASCUS, LSIL, and HSIL were found in 8%, 5%, and 3%, respectively, of women examined with Pap smears by Padmini et al. (2015).[22] In a research by Nayani & Hendre (2015), 8.6% of abnormalities were LSIL, and 3.8% were HSIL.[23]

Cultural variations, age, occurrence of associated illnesses, and knowledge of screening may explain the high occurrence of cytological abnormalities seen in these investigations. Insufficient screening programs were shown to be the cause of the lower identification rates for epithelial pathological diagnosis of SIL and the greater incidence of SIL (4.9%), according to a research by Magdy HB et al. (2011).[24] In addition, 5.92% of participants had ASCUS, which was shown to be the most prevalent cytological abnormality in a research study by Saha et al. (2017),[25] and an association between HPV infection and several of the factors examined in this research, such as high-risk HPV (HR-HPV) with smokers, was discovered. The incidence of HR-HPV and low-risk-HPV infections was also greater in individuals taking hormonal contraception and those with a STD. It is important to highlight that the relationship between HPV and cervical dysplasia and cancer is now well acknowledged by the medical community.[26]

A research study by Gayed et al. (2009) found that a variety of variables, including smoking, STDs, and persistent immunosuppression, may contribute to the development of cancer.[27] The findings of the Rachel et al. (2017) research also found that 6% of women with abnormal cervical cytology and HPV infection had a history of STDs.[28] CC has been linked to HPV infection by a research study by in Smith et al. (2003), and it seems that OCP may be functioning as an accelerator of neoplastic progression. In addition, women who take hormonal contraception may engage in more unprotected intercourse, increasing their chance of contracting HPV and other STDs and their subsequent complications.[29] Furthermore, in the 100 patients with abnormal cytology, HPV positivity was detected in 20% in a research study by Guerry et al. (2011), and it was found that 15% of the patients used hormonal contraception and 4% used condoms.[30] HR-HPV was linked to an increased incidence of ASCUS, HSIL, and LSIL abnormalities using Pap smears, according to this research. Prevalence of HPV infection was found to be 3.8%[31] in a research by Swangvaree et al. (2013), whereas in regions with high CC occurrence, HPV infection was found to be in 8.0% of cases as indicated by Sukvirach et al.[32] Cervical and vulvar HPV-16 lesions are the most common, according to a research study by Siriaunk

et al. (2014).[33] According to a research conducted by Solomon et al. (2001), ASCUS is identified in 66.6% of individuals with abnormal Pap cytology results and HR-HPV infection was discovered in 14.2% of ASCUS subjects.[34]

Due to our conservative society's stringent cultural and religious standards, sexual activity normally begins after marriage and multiple sexual partners are discouraged, which reduces the chances of HPV and other STD infections. Male circumcision and low smoking rates among Iraqi women owing to their cultural setting may also have a significant influence, which results in some differences with other studies.

CONCLUSIONS

Precancerous cervical epithelial lesions may be detected with Pap smear testing, which is an easy, safe, and cost-effective screening process. It should be used as a standard screening practice to minimize treatment cost, morbidity, and fatality. Detection of CC is strengthened when the Pap test is paired with an HPV DNA test.

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