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Impact of Age Factor in Cervical Abnormalities and Cancers Incidence in Some Iraqi Married Women

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Abstract: Cervical cancer is the third most common cancer in women worldwide, and it has the fourth highest mortality rate among cancers in women. The present study aimed to reveal the impact of age factor in cervical abnormalities and cancers incidence in some Iraqi married women**.** 150 scraping cervical cells samples were collected from the women clinically diagnosed with cervical abnormalities and cancer who were divided into two groups; the first group included the women with abnormal pap smear which revealed 13.33% of women were less than 30 years and followed by 66.66% of women whose age between 30-50 years and 20% of them were more than 50 years old. While the second group iclude the women with normal Pap smear (Healthy women) which revealed that 26.66% of women were less 30 years, followed by 53.33% of women whose age between 30-50 years and 20% of them were more than 50 years old. The results showed that the highest percentage of precancerous stage was founded in 30-50 years old women, wherease the highest percentage in advanced stage represented by squamous cervical cancer and adenocarcinoma was founded in more than 50 years old women. In addition, the results of current study exhibted that the rates of ASC-US were 43% and 50%, while the rates of LSIL were 42% and 52% in less than 30 years old and 30-50 years women respectively. Wherease the rates of ASC-US and LSIL were 6.6% and 4.7% in more than 50 years old women. As well as the results revealed that the rates of HSIL and SCC were higher in over 50 year's women with percentages 40% and 63.63%, respectively.

Keywords: Cervical abnormalities, cervical cancer, married women.

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Introduction:

Cervical cancer is the third most common cancer worldwide and a major fatal malignancy among women, causing about 275,000 deaths annually worldwide, mostly in developing countries. It can be a preventable disease if identified at its early (precancerous) stages and treated by ablation (1,2). Since the initiation of Papanicolaou (Pap) method as cervical cancer screening tool, it decreased the cervical cancer rates in most developed countries. Mortality rate is higher in countries where screening and appropriate treatment facilities are not available (3,4,5). In developing countries, approximately 5% of women have been screened for cervical dysplasia compared with 85% in developed countries in the past 5 years(6).

One fifth of cervical cancer cases and one third of cervical cancer deaths occurred among women aged ≥65 years in the U.S. in 2013 (7). Cervical cancer screening is effective at preventing invasive cases and deaths from cervical cancer among older women (8,9). Professional organizations recommend that routine cervical cancer screening be discontinued for average-risk women aged >65 years after three consecutive

negative cytology results or two consecutive negative co-test results within the previous 10 years, with the most recent test performed within the past 5 years (10,11,12).

Substantially lower risk of cervical cancer after age 65 years was associated with adequate screening at age 50-64 years, suggesting benefits of increasing screening uptake prior to and, if needed for catch-up, after age 65 years (13).

Regular screening allows the detection of early lesions that can be treated before developing into invasive cancer. Pap smear screenings have shown convincingly to decrease CC mortality (14).

Disease burden caused by cervical cancer in women of vulnerable age groups can be decreased by vaccination for HPV before viral exposure, cervical cytology screening using Pap method and safe sexual practices (15).

Due to under usage of Pap smear screening in elderly women, there is relatively higher incidence of invasive cancer. One of the most common cancers among women in India is cervical cancer. It occurs in about one in 53 Indian women compared with one in 100 women in more developed regions of the world during their lifetime (6).

The present study was aimed to evaluate the impact of age factor in cervical abnormalities and cancers incidence in some Iraqi married women and study the association of the age factor with stage of cervical abnormalities and cancers in those women.

Material and Methods:

Study design:

This study was carried out in Baghdad Medical City and Al-Elwiya Maternity Teaching Hospitals in Baghdad City, during period from beginning of March 2017 to the end of September 2017.

Study population:

The study included cervical samples of 150 women who were divided into two sub groups: i) Sub group I (Patient Group) comprised 120 patients who visited the Gynecology Oncology Clinic with different gynecologic complaints, and ii) Sub group II (Healthy Control Group) included 30 healthy individuals with normal Pap smear findings.

Specimen collection and cytological examination:

Cervical scrape smears were obtained by Ayre's spatula, and specimen was fixed in 95% ethyl alcohol. Subsequently, smears were stained with Pap method. The slides were categorized into negative for intraepithelial lesion or malignancy (NILM) and epithelial cell abnormalities according to Bethesda

system for reporting cervical cytology 2014. Reactive cellular changes associated with inflammation and atrophy was considered NILM, atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SSC) or adenocarcinoma was considered epithelial cell abnormalities (17).

Statistical Analysis:

The Statistical Analysis System-SAS (16) program was used to detect

the effect of difference factors in study percentage. Chi-square test was used to significant compare between percentage (0.05 and 0.01 probability) in this study(16).

Results and Discussion:

Sub group I (Patient Group) was divided to eight groups according to cytological examination: scraping cervical cells were collected from 120 patients with cervical abnormalities. These samples include; i) Atypical squamous cells of undetermined significance (ASCUS) 30 samples, ii) low grade squamous intraepthelial lesion LSIL 21 samples, iii) High grade squamous intraepthelial lesion HSIL 15 samples, iv) Squamous cervical cancer 11 samples, v) Atypical glandular cells of undetermined significance 2 samples, vi) Adenocarcinoma 1 sample, vii) Cervicitis 22 samples, and viii) Cervicitis with squamous metaplatia 18 samples.

The samples were also including 30 specimens (scraping cervical cells) of healthy women used as a control attended to Medical city and hospitals in Baghdad (Table 1).

Table (1) : Distribution of samples study according to cytological examination.

Cytological examination	No. of cases	Percentage of cases (%)
ASCUS	30	25.00
LSIL	21	17.50
HSIL	15	12.50
Squamous cervical cancer	11	9.16
AGUS	2	1.66
Adenocarcinoma	1	0.83
Cervicitis	22	18.33
Cervicitis with squamous metaplasia	18	15.00
Total	120	100%
Chi-square value	-	9.074 **
P-value	-	0.0005
** (P<0.01).		

ASC-US: Atypical squamous cells of undetermined significance, **LSIL:** Low-grade squamous intraepithelial lesion, and **HSIL:** High-grade squamous intraepithelial lesion. AGUS atypical glandular cells of undetermined significance.

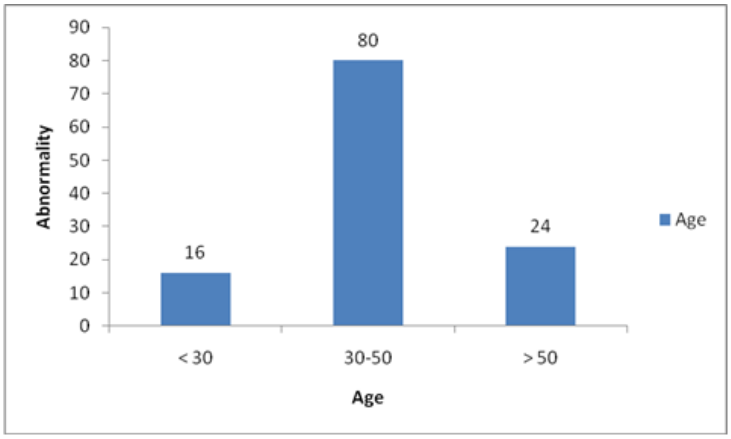

Figure (1): Relationship between age and cervical cancer abnormalities in Iraqi married women.

Relationship between Age of women and cervical abnormalities:

The age of all women was divided into three categorize according to Melnikow et al. and Kim et al. (19, 22) ; i) less than 30 years, ii) 30-50 years, and iii) over 50 years. (Figure 1, Table 2) revealed that 16% of the study women in general were less than 30 years old while 64 % were between 30-50 years and 20% over 50. This points out that may leads to conclude that group 2 constituted the greatest number groups in the present study. They were two subgroups in this study, the first group the women with abnormal pap smear revealed that 13.33% of the women were less than 30 (<30) years and followed by 66.66% of women whose age between 30-50 years and about 20% more than 50 years old (>50) years. The second group the healthy women (with normal Pap smear) revealed that 26.66% of the women were about (<30) years and followed by 53.33% of women whose age between 30-50 years and about 20% more than 50 years old (>50) years (Table 2).

Table (2): Distribution of sample study according to age group.

Group No.	Age group (years)	Study group		The sub groups			
		No.	%	Women with abnormal pap smear		Healthy women (Normal)	
				No.	%	No.	%
1	Less than 30	24	16.00	16	13.33	8	26.66
2	30-50	96	64.00	80	66.66	16	53.33
3	More than 50	30	20.00	24	20.00	6	20.00
Total		150	100%	120	100	30	100
Chi-square value		---	11.309 **	---	11.584 **	---	9.941 **
P-value		---	0.0001	---	0.0001	---	0.0002
**** (P<0.01).**							

The results agreed with those reported by Wright (18) who displayed that the aging is a risk factor for persistent infection (18). The result reported that the highest in precancerous stage in age between 30-50 years and the highest in advanced stage in more than 50 years old (>50) years, Squamous cervical cancer and adenocarcinoma (Table 3).

Table (3): The distribution of precancerous stage and advanced stage according to age factor in married women clinically diagnosed with cervical abnormalities and cancers.

Age (year)	Abnormal cytology						No.(%)
	ASCUS	LSIL	HSIL	SCC	AGUS	Adeno-carcenoma	
≤30	13/30 (43%)	9/21 (42.85%)	4/15 (26.60%)	1/11 (9.00%)	0/2 (0.00%)	0/1 (0.00%)	27/80 (33.75%)
30-50	15/30 (50%)	11/21 (52.38%)	5/15 (33.30%)	3/11 (27.27%)	2/2 (100%)	0/1 (0.00%)	36/80 (45%)
≥50	2/30 (7%)	1/21 (4.70%)	6/15 (40.00%)	7/11 (63.63%)	0/2 (0.00%)	1/1 (100%)	17/80 (21.25%)
Total	30/80 (37.5%)	21/80 (26.25)	15/80 (18.75%)	11/80 (13.75%)	2/80 (2.50%)	1/80 (1.25%)	80
Chi-square value	10.923 **	11.036 **	5.024 *	12.744 **	15.00 **	15.00 **	9.183 **
P-value	0.0001	0.0001	0.0251	0.0001	0.0001	0.0001	0.0004
**** (P<0.05), ** (P<0.01).**							

In present study, the results of current study exhibted that the rates of ASC-US were 43% and 50%, while the rates of LSIL were 42% and 52% in less than 30 years old and 30-50 years women respectively. Wherease the rates of ASC-US and LSIL were 6.6% and 4.7% in more than 50 years old women. As well as the results revealed that the rates of HSIL and SCC were higher in over 50 year's women with percentages 40% and 63.63%, respectively.

Discussion:

Cervical cancer is rare before age 21 years (19). Exposure of cervical cells to hrHPV during vaginal intercourse may lead to cervical carcinogenesis, but the process has multiple steps, involves regression, and is generally not rapid. Because of the slow progression of disease and the high likelihood of regression in this age group, evidence suggests that screening earlier than age 21 years, regardless of sexual history, would lead to more harm than benefit. Treatment of CIN 2 or CIN 3 among women younger than 21 years may increase risk for adverse pregnancy outcomes (19,20).

Joint guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (ACS/ASCCP/ASCP) define adequate prior screening as 3 consecutive negative cytology results or 2 consecutive negative cotesting results within 10 years before stopping screening, with the most recent test occurring within 5 years. The guidelines further state that routine screening should continue for at least 20 years after spontaneous regression or appropriate management of a precancerous lesion, even if this extends screening past age 65 years. Once screening has stopped, it should not resume in women older than 65 years, even if they report having a new sexual partner (21). Current evidence indicates that there are no clinically important differences between liquid-based cytology and conventional cytology. A variety of platforms are used to detect hrHPV; most use either signal or nucleic acid amplification methods. Published trials of hrHPV testing used in situ hybridization, polymerase chain reaction, and hybrid capture technology to test for HPV strains associated with cervical cancer. hrHPV testing has been used for primary screening, cotesting with cytology, and follow-up testing of positive cytology results (reflex hrHPV)(19).

Screening with cytology alone, hrHPV testing alone, and both in combination offer a reasonable balance between benefits and harms for women aged 30 to 65 years; women in this age group should discuss with their health care professional which testing strategy is best for them. Evidence from randomized clinical trials (RCTs) and decision modeling studies suggest that screening with cytology alone is slightly less sensitive for detecting CIN 2 and CIN 3 than screening with hrHPV testing alone. Although screening with hrHPV testing alone or in combination with cytology detects more cases of CIN 2 and CIN 3, this method results in more diagnostic colposcopies for each case detected (19,22).

There are a number of different protocols for triage of abnormal results from screening with cytology, hrHPV testing, or cotesting. Clinical trial evidence and modeling suggest that different triage protocols have generally

similar detection rates for CIN 2 and CIN 3; however, proceeding directly to diagnostic colposcopy without additional triage leads to a much greater number of colposcopies compared with using other triage protocols.

Maintaining comparable benefits and harms of screening with cytology alone or hrHPV testing alone requires that patients, clinicians, and health care organizations adhere to currently recommended protocols for repeat testing, diagnostic colposcopy, and treatment (21,23).

In developed countries, Pap test was introduced in the 1940s which lead to a major decrease in rates of cervical cancer morbidity and mortality during the last half of the 20th century. Persistent HPV infections leading to dysplasia generally take about 10 years to develop. Hence, expanded screening should focus on women aged 30 years and older, who are most at risk (24). Because middle‑aged or older women are at heightened risk for cervical cancer, anything less than universal screening for eligible middle‑aged or older women constitutes an unacceptable risk for cervical cancer(25).

Most organizations recommend cessation of regular screening for cervical cancer between the ages of 60 and 75 if the last two or three examinations in the past decade have negative results. The frequency of screening and the age at which screening can be stopped remains controversial. However, a woman of any age who has not had a Pap smear in the recent past should be screened with at least two Pap smears that are 1 year apart; because many elderly women have not undergone regular screening(25). When it comes to cervical adenocarcinoma, incorporating HPV testing with cytology could detect women at high risk of cervical cancer, which is poorly identified by Pap tests(28).

The prevalence of cervical cytological abnormalities varies between 1.5% and 6% in developing countries (28). In India, studies have revealed the prevalence of cervical cytological abnormalities to be approximately 5% by Bal *et al.,* (29) Gupta *et al.,* (30) detected this value to be 3.2% and Banik *et al.*, (31) detected this value to be 8.18% in the general population. In the present study, the prevalence of overall epithelial cell abnormality was found to be 5.5%. The studies mentioned above included women of all ages, but other study includes only postmenopausal and elderly women.

Furthermore, the higher prevalence of epithelial cell abnormality in the study in elderly women is could be due to this age difference. Screening up to age 65 years greatly reduces the risk of cervical cancer in the following decade. However, protection becomes weak when time goes on and is substantially <15 years after the last screen (32). Currently, certain countries stop screening cervical cancer between the ages 60 and 69 years and it appear to be inappropriate (33).

Few authors reported that in perimenopausal and postmenopausal women, nuclear enlargement in the absence of significant hyperchromasia has been related to either endogenous or exogenous hormonal changes (34,35). A study done by Johnston and Logani (36), found that 73% of ASC‑US specimens in patients aged 40 years were negative for HPV DNA. There are

no standard guidelines associated with cervical cancer screening in postmenopausal and elderly females in India. In recent study, the prevalence of epithelial cell abnormality in elderly women was higher than postmenopausal women (19).

In contrast, a study done by Meyer *et al.,* (37) observed that prevalence of epithelial cell abnormality in a group of women aged over 65 was 1.4%. According to this study, precancerous lesions and cervical cancer can be discovered after the age of 65, despite an adequate previous follow up.

In the present study, the rates of ASC‑US, ASC‑H, and LSIL were similar in the both groups, but HSIL was slightly higher in elderly group. The probable cause of higher prevalence of epithelial cell abnormality in the group of women over 65 years age in our study was due lower follow‑up rates for cervical screening. Similarly, in the postmenopausal women as well as the elderly female, rates of cervical screening follow‑up were found lower. Most studies have shown that women with abnormal Pap smears or no Pap smears in the past are at higher risk of developing cervical cancer than women who have been screened regularly (29).

Cancer of the uterine cervix is mainly a disease of middle-aged and older women (39). Multiple studies have demonstrated that older women have advanced-stage disease at the time of diagnosis. Brun et al reported that older women present with more advanced disease in France (40). Similarly, Ioka et al reported older women in Japan to present with a later stage at diagnosis and have a poorer outcome, likely from underutilization of Pap smears (41). We discovered a majority of older patients in our study had advanced-stage disease at diagnosis. The present study was reported observed that prevalence of epithelial cell abnormality in a group of women aged over 50 was 63.63%.

According to this study, cervical cancer can be discovered after the age of 50. In the present study, the rates of ASC‑US, and LSIL were similar in the both groups, but HSIL was slightly higher in elderly group. The probable cause of higher prevalence of epithelial cell abnormality in the group of women over 50 years age in our study was due lower follow up rates for cervical screening. Similarly, in the postmenopausal women as well as the elderly female, rates of cervical screening follow up were found lower. Most studies have shown that women with abnormal Pap smears or no Pap smears in the past are at higher risk of developing cervical cancer than women who have been screened regularly (38).

Conclusion:

We concluded that the highest percentage of precancerous stage was founded in 30-50 years old women, wherease the highest percentage in advanced stage represented by squamous cervical cancer and adenocarcinoma was founded in more than 50 years old women. In addition, we cocluded that the rates of ASC-US and LSIL were higher in less than 30 years old and 30-50 years women respectively. Wherease the rates of ASC-US and LSIL were lower in more than 50 years old women. As well as the results revealed that the rates of HSIL and SCC were higher in over 50 year's women, respectively.

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