Demographic and Clinical Study on Patients Referred to the National Cancer Research Center in Baghdad for Pap Smears

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Abstract:

Background: Cervical cancer ranks the fourth most common cancer among women worldwide and the eighth cancer overall. It is considered as one of the most preventable malignancies, and can be controlled through screening and Pap smears.

Objectives: To explore the demographic and clinical characteristics of a sample of Iraqi patients who were referred to the National Cancer Research Center of the University of Baghdad for Pap smear test.

Patients and methods: The study enrolled 175 female participants who were subjected to clinical examination and Pap smear tests. A questionnaire was filled for each patient on which demographic and clinical variables were recorded. Cellular specimens were collected, fixed, stained by Papanicolaou stain and examined cytologically. The corresponding cytological findings were correlated with the studied variables and tabulated accordingly.

Results: 60% of the 175 women were housewives, 40% got married before the age of 20 years, 35.4% had used contraceptive pills and 10.3% were nulliparous. The mean ages at marriage, pregnancy and first child birth were 20.2, 22.0 and 23.0 years respectively. On clinical examination, cervical erosions were obviously apparent in 41.7% of the cases and genital warts were noted in only one case (0.6%), while koilocytotic cellular atypia was observed in 4.0%. Pap smears revealed infections with Moniliasis and Trichomonas Vaginalis in 16.5% and 1.1% respectively. Atypical metaplastic changes, AGUS (atypical glandular cells of uncertain significance) and ASCUS (atypical squamous cells of undetermined significance) were displayed in 21.1%, 5.7% and 22.3% respectively. Diagnoses of CIN I (LSIL) (cervical squamous intraepithelial neoplasia 1 - low-grade squamous intraepithelial lesion), CIN II and CIN III (HSIL) (high-grade squamous intraepithelial lesion) were reported in 26.8% and 2.3% respectively. Among patients with cervical erosions, the Pap smear findings illustrated more pronounced cellular changes consistent with atypical squamous metaplasia, AGUS and ASCUS (43.8%, 19.2% and 45.2% respectively). On the other hand, LSIL, kiolocytotic atypia and HSIL in these cases were registered in 15.1%, 6.8% and 1.3% respectively.

Conclusions: The demonstrated young ages at marriage, pregnancy and childbirth of the examined patients, reflecting the early onset of sexual reproductive activities, and the associated cellular changes urge the necessity for promoting public awareness on the significance of Pap smear screening among Iraqi females. The Bethesda system facilitates easier interpretation of the results; thus fostering the communications between the examining pathologists and the gynecologists.

Key words: Demograph , clinic, Pap, smears, women.

Introduction:

Globocan estimates worldwide for 36 cancers in 185 countries shows that cervical cancer ranks as the fourth most common cancer among women and the eighth cancer overall. There were over 500,000 new cases in 2018 (1). This malignancy usually develops slowly and has readily detectable lesions that can be easily managed through early diagnosis and

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treatment (2). The most significant risk factor for becoming susceptible to develop cervical cancer is infection by the carcinogenic types of Human Papilloma Virus (HPV), namely 16 and 18. Nevertheless, other established causes include promiscuous life style associated with exposure to early sexual experience, high number of sexual partners, smoking and low socio-economic status (3).

Although the prevalence rates of cervical cancer recorded by the Iraqi Cancer Registry is low, similar to other Islamic countries, many of the registered cases often present in advanced stages thus hindering the chances for cure (1,4-8). Previous

studies from Iraq have directed the attention to the importance of promoting Pap smears to diagnose cervical intraepithelial neoplastic (CIN) lesions among Iraqi females focusing on the significance of increasing awareness on the preventive measures to control that disease (5-8). Incorrect knowledge, attitudes and practices related to breast cancer (9-10), cervical cancer and Pap smears (8) were reported among educated Iraqi females.

In general, awareness on the prevention and treatment strategies for cervical cancer are sub-optimal in developing countries where the disease is most prevalent (1,3). Cervical cancer control programs have been developed by the WHO for implementation in low-resource settings provisionally based on promoting public education on screening using Pap smear test, HPV detection and visual inspection of the cervix (3,11,12). In more developed countries, colposcopy, cervical cytology and HPV detection remain the main screening tools for detecting cervical cancer (2,3, 8-13).

This study was conducted to explore the demographic and clinical characteristics of a sample of Iraqi patients who were referred to the National Cancer Research Center of the University of Baghdad for Pap smear tests.

Cases and Methods:
Patients: A total of 175 female patients 16-67 years of age (mean 39 ±10) referred by senior gynecologists to the National Cancer Research Center (NCRC) of the University of Baghdad during (January of 2014- December of 2017) for checking-up and inspection. All the referred patients were fully aware about the Pap smear test before the procedure was undertaken. A questionnaire was filled for each patient where demographic and clinical variables were recorded including age, marital, menstrual and menopausal status, and parity, history of contraception or hormone replacement therapy. The cervical appearance was assessed clinically and were correlated with the cytological findings.

Cervical Examination and Pap Smears
After thorough history, each patient was subjected to clinical and gynecological examinations at the Colposcopy Clinic of the Clinical Examination Department belonging to the NCRC. The patients were placed in lithotomy position where visual inspection of the cervix was carried out to record the cervical and vaginal appearances. Then, the Pap smears were collected from the participants using Ayre's spatula and a broom brush after appropriate explanation of the procedure to the woman (14). The spatula and the pointed tip of the brush were introduced through the external cervical os where the squamo-columnar junction was scraped by rotating 360 degrees to include cells from the internal os. Then the specimens were directly smeared in an even manner onto prepared frosted slides on which the patient's name and serial number

were recorded. Slides were immediately fixed in 99% ethanol or absolute alcohol for at least 20 minutes.

The fixed smears were stained according to Papanicolaou. Slides were dipped in descending concentrations of ethanol (95%, 80%, 70% and 50%) each for 10 dips, and then dipped for 10 times in distilled water. That was followed by immersing for 1-2 min in a jar containing Hematoxylin stain. Excessive stain was removed by subjecting the slides to running tap water, followed by ascending concentrations of ethanol (50%, 70%, 80% and 95%) dipping slides for 10 times in each concentration. Subsequently, the slides were placed in Orange-G stain for 2 min, followed by 10 dips in 95% ethanol and then Eosin stain for another 2 minutes. That was followed by immersing the slides in 95% ethanol twice, absolute ethanol and a mixture of 50:50 absolute ethanol and Xylene for 5 minutes. Finally, the slides were left in Xylene for at least 30 minutes to be mounted with Canada Balsam or DPX (mixture of distyrene, a plasticizer, dissolved in Xylene).

All the slides were examined by senior pathologists under the light microscope using different magnifications within the Department of Pathology Research of the NCRC. Pap smears were classified according to the CIN (Cervical Intra-epithelial Neoplasia) terminology and the Bethesda system. The corresponding examined cytological findings were linked with the studied demographic and clinical variables.

Statistics
The data was analyzed by using computer software Statistical Package for Social Sciences (SPSS Inc,.Chicago, IL, USA) version16. Data was represented as frequencies, percentages, means and standard deviations (SD) of the variables. The results were tabulated according to the observed clinical and cytological findings.

Results:
Table (1) shows the main demographic and clinical features of the cases included in the study. The peak age frequency was in the fifth decade of life; 60% were housewives and 37.1% were employed. The majority (96%) said that they were married at the time of the study; 30.3% have never used any contraception while 35.4% have used contraceptive pills. More than 40% got married before the age of 20 years and only 1.7% got married at the age of 40 years or over. The menstrual period was regular in 64.6%; 10.3% were nulliparous while approximately 60% had more than two children. The main reasons for referral were abnormal vaginal discharge (35.4%), routine check-up (23.4%) and post-coital bleeding (22.3%). History of performing previous Pap smears was reported by 35.4% of the referred patients.

Table (1): Demographical and Clinical Characteristics of the Study Sample

Characteristics of the Study Sample	No of Cases	%	Characteristics of the Study Sample	No of Cases	%
Current Age (years)			Age at Marriage (years)		
< 20	3	1.7	< 20	71	40.6
20-29	38	21.7	20-29	82	46.9
30-39	47	26.9	30-39	19	10.9
40 -49	64	36.6	40 or >	3	1.7
> 50	23	13.1			
Occupation			Marital Status		
House Wife	105	60.0	Married	168	96
Employed	65	37.1	Widowed	5	3.4
Retired	1	1.7	Divorced	2	0.6
Student	2	1.1			
Contraception			Menstrual Period		
No Use	53	30.3	Regular	113	64.6
Pill	62	35.4	Irregular	62	35.4
Condom	23	13.1			
Coitus Interruptus	6	3.4			
IUD	26	14.9			
the purpose from the visit			Parity		
Routine Check-up	41	23.4	Nil	18	10.3
Post-coital bleeding	39	22.3	1-2	53	30.3
Dyspareunia	21	12	3-5	81	46.3
Irregular vaginal bleeding	12	6.9	6 +	23	13.1
Abnormal vaginal discharge	62	35.4			
History of Pap Smear					
Yes	62	35.4			
No	113	64.6			
Total	175	100	Total	175	100

The age of the patients in this study ranged between 17-67 years with a mean of 38.8 ± 10.68 (Table 2). The mean ages at first marriage, first pregnancy and first child birth were 20.2, 22.0 and 23.0 years respectively. The youngest reported ages at first marriage, first pregnancy and first child birth were 12, 14 and 15 years respectively. The ages of the patients who have reached menopause ranged between 38-55 years with a mean of 48.7.

Table (2): Correlation of Age with the Reproductive Status.

Variable	No. of Cases	Range	Mean	Standard Deviation
Age (years)	175	17-67	38.8	10.68
Age at Marriage	175	12-45	20.2	6.36
Age at Pregnancy	157	14 -42	22.0	8.43
Age at First Child Birth	157	15-43	23.0	8.46
Age at Menopause	22	38-55	48.7	4.45

On visual inspection of the uterine cervix of the examined patients, Table (3) illustrates that in 40.5% the cervix looked normal while erosion was obviously apparent in 41.7% of the cases. Genital warts were noticed in only one case (0.6%). Papanicolaou stained smears revealed non-specific inflammatory cellular changes in 82.3%; Candida albicans (Moniliasis) and Trichomonas Vaginalis were reported in 16.6% and 1.1% of the cytologically examined cases respectively. Atypical

changes within the metaplastic cells were displayed in 21.1%, AGUS (Atypical Glandular Cells of Undetermined Significance in 5.7% and ASCUS (Atypical Squamous Cells of Undetermined Significance in 22.3%. CIN I (Cervical Intraepithelial Neoplasia type I) classified by the Bethesda system as LSIL (Low-Grade squamous Intraepithelial Lesion), CIN II and CIN III classified by the Bethesda system as HSIL (High-Grade squamous Intraepithelial Lesions) were diagnosed in 26.9% and 2.3% respectively. Koilocytotic cellular atypia suggesting HPV infection (classified within LSIL) was noted in seven cases (4.0%).

Table (3): Clinical and Cytopathological Findings on Cervical Examination.

Clinical and Cytological Findings		No.	%
Visual Inspection			
Normally looking		71	40.6
Genital warts		1	0.6
Erosion		73	41.7
Translucent / Opaque lesions		14	8.0
Cytological Changes in Pap Smears			
Inflammation (Cervicitis)			
Specific inflammation	*Candida albicans*	29	16.6
	Trichomonas vaginalis	2	1.10
Non - Specific inflammation		144	82.3
Atypical Metaplasia – inflammatory induced		37	21.1
AGUS*		10	5.7
ASCU**S		39	22.3
CIN I (LSIL / Koilocytotic Atypia) ***		47	26.9
CIN II (HSIL) ****		3	1.7
CIN III (HSIL) ****		1	0.6
Total		175	100

*Atypical Glandular Cells of Undetermined Significance

**Atypical Squamous Cells of Undetermined Significance
***Cervical Intraepithelial Neoplasia (Low-Grade squamous Intraepithelial Lesion)
**** High-Grade squamous Intraepithelial Lesion

Among the 73 patients who had cervical erosions, the Pap smear findings revealed specific cervicitis due to Moniliasis and Trichomonas Vaginalis in 13.7% and 1.4% respectively. More pronounced cellular changes consistent with atypical squamous metaplasia, AGUS and ASCUS were observed in 43.8%, 19.2% and 45.2% respectively. On the other hand, the rates of CINI (LSIL) and CIN II (HSIL) did not exceed 15% and 1.4% respectively. While no case showed cellular changes consistent with CIN III,

Table (4): Cytopathological Findings in Pap smears of Patients with Cervical Erosions.

Cytopathological Findings in Pap Smears		No.	%
Specific inflammation	*Candida albicans*	10	13.7
	Trichomonas vaginalis	1	1.4
Non-specific inflammation		62	84.9
Atypical Metaplasia – inflammatory induced		32	43.8
AGUS		14	19.2
ASCUS		33	45.2
CIN I (LSIL / Koilocytotic Atypia)		11	15.1
CIN II (HSIL)		1	1.4
CIN III (HSIL)		---	---
Total		73	100

Discussion:
In developing countries, where awareness and facilities for the prevention and treatment of the diseases are obviously inadequate, cervical cancer ranks as one of the most common cancers among women and the leading cause of cancer related mortality (1,3). The World Health Organization has developed guidelines for cervical cancer control strategies in low-and middle resource settings focusing upon promoting public health education and screening for that type of malignancy through Pap smears, detection of HPV and visual inspection of the cervix (3, 10-14). The National Cancer Research Center of the University of Baghdad was established to emphasize the role of research in adopting the national cancer control strategy, to raise the awareness of the Iraqi population to the signs and symptoms of common cancers through public education and to build capacities of the health professionals through training in the fields of cancer diagnosis and treatment (15, 16). This study documented the demographic and clinical characteristics of the patients who were referred to the center for checking up and consultation. The early age at first marriage, pregnancy and birth in the study group points out to the critical role of early sexual activity on exposure of the reproductive system to infectious agents and carcinogens including HPV (17,18). Over 35% of the cases had positive history of using oral contraceptive pills. Although earlier studies showed that there might be

a significant correlation between abnormal Pap smear findings and hormonal contraception (19), yet a more recent Australian cross-sectional study documented that the duration of oral contraceptive use among women with Pap smear changes consistent with CIN was significantly shorter than those without abnormalities; indicating that oral contraceptives could be inversely associated with CIN (20). The value of Pap smears in detecting cellular abnormalities has been well documented in the literature as the most successful screening tool for cervical cancer; specifically when applied together with Colposcopy and HPV tests (3, 11-14). Studies from Iraq found that the high agreement rate between cervical cytology and colposcopy indicates that conventional Pap smear could be considered as a dependable screening test in spite of its relatively low sensitivity (8, 22). Nevertheless, better results could be achieved through the liquid-based cytology procedure in which a suspension from the sample is used to produce a thin layer of cells on a slide; thus allowing clearer vision and accurate diagnosis. That technique could be maneuvered manually in scarce resource settings (23). Pap smear examination of the specimens in the current study showed that in 16.5% of the cases there was evidence of fungal spores indicating Moniliasis while moderate-severe cervicitis extending to the endocervix was observed in 39%. Thus it was not surprising that the main reasons for referral were abnormal vaginal discharge (35.4%) and post-coital bleeding (22.3%). In a previous Iraqi study it was reported that vaginal secretions, abdominal pain and itching were the most important signs of cervical inflammation (22). Severe cervicovaginitis could obscure serious CIN lesions resulting in false negative findings (14). Although it is claimed that such dilemma could be reduced by applying liquid based cytology, yet some studies failed to reveal a significant difference in the overall accuracy of conventional Pap test versus liquid based cytology (24). Overall, atypical cellular changes in the form of atypical squamous metaplasia, AGUS and ASCUS were diagnosed in 21.1%, 5.7% and 22.3% while CIN I (LSIL), CIN II and CIN III (HSIL) were diagnosed in 26.8% and 2.3% respectively. Koilocytotic cellular atypia suggesting HPV infection (classified within LSIL) was noted in seven cases (4.0%). The NCRC reports cervical cytology diagnoses in Pap smears using the Bethesda system as well which was introduced in 1988 and revised in 2001 (25). The terminology reflects the biological concepts underlying pre-cancerous lesions that were earlier referred to as cervical dysplasia (mild, moderate or severe) or cervical intra-epithelial neoplasia (CIN 1, CIN II or CIN III). It comprises low grade squamous intraepithelial lesion (LSIL) which include koilocytotic atypia and high grade squamous intra-epithelial lesion (HSIL). A previous study on symptomatic Iraqi patients referred to the Cytopathology Teaching Laboratory of the Medical City Teaching Hospital demonstrated rates for

ASCUS, AGUS, LSIL and HSIL equivalent to 36.1%, 7.2%, 33.7% and 3.6% respectively (26). The relatively high rates of abnormal Pap smears in this study is attributable to the fact that approximately 77% of the patients were referred to the center complaining of serious signs and symptoms. On visual inspection of the uterine cervix of the examined patients, 40.5% had normal appearance while erosion was obviously apparent in 41.7% of the cases (73 cases). Genital warts were obviously visualized as palpable lesions in only one patient who had Pap smear findings consistent with koilocytotic atypia. Pap smear cytological specimens from the erosive cervices showed relatively higher rates of mild atypical cellular changes; yet they were not associated by more serious intraepithelial neoplastic cellular changes. Koilocytotic atypia suggestive of HPV infection was displayed cytologically in 6.8% of the patients who were complaining of cervical erosions in this study. In general, it has been reported that cytological or histological signs of HPV infection cannot be detected in a majority of women who are positive for HPV (27); since the presence of koilocytes may be difficult to diagnose specifically when there are slide fixation or dehydration artifacts resulting in cells exhibiting peri-nuclear halos (28).

Conclusions

The demonstrated young ages at marriage, pregnancy and childbirth of the examined patients, reflecting the early onset of sexual reproductive activities, and the associated cellular changes urge the necessity for promoting public awareness on the significance of screening among the Iraqi female community. Pap smear remains a safe, acceptable, cost effective and reproducible technique for early detection of cervical cell abnormalities. The Bethesda system facilitates easier interpretation of the results; thus fostering the communications between the examining pathologists and the gynecologists and allowing clear guidance for clinical management.

Authors' contributions:

This study was designed and drafting the manuscript was done by Nada A. Alwan. The study was conceived, input and output the data in the statistical program by Huda H. Alabbody. The results were analyzed by Nada A. Alwan, Huda H. Alabbody and Safana A. Yaseen[3]

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دراسة ديموغرافية وسريرية للمريضات المحالات إلى المركز الوطني لبحوث السرطان في بغداد لأجراء مسحات عنق الرحم

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الخلاصة:

الخلفية: يصنف سرطان عنق الرحم السرطان الرابع الأكثر شيوعا بين النساء في جميع أنحاء العالم والثامن على السرطانات عموما. وهو من أكثر أنواع الأورام الخبيثة التي يمكن الوقاية منها والسيطرة عليها من خلال التحري ومسحة عنق الرحم .

هدف الدراسة: هدفت هذه الدراسة الى استكشاف الخصائص الديموغرافية والسريرية لعينة من المريضات العراقيات اللوتي أحلن إلى المركز الوطني لبحوث السرطان التابع الى جامعة بغداد لاختبار مسحة عنق الرحم.

المنهجبة: شمل البحث 175 امرأة خضعن للفحص السريري واختبارات مسحة عنق الرحم حيث تم إعداد ملف استبيان لكل مريضة سُجلت فيه البيانات الديموغرافية والسريرية ومن ثم تم جمع العينات الخلوية وفحصها بالمجهر. وقورنت النتائج الخلوية مع المعلومات الخاصة بكل مريضة تبعا لذلك .

النتائج: بينت النتائج ان 60% من المريضات المحالات كن ربات بيوت، 40% تزوجن قبل بلوغ 20 عامًا، و 35.4% منهن استخدمن حبوب منع الحمل بينما 10.3% لم يسبق لهن الولادة. وكان معدل الأعمار عند الزواج والحمل والولادة الأولى 20.15 و22.02 و22.99 سنة على التوالي . وأوضح الفحص السريري تآكل عنق الرحم في 41.7% من الحالات ووجود الثآليل التناسلية في حالة واحدة فقط (0.6)% (وكشفت مسحات عنق الرحم عن عدوى التغيرات الحبيبية غير الطبيعية في الخلايا الحرشفية والغدية في 21.1%، 5.7% و 22.3% على التوالي. كما تم تشخيص تغيرات ورمية داخل الخلايا من النوع الخفيف والشديد في 26.8% و 2.3% على التوالي. وفيما يتعلق بالمريضات اللواتي يعانين من تآكل عنق الرحم أظهرت نتائج مسحة عنق الرحم تغييرات أكثر وضوحا بما يتفق مع حؤول حرشفية شاذة 43.8%، 19.2% و 45.2% على التوالي. من ناحية أخرى، تم تسجيل حالات الثدن الخفيف والشديد في 15.1% و 1.3% على التوالي.

الإستنتاجات والتوصيات: إن صغر عمر المريضات العراقيات الذي بينته الدراسة عند الزواج والحمل والولادة والذي يعكس بداية النشاط الإنجابي الجنسي والتغييرات الخلوية في عنق الرحم المرتبطة بذلك يحتم ضرورة تعزيز الوعي العام بأهمية فحص مسحة عنق الرحم بين النساء في المجتمع العراقي. و نظام بثزدا هو الاسهل في تفسير النتائج وبالتالي يعزز الصلة والمشورة بين اختصاص الامراض واختصاص النسائية.

الكلمات المفتاحية: ديموغراف ,الطب السريري ,مسحة .باب ,النساء.