

Significance Of Cervical Cytology Screening (Pap Smear) In The Detection Of Precancerous Cervical Lesions

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Summary:

Background: The incidence of cancer of the cervix is comparatively low in Iraq, as in most other Islamic countries. Pre invasive lesions of the uterine cervix can be detected by Pap smears in their preclinical course, a fact which documents the significant role of cervical cytology in gynecological practice.

Objective: To emphasize the role of cervical cytopathology (Pap smears) in the detection and follow up of various cervical lesions that may predispose to cervical carcinoma with special emphasis on Cervical Intraepithelial Neoplastic (CIN) conditions or dysplasias.

Patients and Methods: This retrospective study was performed on 1500 women aged 20 years and above who attended the private clinical laboratory of the senior investigator during the period between (May 2000 to May 2001). Cases were randomly selected. All relevant clinico-pathological data were recorded within a standardized interview report. After careful examination of the external genitalia, a Pap smear was obtained using Ayre's wooden spatula. Results were recorded and statistically analyzed.

Results: Cytological diagnosis revealed:
1065 cases (71.01%) of non specific cervicitis.
392 cases (26.13%) of specific cervicitis.
30 cases (2%) of cervical polyp.
172 cases (11.47%) of CIN₁ (mild dysplasia).
31 cases (2.07%) of CIN₂ (moderate dysplasia).
10 cases (0.67%) of CIN₃ (severe dysplasia).

According to the Bethesda system, atypical squamous cells of undetermined significance (ASCUS) was the most common epithelial cell abnormality representing (24.27%) of total group studied, while low grade squamous intraepithelial lesions (LGSIL) and atypical glandular cell of undetermined significance (AGUS) represented (13.27 %) and (16.2 %) of total group studied respectively. High grade squamous intraepithelial lesions (HSIL) were detected in (2.73 %) of the examined smears.

Clinical examination revealed that the grades of CIN were higher in patients with older age groups and a statistically significant correlation was shown between parity and the severity of cervical lesions. Cervical erosions, hypertrophy and congestion were reported in a significant proportion of cases among our study population.

Conclusion: Pap smear cytology remains as one of the most effective tools used in the early detection and follow up of many gynecological disorders specifically precancerous lesions of the uterine cervix.. Cytological diagnosis of these lesions with treatment of the associated inflammations could be helpful in preventing their progression into more serious cervical pathology.

Keywords : Pap smear, cervical cytology, dysplasia, CIN.

Fac Med Baghdad
2007; Vol. 49, No.3
Received April 2007
Accepted June 2007

Introduction:

Cervical cytology has been identified as one of the major tools used in screening for cervical carcinoma.⁽¹⁾ According to latest Iraqi Cancer Registry records, cervical cancer ranks the 10th among the most common female cancers (accounting for 2.9 % of total female malignancies).⁽²⁾

Cervical cancer is one of the few cancers that can be detected relatively easily in its pre – malignant form not only because it has a relatively long pre – invasive phase but also due to the fact that the cervix is easily accessible for direct visualization^(3,4). Detection at the early pre –

invasive stages provides an opportunity for treatment to prevent progression into invasive cancer. Much credit for these dramatic gains belongs to the effectiveness of the Pap test in detecting cervical pre cancers.^(5,6)

The cervico- vaginal smears (Pap smears) are the most popular method utilized in the investigation of various gynecological diseases. Despite all of the technological advances which have occurred in the field of medicine within the last 100 years , the Pap smear, named after its developer Dr. George Papanicolaou, remains as one of the few methods available currently for the diagnosis of preneoplastic cervical lesions^(7,8)

Since the introduction of Pap smear, four different systems have been used in reporting cervico- vaginal cytology diagnosis. Those are summarized in the following table:⁽⁹⁾

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Table 1: Terminology for reporting Pap smear abnormalities

Papanicolaou Class (obsolete)	Dysplasia/ CIS spectrum	CIN (Cervical intraepithelial Neoplasia, Richart,)	Bethesda System (NCI- ACOG, 1988)
Class I : <i>Normal smear, no abnormal cells</i>		Negative	Negative for intraepithelial Lesion (NIL)
Class II : <i>Atypical cells present below the level of cervical neoplasia</i>	Reactive Atypia Nonspecific reactive changes		Regeneration and repair ASC-US/ ASC-H/AGUS ASC-US/AGUS (Atypical cells of undetermined significance)
Class III : <i>Smear contains abnormal cells consistent with dysplasia</i>	Mild Dysplasia Moderate Dysplasia Severe Dysplasia	CIN 1 CIN 2 CIN 3	LSIL (Low grade squamous intraepithelial lesion). HSIL (High grade squamous intraepithelial lesion)
Class IV : <i>Smear contains abnormal cells consistent with carcinoma in-situ</i>	Carcinoma in-situ	CIN 3	High grade squamous intraepithelial lesion
Class V : <i>Smear contains abnormal cells consistent with invasive carcinoma of squamous cell</i>	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma

Patients and Methods

This is a retrospective study obtained from examination of 1500 patients (aged 20 years and above)who were referred to the private clinical laboratory of the senior investigator during the period between May 2000 to May 2001. Non of those patients were pregnant.

According to Pap smear cytological findings, cases were categorized into:

Cervicitis (specific and non specific).

Cervical polyp.

CIN

Cervical carcinoma.

Patients were also classified according to the Bethesda system as follows:

ASCUS (atypical squamous cells of undetermined significance).

LSIL (Low grade squamous intraepithelial lesion) including Koilocytotic atypia (HPV)

HSIL (High -grade squamous intraepithelial lesion)

AGUS (atypical glandular cells of undetermined significance)

A case report questionnaire was prepared for each patient in which the following information were recorded: name, age, date, the date of her last menstrual period, gravidity, parity, last child birth , age at menopause , the type of contraception used including intrauterine contraceptive device (IUCD), any history of previous abnormal Pap smears, history of previous treatment for any abnormality found on Pap smear, history of cauterization, history of hormonal replacement therapy or history of surgical intervention .Any

signs of pelvic or vaginal infection were recorded as well as any history of abnormal vaginal bleeding (including intermenstrual bleeding, post coital bleeding and post menopausal bleeding).

Two slides were prepared for each patient on which the name, date, identification number were written with a diamond – tipped pencil. The patient was placed in the dorsal lithotomic position on the examination table.

To prevent any interruption; all of the necessary equipments should be prepared in the examination room at the beginning of the procedure. After careful examination of the external genitalia and with the use of talc powder free gloves, a bivalve or cusko`s speculum was introduced without lubrication into the vagina and correctly positioned so as to expose the entire cervix.

The smears were obtained by using an " Ayre`s" wooden spatula (and if necessary a cytobrush). With the small end of spatula placed in the external os of the endocervix and rotated 360 ° , the entire surface of the external os and part of the internal os were synergistically scraped. The specimen was smeared with a lateral motion on a slide, which was immediately dropped into a bottle of fixative containing 99 % of ethyl alcohol. By introducing the other end of the spatula into the posterior vaginal fornix another smear was obtained from the mucous and desquamated epithelia which usually accumulated there.

The smears were kept in alcohol for at least 20 minutes and then stained by Papanicolaou stain.

Results

The results were based on the analysis of clinical and cytopathological findings obtained from 1500 patients included in the study sample. On recording the clinical features, regardless of vaginal discharge and pain which were present in most of the cases, the most common complaint was itching (recorded in 21.67% cases) followed by intermenstrual bleeding (18.27%) and postcoital bleeding (11.7%).

While the most common gross findings observed by visual inspection were cervical erosion in (648) cases (43.2% of total group studied "TGS"), hypertrophy in (581) cases (38.73% of TGS) and congested cervix with bleeding on touch which was demonstrated in (189) cases (12.6% of TGS).

Sixty one cases of specific cervicitis associated with CIN (4.07 % of TGS) .In 54 cases (3.6% of TGS) it was associated with CIN1 which was statistically highly significant (p<0.01), 48 cases (3.20% of TGS) were associated with (metaplasia

and CIN) and three cases were associated with polyp (0.20 % of TGS).

Three major types of specific cervicitis were reported; those included Moniliasis (290 cases, 19.33% of TGS), Trichomonas Vaginalis (75 cases, 5% of TGS) and Koilocytotic atypia (signifying HPV) which was observed in (27 cases, 1.8% of TGS) .

Cervical polyps were diagnosed clinically in 30 cases (2% of TGS). Cervical smears of these patients revealed polypoidal masses with no other lesions in nine cases (0.6% of TGS). Ten cases were associated with metaplasia (0.67% of TGS), this association was statistically significant (p<0.005). These polyps also coexisted with CIN1 in six cases (0.40% of TGS). Only one case of CIN2 and another of CIN3 were associated with cervical polyp. Therefore, the association between CIN or dysplasia as a whole and cervical polyps was found in eight cases (0.53% of TGS). Figure (1)

Table(2): Distribution of CIN lesions (Dysplasia) observed in cervical smears of 213 patients

Cytologic Diagnosis	No. of cases	% of total	% of
CIN1 (mild dysplasia)	172	80.75	11.47
CIN2 (moderate dysplasia)	31	14.55	2.07
CIN3 (severe dysplasia/CIS)	10	4.69	0.67
Total	213	100.00	14.20

Table (3): Distribution of CIN1 (mild dysplasia) in cervical smears

Cytologic Diagnosis	No. of cases (172)	% of total CIN1	% of TGS
CIN1 + Specific Cervicitis	54	31.40	2.09
CIN1 + Metaplasia	140	81.40	5.43
CIN1 + Metaplasia + Specific Cervicitis	41	23.84	1.59
CIN1 + Polyp	6	3.49	0.23

(P<0.01) for the above two categories.

Table (3) showed that CIN1 (Mild dysplasia) was found in 172 cases (80.75% of TCIN ,11.47 % of TGS).

CIN2 was observed in 31 cases (14.69 % of TCIN , 2.07% of TGS) as follows: CIN2 with squamous metaplasia was reported in 23 cases (74.19 % of TCIN2 ,1.53 % of TGS) which was highly significant. CIN2 associated with squamous metaplasia and specific cervicitis was found in seven cases (22.58 % of TCIN2, 0.47 % of TGS), while only one case of CIN2+ polyp was observed in (3.23 % of TCIN2, 0.07 % of TGS). Figure (6)

CIN3 was reported in 10 cases (4.74 % of TCIN, 0.67 % of TGS); CIN3 alone in eight cases

while CIN3 with squamous metaplasia was demonstrated in only one case (3.22 % of TCIN3, 0.07 % of TGS). In only one case CIN3 was associated with cellular changes of cervical polyp (8.33 of TCIN3, 0.07 % of TGS). Figure.(8)

Squamous cell carcinoma was reported in only two cases (0.13% of TGS) while adenocarcinoma of cervical origin was not detected in any case. On the other hand, there were two cases of adenocarcinoma of endometrial origin. According to the Bethesda system classification, the cytological findings of epithelial cell abnormalities were categorized as shown in Table 4.

Table (4): The frequency of different epithelial cell abnormalities according to the Bethesda system

Cytologic Diagnosis	No. of cases 847	% of total	% of TGS
Minimal Epithelial cell Abnormalities (ASCUS , AGUS , LGSIL)	806	95.16	53.73
ASCUS	364	42.98	24.27
AGUS	243	28.69	16.20
LGSIL (CIN1 + Koilocytosis)	199	23.49	13.27
HGSIL(CIN II+CIN III)	41	4.84	2.73

Atypical squamous cells of undetermined significance (ASCUS) was the most common epithelial abnormality representing (24.27%) of total group studied, while low grade squamous intraepithelial lesions (LGSIL) and atypical glandular cell of undetermined significance (AGUS) represented (13.27 %) and (16.2 %) of total group studied respectively. High grade squamous intraepithelial lesions were detected in (2.73 %) of the examined smears

Correlation of clinical findings with the various cervical lesions showed the following:

Regarding the age, the highest frequency of lesions in women with specific cervicitis and CIN1 occurred during the period (30 – 39) years. On the other hand, the highest frequencies for squamous metaplasia + CIN (CIN1, CIN2) and CIN2 lesions occurred at the age group between (40– 49) while those for CIN3 and cervical carcinoma in the period between (50–59) years.

Table (5): Frequency of patients complaining of Post-coital bleeding (PCB), Intermenstrual bleeding (IMB) and Post-menopausal bleeding (PMB) according to the cytological diagnosis

Cytologic Diagnosis	PCB	PCB	Total No. of cases	IMB	IMB	*Total No. of cases	PMB	PMB	**Total No. of cases
	No.	%		No.	%		No.	%	
Specific Cervicitis	35	8.93	392	57	15.08	378	2	14.29	14
Metaplasia + Polyp	5	50.00	10	3	30.00	10	0	0.00	0
CIN1	12	6.98	172	40	24.84	161	3	27.27	11
CIN2	7	22.58	31	5	20.83	24	3	42.86	7
CIN3	3	30.00	10	1	33.33	3	2	28.57	7
CIN+ Metaplasia	9	5.49	164	17	11.41	149	5	33.33	15
CIN + Specific Cervicitis	1	1.64	61	5	8.47	59	0	0.00	2
Cervical Carcinoma	1	50.00	2	0	0.00	1	1	100.00	1

In view of parity, the highest frequency in patients harbouring metaplasia + (CIN1,CIN2), and in patients diagnosed with CIN1 was observed in women who had borne (3 – 5) children .In patients with CIN3 and cervical carcinoma , the peak number of children was (6 – 8) .

History of PCB was revealed in 7% of those harbouring CIN I alone, 22.6% in patients with CIN2 and in 30% of those with CIN3. History of IMB was demonstrated in 24.9%, 20.9% and in 33.3% of patients with CIN1, CIN2 and CIN3 lesions respectively; while PMB was the complaint recorded from 32% of postmenopausal patients who were diagnosed as harboring CIN lesions in this study.

The clinical examination of the cervix demonstrated that cervical erosion was displayed

clinically in 648 cases (43.2 of TGS); namely in 56 cases (32.56%) of CIN1 , 14 cases (45.16%) of CIN2, two cases (20%) of CIN3 and in one of the two cases (50 %) of cervical carcinoma (squamous cell carcinoma).

Hypertrophy was clinically diagnosed in 300 cases (38.73% of TGS): 72 cases (41.86 %) of CIN1, 15 cases (48.39%) of CIN2 and only one case of CIN3 (10%). Cervical hypertrophy was also seen in four cases (40%) of metaplasia + polyp..

Bleeding on touch (congested cervix) was recorded in 189 cases (12.6 % of TGS): 70 cases (40.7%) of CIN1 , 18 cases (58.06 %) of CIN2 and five cases (50%) of CIN3 and in one of the two cases (50%) of cervical carcinoma.



Figure (1) : Polyp (eosinophilic finger like projection). Pap Smear.

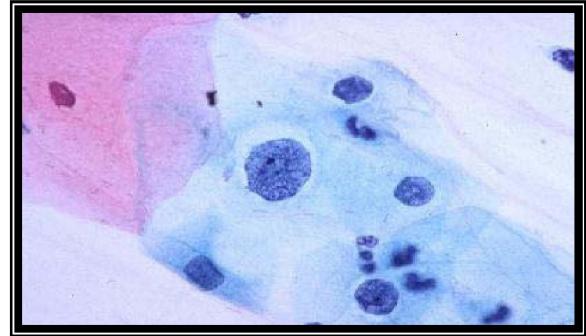


Figure (5) Mild dysplasia (CIN1)- LSIL. Pap Smear.

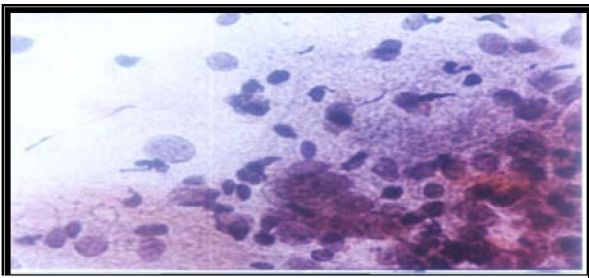


Figure (2) Atypical glandular cells of undetermined significance (AGUS) . Pap Smear.

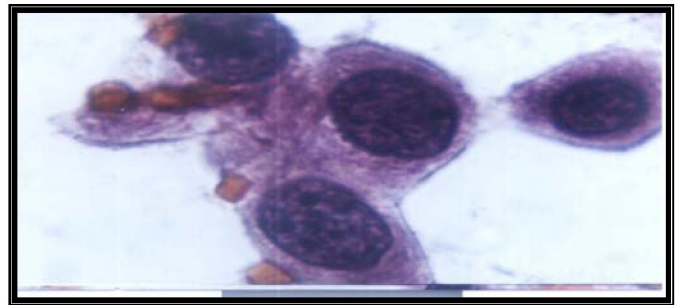


Figure (6) Moderate dysplasia (CIN2) – HSIL. Pap Smear.

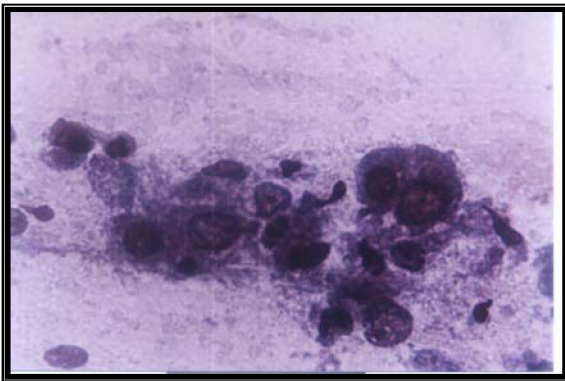


Figure g(3) Atypical metaplasia (ASCUS) . Pap Smear.

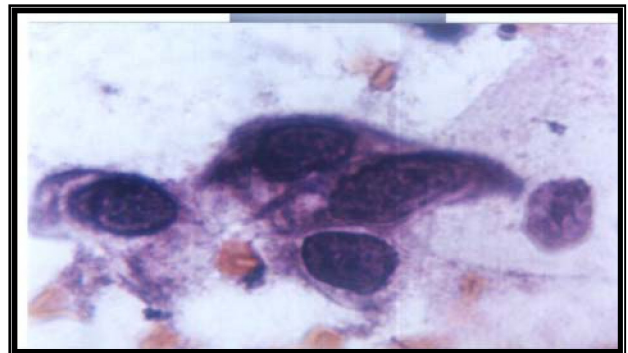


Figure (7) Moderate to sever dysplasia (HSIL) . Pap Smear.

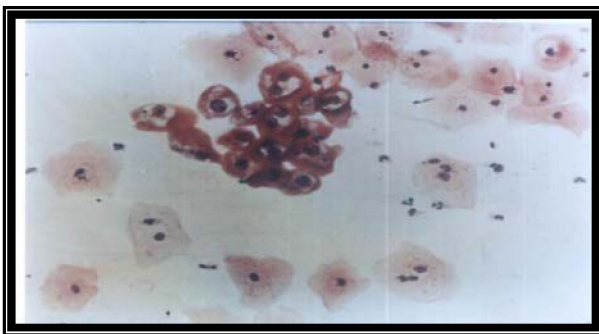


Figure (4) Koilocytosis-LSIL. Pap Smear.



Figure (8) Severe dysplasia (CIN3-HSIL) . Pap Smear.

Discussion:

Cervical cancer prevention efforts worldwide have focused on early detection and screening women who are at risk of developing cervical cancer using Pap smears, and treating preneoplastic cervical lesions. Cytological screening continue to be an effective tool for detecting cervical neoplasia in a preinvasive state due to the long natural history of progression from low grade dysplasia to invasive carcinomas⁽¹⁰⁾

Although the incidence rates of cervical cancer in Iraq are relatively low, as in most other Islamic countries, the majority of the cases usually present in advanced stages with poor prospects of cure. A feasible control strategy would be to encourage Iraqi women to seek early detection for cervical intraepithelial neoplasia.⁽¹¹⁾

In the current cytological study, the encountered various cervical lesions were recorded with special emphasis on cervical cancer precursors. An element of cervicitis was found to be present in almost all of the cases studied which include both specific and non-specific cervicitis. Because of its importance in the pathogenesis and fate of precancerous cervical lesions, cases with specific cervicitis were stressed upon in the present work.

According to our cytological findings, *Candida* was the most common specific microorganism detected in cervical smears of patients with specific cervicitis (19.35 of TGS). Our findings were comparable to those recorded by Al-Alwan (1987), Al-Anbari (2002) and others in this respect.^(12,13,14) *Trichomonas vaginalis* was the second most common demonstrated specific infection; observed in (5% of TGS) which is quite in accordance to the figure reported by Hasan (1989) and Karen et.al.(1999).^(15,16)

On the other hand, Sheila et al. (2001) recorded in their series that the frequency of Candidiasis was 22.5%, while Trichomoniasis was reported in 3.4 %.⁽¹⁷⁾

The incidence of Human Papilloma Virus (HPV) infection, as a sexually transmitted disease of the female genital tract is increasing worldwide. In our study koilocytotic atypia (signifying HPV infection) was observed in (6.89% of total specific cervicitis, 1.8 % of TGS). Although our figure is close to that displayed by Hasan (1989 : 1.1% of TGS),⁽¹⁶⁾ yet it is lower than those recorded in the studies of Al-Alwan (2000) and Adam et al (2000).^(18,19,20) probably attributable to the fact that the investigators in the latter studies used additional techniques in the diagnosis of HPV along with cervical cytology and also due to the lower frequency of HPV in the eastern population.^(10,28)

The association of cervical polyps with squamous metaplasias and cervical dysplasias has been reported by others^(12,21). It has been concluded that cervical polyps are usually not precancerous, but cancer might arise from their atypical metaplastic epithelium.^(22,23)

The frequency rates of CIN lesions demonstrated in the present report coincides with those recorded in other studies from Iraq (Al-Alwan (1987,1995), Al-Rubai'ee (2002), Al-Anbari (2002)).^(10,19,24) Kubba in 1971 found that the incidence of CIN3 (carcinoma in situ) in Iraqi patients with gynecologic complaints was (0.3%).⁽²⁴⁾, which is close to our figure (0.6%)

Only two cases of squamous cell carcinoma of the cervix were detected in this work representing (0.13% of TGS). While it coincides with the results demonstrated in other studies from our country).^(10,16), it reemphasizes the fact that the incidence of cervical carcinoma is relatively low in Iraq.

According to the Bethesda system classification of cervical cell abnormalities, minor or minimal epithelial cell abnormalities were much more common than HSIL. Similar observations were recorded by other Iraqi investigators^(10,19,25); ASCUS representing the most common abnormal Pap smear findings^(10,19,20,25)

The recorded frequency of AGUS in our study was lower than that displayed by Kayoon (2003)⁽²⁶⁾ but higher than what was observed by others^(10,19,27)

It is worthy mentioning that most of the AGUS cells in this study favored inflammatory conditions; thus accounting for the relatively high frequency observed in the current study (since an element of cervicitis accompanied almost all cases).

The reported frequency of HGSIL agrees with what was displayed in other studies from Iraq and adjacent countries^(10,25,27) but lower than those observed in other reports specifically from western population. That probably reflects the difference in the incidence of cervical cancer in our society compared with the west where there is a higher prevalence of risk factors for cervical cancer despite the availability of screening programs (illustrated mainly in promiscuous sexual behaviour)⁽²⁷⁾.

Clinical Study revealed that with respect to age which has long been correlated with an increasing incidence of malignancies, there is a significant correlation with the severity of the disease in precancerous lesions. The results of our study showed that the grade of CIN gets higher in patients with older age groups.

Multiparity has been considered as one of the important factors in the etiology of cervical carcinoma. This was demonstrated clearly in our data where patients who had borne (6 and more) constituted an obvious higher proportion in both cervical carcinoma and the HSIL groups as compared to the LSIL group (where the peak frequency in those lesions occurred in women with 3 –5 children). Thus, a statistically significant correlation was shown between parity and the severity of cervical lesions .

The increased risk for CIN with increasing parity has been noted by others who recorded two

folds increased risk for CIN3 associated with high parity and five folds increased risks for invasive cancer.(29)

The most common clinical patient complaints recorded in our study and in others were mainly vaginal discharge, lower back and abdominal pain, and itching; obviously related to cervicitis^(17,19)

Regarding the association of CIN with abnormal vaginal bleeding, it has been repeated in many literatures that CIN is usually free from symptoms and that the condition owes its existence as an entity only to assign "the presence of abnormal smear". Al-Alwan reported that the coexistence of CIN with abnormal vaginal bleeding is mostly due to the associated cervical lesions or other systemic abnormalities in these patients.⁽²⁴⁾

However; it has been shown that the frequency of PCB increased with the severity of the CIN lesion, probably because the fragile epithelium become detached during intercourse. PMB was found in (32 %) of postmenopausal women who had CIN.

On gross examination, it was displayed that 43.2 % of TGS had cervical erosions that may bleed on touch and that erosion was statistically associated with CIN lesions. It has been reported that cervical erosion is a potential outcome of untreated dysplasia caused by sexually transmitted diseases and that erosion could be an early sign of cervical cancer.⁽²⁹⁾

On the other hand, we believe that this high frequency of cervical erosions determined in our report was mainly attributable to the fact that inflammation of the cervical epithelium was present in almost all patients; cervical erosion was obviously demonstrated as well in 67.2 % of the patients who had CIN + specific cervicitis. Accordingly, it is proposed that severe cervicitis could act as an important factor in this association. Similarly, findings of cervical hypertrophy and congestion were reported in a significant proportion of cases among our study population (23.33% and 12.6% respectively). It has been reported (28) that hypertrophied and congested cervixes were specific findings associated with certain types of specific infections thus leading to prominent vascularity and hypertrophy of the cervical ectropion which may bleed on touch during examination..

In conclusion, our study emphasized that Pap smear cytology in Iraq remains one of the main useful tools in the early detection and follow up of many gynecological disorders specifically cancerous and precancerous lesions of the uterine cervix. The detection of various specific infections could be helpful in directing the gynecologists to choose and plan for the most appropriate therapy. Cytological diagnosis of these lesions with treatment of the associated inflammations could be helpful in preventing their progression into more serious cervical pathology.

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