Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-nahrain.edu.iq

Cervicovaginal Smears' Classification Using the Bethesda System (TBS) 2001: A Cytopathological Study

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Abstract

Background The Bethesda System (TBS) aims to simplify cervical smear report and make it more reproducible and facilitates the communication between pathologist and clinician.

Objectives To evaluate 2001 Bethesda System of cervicovaginal smear classification in the diagnosis of different pathologies seen in women having different gynecological complaints.

Methods A prospective study of cervicovaginal smears that obtained from 360 female patients (aged 15-75 years) attending Gynecological Consultation Clinic in Al-Imamian Al-Kadhimiyian Medical City – Baghdad- Iraq for the period from November 2011 to April 2012. Smears were stained by Pap stain to evaluate according to Bethesda system 2001.

Results A total of 360 cases were evaluated, 317 cases (88%) had satisfactory smears for evaluation. 246 cases (68.3%) had negative cervical smears for intraepithelial neoplasia (TBS 2001). Seventy one cases (19.72%) had abnormal cervical smears (AS). Minimal cervical smear abnormalities (ASC-US, ASC-H, AGC, LSIL), includes (53) cases (74.64% of AS). HSIL (CIN- II, CIN-III, & carcinoma in situ), includes (18) cases (25.36% of AS).

Conclusion Pap smear is a screening test, it is not a diagnostic test; positive result indicates that there may be a problem and that further diagnostic procedures must be done. The Bethesda system is of validity in providing a uniform format for cervical cytology report.

Key words Pap smear, cervical intraepithelial Neoplasia (CIN), LSIL, HSIL, 2001 Bethesda System (TBS).

Introduction

The fundamental goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer. The optimal screening strategy should identify those cervical cancer precursors likely to progress to invasive cancers (maximizing the benefits of screening) [(1)].

Cytology (Pap test) screening has been very successful in lowering cancer incidence and mortality in countries where good quality screening is available [(2)].

According to the latest Iraqi Cancer Registry records (2008), cervical cancer ranks the 8th among the most common female cancers in IRAQ accounting for 0.8% of total female malignancies [(3)].

Fewer than 5% of women in developing countries have ever had a Papanicolaou (Pap) test; in contrast, 89% of women in the United States report having had a Pap test in the preceding 3 years [(4)].

High-income countries have effectively integrated Pap smear–based cervical cancer

screening services into both medical and public health services and have achieved reasonably high coverage rates, effectively reducing incidence and mortality over the past seven decades [5].

The expanding use of effective prophylactic vaccines for preventing infection with human papillomavirus (HPV) types 16 and 18, common etiologic agents for cervical cancer, offers even greater promise for eventual elimination of cervical cancer as a major public health problem [6].

The 20th century witnessed a remarkable decline in the mortality from cervical cancer in many developed countries; this achievement is directly attributable to the implementation of the Papanicolaou's (Pap) test [7]. In the 1930s, before Pap screening was introduced, cervical cancer was the most common cause of cancer deaths in women in the United States. Today, it is not even one of the top ten [8]. The Pap smear is a cytologic screening test used to detect cervical intraepithelial neoplasia (CIN) and early cervical cancer so that these conditions can be managed or treated to prevent disease progression to invasive cancer. Cervical cytology results are not diagnostic of CIN or cancer, as biopsy and histologic confirmation are required for diagnosis [9].

Terminology forms the basis for effective communication between the laboratory and clinician. The use of a uniform diagnostic terminology facilitates communication by establishing a common language that, in theory, does not vary significantly from cytologist to cytologist or laboratory to laboratory [10].

The Bethesda System 2001 and its 1991 and 2001 revision aim to simplify Pap smear reporting and make it more reproducible. It redefines the Pap smear request as a medical consultation [11].

The objective of this study is to evaluate 2001 Bethesda System of cervicovaginal smear classification in the diagnosis of different pathologies seen in women having different gynecological complaints.

Methods

The study is a prospective one. Cervicovaginal smears were obtained from 360 female patients with different gynecological complaints (aged 15-72 years) all were married and non pregnant attending Gynecological Consultant Clinic in Al-Imamian Al-Kadhimiyian Medical City, Baghdad, Iraq for the period from November 2011 to April 2012.In this study cervicovaginal smears were evaluated and assessed using, the Bethesda System (TBS) 2001 with special emphasis on premalignant lesions, with exclusion of cases which were unsatisfactory for evaluation. Patients were categorized according to the Bethesda System into:

- Cases of atypical squamous cells (ASC) including:atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude HSIL (ASC-H)
- Cases of low-grade squamous intraepithelial lesion (LSIL)
- Cases of high-grade squamous intraepithelial lesion (HSIL)
- Cases of atypical glandular cells (AGC)

Pap smear technique: Two cervicovaginal smears were prepared for each patient, after fixation with95% ethyl alcohol, slides stained by Pap stain [4,10].

Papanicolaou stain (progressive method):

1. **Rehydration:** put the fixed smear in 80% then 70% then 50% ethyl alcohol and then in tap water for each rinse 10 dips.
2. **Nuclear stain:** Harris Hematoxylin, put the smear in this dye for 45sec. to 1 minute**.**
3. **Rinse:** rinse the smear in 2 water rinses for each rinse 10 dips.
4. **Dehydration:** put the smear in 50%, 70%, 80% and 95% ethyl alcohol and for each rinse 10 dips.
5. **Cytoplasmic stain:** put the smear in Orange G-6 for 1¼ minute.
6. **Rinse:** rinse the smear in 3 rinses 95% ethyl alcohol and for each rinse 10 dips.
7. **Cytoplasmic stain:** Eosin Azur- 65 (EA65) for 3 minutes.
8. **Rinse:** rinse the smear in 3 rinses 95% ethyl alcohol and for each rinse 10 dips.

9. **Dehydration:** rinse the smear in 3 rinses absolute ethyl alcohol and for each rinse 10 dips.
10. **Clearing:** rinse the smear in 3 rinses xylene and for each rinse 10 dips.

Statistical analysis: Statistical analysis was done using student t-test. P value of less than 0.05 was considered statistically significant. The statistical significance of association between two categorical variables was assessed by chi-square test.

Results

The total number of pap smears was 360; 317 were adequate and 43 smears were inadequate for evaluation.

Clinical data of the total study sample:

Theage range was (15-75 years) with a mean age of (37.98 years ± 10.97).The chief complaints of the patients were vaginal discharge, postcoital bleeding, intermenstrual bleeding, postmenopausal bleeding, vaginal and perianal warts (Table 1).

Table 1. The classification of patients according to the clinical symptoms

Signs and symptoms	No.	%
Vaginal discharge	229	63.61
Postcoital bleeding	38	10.55
Intermenstrual bleeding	76	21.12
Postmenopausal bleeding	9	2.5
Vaginal & perianal warts	8	2.22
Total	360	100

Cytological cervical smear results of (360 cases) were categorized according to The Bethesda System (TBS) 2001 into the following [10]: 317 cases (88%) were satisfactory for evaluation (presence of endocervical/ transformation zone components with adequate squamous cellularity), 43 cases (12%) were unsatisfactory for evaluation (absence of endocervical / transformation zone components, autolysis, obscuring blood, obscuring inflammation and small amount of material). Two hundred and forty six cases (68.3%) had negative cervical smears for intraepithelial neoplasia (TBS 2001). Seventy one cases (19.72%) had abnormal cervical smears (AS), smears with intraepithelial lesions. In which:

a. Minimal cervical smear abnormalities. (ASC-US, ASC-H, AGC, LSIL) This category includes (53) cases (74.64% of AS: abnormal smears, 14.72% of studied group).

b. HSIL. (CIN- II, CIN-III, and carcinoma in situ). This category includes (18) cases (25.36% of AS, 5% of studied group).

LSIL, as a single entity, was the most common cytological abnormality 28 cases (39.43% of AS, 7.7% of studied group). ASC includes 14 cases (19.71% of AS, 3.88% of studied group); which is subdivided into: ASC-H includes 8 cases (11.26% of AS, 2.22% of studied group); ASC-US includes 6 cases (8.45% of AS, 1.6% of studied group).AGC includes 11 cases (15.5% of AS, 3.05% of studied group as demonstrated in table 2.

Table 2. The outlines of cytological examination of the Total study group

Cytology	No.	Group (%)	
		studied N = 360	AS N = 71
-ve cervical smear	246	68.3	
Inadequate	43	11.95	
ASC- US	6	1.7	8.45
ASC-H	8	2.2	11.26
LSIL	28	7.8	39.43
HSIL	18	5.0	25.36
AGC	11	3.05	15.5
Total	360	100	100

The mean age at the time of examination for patients with abnormal cervical smears was (39.91 ± 11.5 years). The mean age for patients with HSIL was (45.94 ± 12.3 years) which is higher than that for patients with minimal cervical smear abnormalities (36.88 ± 10.46 years). Also, the mean age for patients with LSIL (38.21 ± 14.3 years) was higher than that for patients with AGC (34.9 years ± 9.72) or ASC

(35.78 ± 9.79 years). The peak age interval for women with AGC was (30-39) years, for women with ASC was (30-39) years, for women with LSIL was (40-49) years (which was statistically significant), and for women with HSIL was (40-49) years (which was statistically not significant).

The frequency of clinical presentations for all patients considered as Abnormal Smear (AS) is as follow:

Vaginal discharge was the clinical presentation for (32) cases (45% of AS). Thirteen cases (18.3% AS) interpreted as LSIL, twelve cases (17% AS) interpreted as HSIL, three cases (4.2% AS) interpreted as ASC-H, two cases (2.8% AS) as ASC-US, and two cases (2.8% AS) as AGC.

Recurrent cervicitis was the clinical presentation for (20) cases (28.15% of AS). Of which, nine cases (12.7% AS) interpreted as LSIL, six cases (8.5% AS) as HSIL, two cases (2.8% AS) as AGC, two cases (2.8% AS) as ASC-US, and one (1.4% AS) as ASC-H.

Intermenstrual bleeding was the clinical presentation for (17) cases (24% of AS). Of which, seven cases (9.8% AS) interpreted as LSIL, four cases (5.6% AS) interpreted as AGC, three cases (4.2% AS) as HSIL, two cases (2.8% AS) as ASC-H, and one (1.4% AS) as ASC-US.

Post coital bleeding was the clinical presentation for (16) cases (22.55% of AS). Of which, five cases (7% AS) interpreted as LSIL, four cases (5.6% AS) interpreted as AGC, three cases (4.2% AS) as ASC-US, two cases (2.8% AS) as ASC-H, and two cases (2.8% AS) as HSIL.

Vaginal and perianal warts were the clinical presentation for (4) cases (5.6% of AS). Of which, two cases (2.8% AS) interpreted as LSIL, one (1.4% AS) as AGC, and one (1.4% AS) as ASC-H.

Post-menopausal bleeding was the clinical presentation for (2) cases (2.8% of AS), of which one case (1.4% AS) interpreted as LSIL, and the other one (1.4% AS) as HSIL (Table3).

Table 3.The frequency and percent of clinical presentation for AS patients

Clinical features	ASC-US		ASC-H		AGC		LSIL		HSIL		Total		P value
	N	%	N	%	N	%	N	%	N	%	N	%	
Vaginal discharge	2	2.8	3	4.2	2	2.8	13	18.3	12	17	32	45.1	0.129
Intermenstrual bleeding	1	1.4	2	2.8	4	5.6	7	9.8	3	4.2	17	24	0.799
Postcoital bleeding	3	4.2	2	2.8	4	5.6	5	7	2	2.8	16	22.5	0.238
Vaginal & perianal warts	0	0.0	1	1.4	1	1.4	2	2.8	0	0.0	4	5.6	0.643
Postmenopausal bleeding	0	0.0	0	0.0	0	0.0	1	1.4	1	1.4	2	2.8	0.865
Total	6	8.5	8	11.2	11	15.5	28	39.3	18	25.5	71	100	
P value	0.542		0.886		0.322		0.942		0.170				0.668

Discussion

In the present study, the results of cytological examination and their interpretation are classified according to The Bethesda System 2001 (TBS) for reporting the results of cervical cytology which is developed as a uniform system of terminology that would provide clear guidance for clinical management. The current study is the 2nd one in Iraq that uses The Bethesda System 2001 (TBS) in the evaluation and interpretation of cervicovaginal smears. However, the first study was done by Al-Guraity (2006) [12] which was retrospective study and including 91 cervicovaginal smears; while present study is a prospective one and the sample size is 360 cervicovaginal smears evaluated by The Bethesda System 2001 (TBS).

Minimal cytologic abnormalities are more common than HSIL. Al-Guraity (2006) [12] reported the same observation (according to TBS 2001). Al-Ani (2001) [13], Al-Ruba'ee (2002) [14], Apgar and Brotzman (1999) [15] reported the same observations (according to TBS 1991). It includes:

LSIL as a single entity, was the most common cytological abnormality in the present study and it includes CIN I and koilocytic atypia. It represented about 61% of SIL (squamous

intraepithelial lesions) findings in cytology. According to similar study in our country; this was lower than that reported by Al-Guraity (2006) which was (88%) [12], because this study is prospective and with a larger sample size, however they are lower than Margolis et al (1999) and other studies due to lower frequency of HPV in the eastern population [16,17], due to widespread difference in the prevalence of risk factors, different sexual habits and probably the availability of screening programs [18,19].

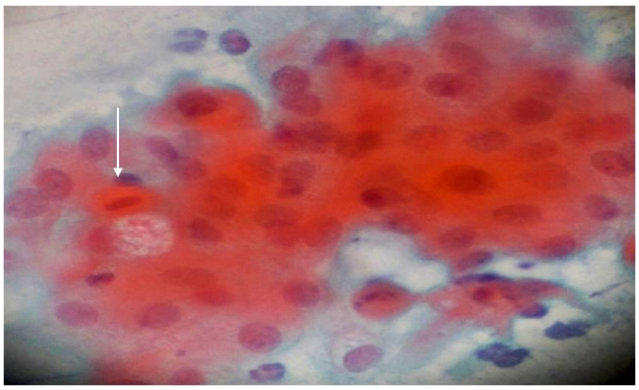

Fig. 1. Cervical smearLSIL: nuclear enlargement with pyknosis and cytoplasmic orangophilia (arrow) X 40 (Pap stain)

ASC was the 2nd common minimal cytological abnormality in this study and it is lower than similar study in Iraq Al- Guraity (2006) [12], because this study is prospective and with a larger sample size.

AGC represented (15.49% AS), this was higher than that reported by Al-Guraity (2006) which was (3.9% AS) Al- Guraity (2006) [12], Al-Rubai'ee (2002) which was (9% AS) - according to TBS 1991[14], also more than that reported by Fadwa (2001) which was (5.7% AS) - according to TBS 1991 [18]. Also our results were higher than Burja et al (1999), who found that incidence of AGUS in their studies were (2.1% Total studied Group) [20].

So different studies gave different rates and number of cases included in different studies may play a rule in the discrepancy between rates. AGC is relatively uncommon cytological interpretation, occurring in approximately 0.18 to 0.74% of cervical smears in screening programs, and representing about 4% of the abnormal cytological findings [21], which is less than our results.

Modifications were incorporated into the 1991 Bethesda System that streamlined the terminology and clarify controversial and borderline cytological abnormalities that lead to introduction of TBS 2001 [10].

In this study HSIL represented (25.36% AS) which is much more than that of Al-Guraity (2006) [12] and other studies in the nearby countries using TBS 1991 for classification Fadwa (2001) [18]. Also, it is much more than that reported by Al-Rubai'ee (2002) using TBS 1991 for classification [14]. Lower percentage was reported by Wertlake (1999), who reported HSIL in (8.5% of AS) [22]. Present study which using TBS 2001 and is prospective taking large size of samples. Current study's results are somehow nearly similar to western studies; unfortunately in these years we have highly increase in STDs (sexually transmitted diseases), and also probably due to the unavailability of screening programs for cervical cancer in Iraq.

ASC/ LSIL ratio was 0.5 in the present study which is lower than that reported by Al-Guraity (2006) [12], which was (1.09). Al-Rubai'ee (2002) reported ASCUS/LGSIL ratio was (1.1) [14], (2.1) reported by Al- Ani (2001) [13] and Davey et al (2000) reported ASCUS/LGSIL ratio was (2.0) [19], with about 80% of laboratories reporting ratios between (0.64) and (4.23) [19].

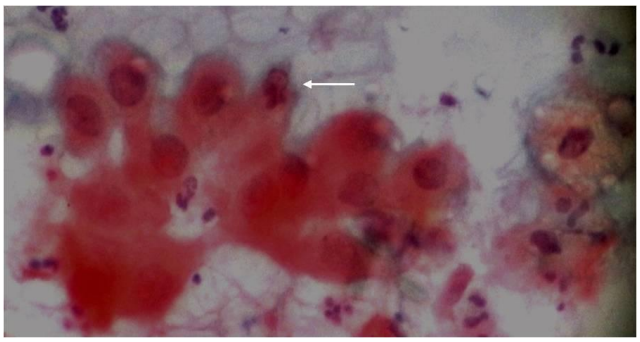

Fig. 2. Cervical smear shows ASC-H: nuclear enlargement with mild hyperchromasia (arrow) X 40 (Pap stain)

LSIL/ HSIL ratio was 1.6 in the present study which is much lower than that reported by Al-Guraity (2006) 7.3 [12]. Al-Rubai'ee (2002) reported LGSIL/HGSIL was 9.1 [14], and Al-Ani (2001) reported LGSIL/HGSIL was 7.0 [13]. The ratio in this study was slightly lower than that reported by Al-Alwan (2001) [23] which were 2.3; and Wertlake (1999) [22] reported a ratio of 3.

As previously mentioned, minimal cytological abnormalities are more common than HSIL in the present study and this also reflects the difference in the incidence of cervical cancer in our country compared to western countries that could be attributed to the promiscuity at early age and multiple sexual relations. In Islamic countries the circumcision, strict observance of religion and, presence of principles and laws that prevents the illegal relationships and extramarital relations may explain the lower incidence of cervical cancer in Iraq compared to western countries [24, 25].

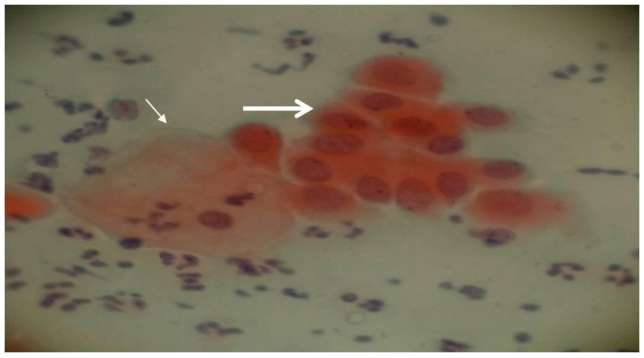

Fig. 3. Cervical smear shows HSIL:increased N/C ratio, irregular nuclear membrane and hyperchromasia (wide arrow) X40 (Pap stain); narrow arrow pointed at superficial squamous cell.

Age has been correlated with an increasing incidence of malignancies, and there is also an age correlation with the severity of the disease in precancerous lesions [23]. In present study, the mean age for patients with abnormal cervical smears was 39.91 years, the mean age for patients with LSIL was 38.21 years, and the mean age for patients with HSIL was 45.94 years. The risk of having LSIL was higher in women aged 40 years and more, as well as women with HSIL (the peak age interval for women with LSIL was 40-49 years which was statistically significant and that for HSIL was 40-49 years which was statistically not significant.

Al-Alwan (1995) reported a peak frequency of mild dysplasia in the age group 30-39 years [16], Al-Ani (2001), Al-Ruba'ee (2002) and Ronald et al reported that women aged 40 years and more are at higher risk of harboring SIL especially the higher grade lesions [13, 14, 26]. Al-Guraity (2006) reported peak frequency of LSIL to be in the (40-49 years) interval, and peak frequency of HSIL was between (50-59 years) [12]. Others, like Blomeur et al (1999) reported a mean age of 35 years to be more likely to have SIL and also Al-Badri (2000) reported the mean age of 39 years respectively [25, 27].

The results of current study, comes in concordance with that of other Iraqi and western studies. Other studies in UK reported that the mean age specific rate for SIL occurs in late 20s [28]. The wide differences, in the mean age of SIL could be explained by the widespread difference in the prevalence of risk factors, different sexual habits, design of study, the availability of screening programs and sample size [12].

The most common complaint that was recorded in the present study and by other studies in Iraq like that of Al-Ruba'ee (2002) [14], Al-Guraity (2006) [12]; was vaginal discharge, followed by intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding, and vaginal and perianal warts. There was no statistically difference found in the incidence of abnormal cervical smears between patients regarding these different clinical features. The incidence of intraepithelial lesions has no significant relation with vaginal discharge or intermenstrual bleeding; (there was a statistically significant relation between vaginal discharge and ASC-H, ($P< 0.05$) which is, similar to results of previous studies from Iraq [12-14], (no statistically significant differences were found in the incidence of SIL of any grade with the above clinical features).

Regarding SIL, many literatures reported that CIN (SIL) is usually free from symptoms and that

the condition owes its existence as an entity only to assign. Al-Alwan (1987) 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 [(29)].

About 20% of cases interpreted as SIL had Intermenstrual bleeding (IMB). Results of the present study agrees with that of Al-Alwan (1987) [(29)] but disagrees with that of Al-Guraity (2006) [(12)] and Al-Anbari (2002) [(24)]; and this may be due to other causes that lead to spotting, irregular menstrual bleeding as hormonal imbalance, or other cause may be due to chronic or severe cervicitis. Postmenopausal bleeding was found in about 4.3% of postmenopausal women who had SIL, which was much lower than that reported by Al-Guraity (2006) [(12)], which could be attributed to different sample size and being a prospective study in comparison to that of Al-Guraity (2006) [(12)] which was retrospective.

Postcoital bleeding was found in about 18% of patients with SIL in current study which is higher than that reported by Al-Guraity (2006) [(12)], but there was agreement with that reported by; Al-Alwan (1987) [(29)], Al-Anbari (2002) [(24)], and Rosenthal et al (2001) [(30)].

Also, Rosenthal et al (2001) reported that although, invasive cancer in women with PCB varies in literature from 0% to 5.4%; in most of the studies it was more frequent than general population. PCB was associated with CIN in 5%-32.7% of cases in different studies [(30)].

A normal cervical smear in women with PCB does not rule out the possibility of SIL or invasive cancer, but most women with postcoital bleeding will have no serious abnormality [(26)].

William (2002) [(31)] believes that, the Pap test is a screening test for malignant and premalignant changes of the cervix. A positive result indicates that there may be a problem and that further, diagnostic procedures (colposcopy or biopsy) must be done. The Pap test is not diagnostic test; it cannot be used to exclude a cancer of the cervix for a person who has symptoms that could be due to a cervical cancer.

This is the single most important lesson to learn: if you have a symptom or a finding that could be due to a cancer of the cervix; a normal Pap test never excludes the possibility of cancer [(31)].

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Received 9th Sep. 2012: Accepted 3rd sep. 2013.