Applications Of The Bethesda System For Cervical Cytological Reporting

Nada S. Al-Rubai'ee* MSc-FICMS
Nada A. Alwan MSc-PhD**

Summary:

Background: *The Bethesda System* ***(TBS)*** *for reporting the results of cervical cytology was developed as a uniform system of terminology that would provide clear guidance for clinical management. According to TBS, the diagnostic report should include a recommendation for further evaluation when appropriate.*

Objective: *The aim of this wok was to use TBS terminology in classification of abnormal cervical Pap smears or with persistent significant inflammatory changes, and correlate the results with the final histopathological findings for optimum evaluation and clinical use.*

Material and Methods: *This prospective study was conducted in the Cytocolposcopic Unit of Teaching Laboratories and Outpatient Department of Medical City Teaching Hospital over a period of one year (Sep. 2001- Sep. 2002). Eighty-three married females were included in the study. A cervical smear was taken followed by a punch biopsy, taken under colposcopic guidness, from the suspicious lesions for histopathological study. All cytological interpretations were reported and categorized according to The Bethesda System (TBS). The rate of different cytological and histopathological findings and a comparison between the results were estimated by a special statistical analysis.*

Results: *Minimal cytological abnormalities were significantly more common than high-grade squamous intraepithelial lesion/HGSIL* ***(95.5%*** *compared to* ***4.5%*** *respectively). Atypical squamous cells of undetermined significance/****ASCUS****, as a single entity, was the most common cytological abnormality* ***(44.8%)****, followed by low-grade squamous intraepithelial lesion/****LGSIL*** ***(41.8%),*** *atypical glandular cells of undetermined significance/****AGUS*** ***(9%)****, and then* ***HGSIL*** ***(4.5%)****.* ***(24.1%)*** *of ASCUS in cytology was associated with underlying CIN (SIL) lesions in histopathology, out of those,* ***(20.7%)*** *had CIN1/LGSIL and* ***(3.4%)*** *had CINII-III/HGSIL.* ***(14.3%)*** *of cases with LGSIL in cytology had CIN II-III (HGSIL) in histopathology, while HGSILs in cytology were associated with 100% high-grade lesions in histopathology. The most common cytologic diagnoses immediately preceding the discovery of* ***histologic HGSIL*** *were LGSIL* ***(57.1%)****, ASCUS* ***(14.3%)****, and then HGSIL* ***(28.6%).***

Conclusion: *Minimal cytological abnormalities in cervical smears were significantly more common than HGSIL. ASCUS, as a single entity, was the most common cytological abnormality. All cases of HGSIL, in cytology, were found to have the same diagnosis by histopathology. So all cases with HGSIL in cytology should be immediately referred for colposcopy for final diagnosis. On the other hand, cases with minor cytological abnormalities were found to have high-grade lesions in histopathology in only 3.3% of women referred with ASCUS smears, and 14.3% of those with LGSIL smears. The latter finding demonstrates that an adjunctive method like colposcopy or close follow-up (particularly with three-smear follow up) is recommended to rule out high-grade lesions.*

Introduction:

Papanicolaou-stained cervicovaginal smear is an easy, safe, cheap, repeatable and acceptable technique. [1] One critical aspect of quality assurance in cervical/vaginal cytology is communication of the cytopathologic findings to the referring physician in unambiguous diagnostic terms that have clinical relevance. Terminology currently used is varied and in some instances ambiguous, resulting in confusion about the clinical implications of the report. [2] The Bethesda System (TBS) for reporting the results of cervical cytology was developed as a uniform system of terminology that would provide clear guidance for clinical management. [3] The most important contribution of TBS System was the creation of a standardized framework for laboratory reports that included a descriptive diagnosis and an evaluation of specimen adequacy. [4,5,6]

Currently, more than 90% of United States laboratories use some form of the 1991 Bethesda System in reporting cervical cytology. [3] Epithelial cell abnormality is a broad term, which includes, according to TBS 1988-1991, Squamous cell abnormalities (ASCUS, Squamous intraepithelial lesions/SIL and Squamous cell carcinoma), Glandular cell abnormalities (AGUS, presence of endometrial cells in postmenopausal woman and adenocarcinoma) and other types of malignant

**From the Department of Pathology, Al-Kindy College of Medicine, Baghdad University*
***From the Department of Pathology, Baghdad College of Medicine, Baghdad University*

epithelial cells. [2,4] The term minimal abnormalities combines (ASCUS, AGUS, and low-grade SIL). Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN1. [7]

With the increased utilization of new technologies and recent findings from research studies, 2001 was considered an opportune time to reevaluate TBS. The 2001 Bethesda System differs in several fundamental ways with regard to reporting equivocal results. First, "atypical squamous cells" are now qualified as "of undetermined significance (ASC-US)" or "cannot exclude HSIL" (ASC-H). Accordingly, the category of "ASCUS, favor reactive" was eliminated in TBS (2001). [3]

Also, according to TBS, the diagnostic report should include a recommendation for further evaluation when appropriate. [2] There is agreement that patients with Pap smears showing HGSIL should undergo immediate colposcopic evaluation because they have a significant incidence of high-grade dysplasia. [8] Several algorithms for the management of mild squamous epithelial abnormalities (ASCUS, and LSIL) have been proposed, but they represent only preliminary attempts at defining the best triage plan. Currently, triage protocols include repeating the Pap smear at specific intervals, referring all patients initially for colposcopy, or using an adjunctive test such as cervicography or human papilloma virus (HPV) testing such as hybrid capture (HPV) test. [9,10,11]

According to the generally accepted criteria, cervical intraepithelial neoplasia/CIN in histopathology was subdivided into three grades. [12,13] It is determined by the amount of epithelium involved with these changes. [14] A new terminology was proposed, referred to as the Bethesda classification. In this scheme, which was designed for cervical cytologic specimen but which some would like to see applied also to histologic samples, the preferred generic term is squamous intraepithelial lesion (SIL). [12] Whichever scheme is ultimately chosen, one hopes that it will be applied to both cytologic and histologic specimens. [12,15]

Material and Methods

This prospective study was conducted in the Cytocolposcopic Unit of Teaching Laboratories and Outpatient Department of Medical City Teaching Hospital over a period of one year (Sep. 2001- Sep. 2002). Eighty-three married females were included in the present study. The cases selected were women referred to the colposcopic unit with abnormal cervical Pap smears (epithelial cell abnormalities) or with persistent significant inflammatory changes within cervical Pap smear Pap smears. None of them was pregnant. An " Ayre's" wooden spatula was used in obtaining the cervical smear. Another sample from posterior and lateral vaginal walls was obtained. Sampling from the endocervical canal was obtained using cytobrush.

All cytological interpretations were reported and categorized according to The Bethesda System (TBS). If several findings are present, the general categorization is based on the most clinically significant result (e.g., epithelial cell abnormality). Together with Zeis colposcope plus, which was used in this study, a tray containing the essential solutions and supplies for colposcopy was prepared. After identification of the abnormal area, directed punch biopsies taken by biopsy forceps. The biopsy should be taken from the most suspicious area. If no obvious specific lesion was visualized, a punch biopsy was taken from random positions of the transformation zone. The specimen was then immersed in fixative (formaline) and sent to the histopathology department. Bleeding was usually mild stopped after gentle pressure for 2 minutes using sterile cotton pads.

Histopathological diagnosis: All tissue pieces were processed, stained with hematoxylin and eosin stains, and examined under light microscopy. Diagnostically, findings were classified into *benign changes* (chronic non-specific cervicitis, immature metaplasia, acanthosis, condylomata, and glandular hyperplasia), and *CIN (SIL)* lesions. CIN I was considered as LGSIL and CIN II/III as HGSIL. Atypical immature metaplasia was considered separately (poorly defined squamous lesion of the cervix with uncertain biological and clinical significance).

Data were translated into codes using a specially designed coding sheet, and then interred into a computerized database structure for a Statistical analysis.

Results:

The relative frequency of different cellular cytological findings in the present study was:

1. Sixteen cases (19.3%) had negative Pap smears for intraepithelial neoplasia or malignancy (TBS 2001), or benign cellular changes (TBS 1991) as shown in (Table-1).

2. Sixty-seven cases (80.7%) had abnormal Pap smear cellular (epithelial) changes. The relative frequency of abnormal cellular changes were classified according to TBS, as shown in (Table-1 & Fig. 1), into the followings:

a. Minimal Pap smear abnormality (ASCUS+AGC+LGSIL): sixty-four cases (77.1%), constituting 95.5% of the abnormal Pap smears.

ASCUS: thirty cases (36.1%), constituting 44.8% of the abnormal Pap smears.

AGC: six cases (7.2%), constituting 9% of the abnormal smears.

LGSIL (CIN I +/- koilocytosis): twenty-eighth cases (33.7%), constituting (41.8%) of the abnormal Pap smears.

b. HGSIL: three cases (3.6%), constituting 4.5% of the abnormal Pap smears.

Minimal cytological abnormalities were significantly more common than HGSIL (HGSIL constituting 4.5% of the abnormal Pap smears). ASCUS, as a single entity, was the most common cytological abnormality, followed by LGSIL, AGUS, and then HGSIL.

The final histopathological diagnoses of the specimens taken from the research sample, directed by colposcope, is summarized in Table (2):

1. Forty-four cases (53%) were classified within the group of benign lesions.
2. Thirty-seven cases (44.6%) were with SIL or cervical intraepithelial neoplasia. These were subclassified into 30 cases (36.2%) with LGSIL (CINI), and seven cases (8.4%) with HGSIL (CIN II-III). All HGSIL in this study was CIN II except one case, which was CIN III.

Two cases (2.4%) were considered as atypical immature metaplasia.

High grade SIL/CIN II-III in histopathology was found in 3.4% cases of ASCUS, 14.3% cases of LGSIL and 100% cases of HGSIL in cytology, as shown in Table-3.

For *HGSIL* diagnosed in histopathology, the cytological findings were; five cases out of seven with minimal cytologic abnormalities (71.4%) (one case (14.3%) with ASCUS, and four cases (57.1%) with LGSIL), and two cases (28.6%) with HGSIL, as shown in Table-4.

Figure (1): The relative frequency of different abnormal cellular findings in cytology.

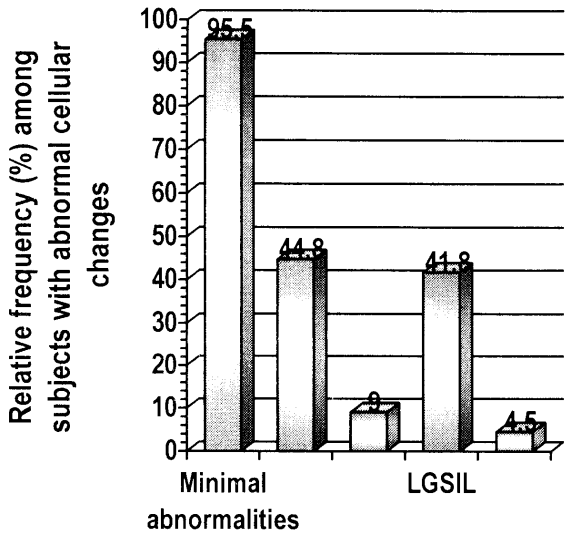

Table 1: The rate of different cellular findings in cytology.

Findings on cytology-Bethesda system (n=83)	N	%
Benign cellular changes (negative for intraepithelial neoplasia or malignancy)	16	19.3
Abnormal cellular changes	67	80.7
Minimal pap smear abnormalities (AGUS, ASCUS and LGSIL)	64	77.1
ASCUS	30	36.1
AGUS	6	7.2
LGSIL (CIN-I +/- koilocytosis)	28	33.7
HGSIL (CIN-II and III)	3	3.6

Table (2): The rate of different findings in histopathology

Histopathological findings (n=83)	N	%
Benign lesions	44	53.0
Chronic cervicitis	19	22.9
Immature metaplasia	10	12.0
Glandular hyperplasia	1	1.2
Acanthosis	6	7.2
Condyloma	8	9.6
Cervical intraepithelial lesions (SIL)	37	44.6
LGSIL (CIN-I with or without koilocytosis)	30	36.2
HGSIL (CIN-II and III)	7	8.4
Atypical immature metaplasia	2	2.4

Table (3): The rate of positive SIL (CIN) changes, LGSIL and HGSIL diagnosed in histopathology by grade of cellular findings on cytology

	Histopathology							
	Positive SIL(CIN)				Positive LGSIL		Positive HGSIL	
Findings on Cytology	N	%	OR	P	N	%	N	%
Benign cellular changes (n.16)	1/16	6.3	Reference		1/16	6.3	0/16	0
Minimal abnormality (n. 63)	34/63	54.0	17.6	<0.001	29/63	46	5/63	7.9
ASCUS (n. 29)	7/29	24.1	4.7	0.13[NS]	6/29	20.7	1/29	3.4
AGUS (n. 6)	2/6	33.3	7.5	0.16[NS]	2/6	33.3	0/6	0
LGSIL (n. 28)	25/28	89.3	125	<0.001	21/28	75	4/28	14.3
HGSIL (n. 2)	2/2	100	**	0.02	0/2	0	2/2	100
	r=0.67 P < 0.001							

Table (4): The relative frequency of different cytological findings for SIL (CIN), LGSIL and HGSIL, diagnosed in histopathology.

	Histopathology					
	SIL(CIN) (n=37)		LGSIL (n=30)		HGSIL (n=7)	
Findings on cytology (Bethesda system)	N	%	N	%	N	%
Benign cellular changes (negative for CIN changes or malignancy)	1	2.7	1	3.3	0	0.0
Abnormal cellular changes	36	97.3	29	96.7	7	100
Minimal pap smear abnormalities	34	91.9	29	96.7	5	71.4
ASCUS	7	18.9	6	20.0	1	14.3
AGUS	2	5.4	2	6.7	0	0.0
LGSIL	25	67.6	21	70.0	4	57.1
HGSIL	2	5.4	0	0.0	2	28.6

Discussion:

Minor or minimal cytologic abnormalities were much more common than HGSIL (95.5% compared to 4.5%). Al-Ani (2001) and Apgar & Brotzman (1999) reported the same observation. [17,18] ASCUS represented the most common abnormal Pap smear finding (44.8%) in the present study. The same was observed in most studies, as by Al-Ani (2001) [17] and Kinney et.al. (1998). [7] The median reporting rates for epithelial abnormalities in screening population were as follows: [19] ASCUS, 4.5%, AGUS, 0.3%, LGSIL, 1.6%, and HGSIL 0.5%. ASCUS representing the most common abnormal Pap smear finding.

AGUS represented 9% of the epithelial cell abnormality. This was relatively higher than that reported by Fadwa (2001), which was 5.7%. [20] Burja et al (1999) found that the incidence of AGUS in their study was 2.1%. [21] Different studies gave different rates. AGUS is a relatively uncommon cytological diagnosis, occurring in approximately 0.18 to 0.74% of cervical smears in screening programs, [22] and presenting about 4% of the abnormal cytological finding.

LGSIL represented (41.8%) of the abnormal cytological smears in the present study. It represented the majority of SIL findings in cytology (90%). Al-Alwan (1995) reported similar rate, which was 87.5%. [23]

HGSIL in cytological smears represented 4.5% of the abnormal Pap smears (3/67) in the present study. The same percentage was reported by Al-Ani 2001 (1/22). [17] Higher percentages were recorded by other studies [19] as Wertlake (1999), [24] who reported HGSIL in 8.5% of abnormal Pap smears. This is expected because of low incidence of cervical cancer in our society compared to western societies.

ASCUS/LGSIL ratio in cytology was 1.1 in the present study compared to 2.1 reported Al-Ani (2001) [17] and 2.0 reported by Davey et al (2000), with 80% of laboratories reporting ratios between 0.64 and 4.23. [19] LGSIL/HGSIL ratio in cytology was about 9.1 in the present study, slightly higher

than that reported by Al-Ani 2001 (7.0) [17] and Al-Alwan 1992 (5.0) [25] in Iraq, but much higher than that reported by Al-Alwan (2001) (in a study done in Geneva University Hospital), [26] which was 2.3 and Wertlake (1999), [24] which was 3. As previously mentioned, minor cytologic abnormalities were much more common than HGSIL in the present study, probably reflecting the difference in the incidence of cervical cancer in the our society compared with western society due to the widespread difference in the prevalence of risk factors, different sexual habits, and probably the availability of screening programs

The overall histopathological results in our study were 53% benign lesions, 44.6% SIL (CIN) lesions and 2.4% atypical immature metaplasia (AIM). Studies report different rates of different findings. This is related mainly to the number of cases, the study design, and selection of cases. In the present study CIN1 (LGSIL) represents about 80% and CINII-III/HGSIL about 20% of the cervical intraepithelial lesions. This was in agreement with Al-Anbari (2002), [27] who reported, 79.8% and 20.2% respectively.

Atypical immature metaplasia represents a heterogeneous group of lesions that defy precise classification. It is found within the cervical TZ and shows immature metaplastic squamous cells with less cytological atypia than is seen in typical high-grade SIL. AIM shares some morphological and pathogenetic features with SIL (CIN), particularly those that are high-grade, and may be seen in association with SILs. [28,29]

Interpretation of cytological findings in relation to histopathological diagnosis: Each cytological category according to TBS was correlated with the histopathological diagnosis. The interpretation of these results can be summarized in the followings:

Out of all Pap smears, with *benign cellular changes, (6.3%)* were found to have CIN (SIL) in histopathology. This is in agreement with Soofer (1997) [30] who reported an approximately 4% follow-up smear incidence of SIL among women with initial reactive cellular smears. Al-Alwan et al (1994) reported that 4.9% of cases of cervicitis in cytology showed CIN lesions in histopathology. [31] Higher incidence was reported by Al-Badri (2000) (26% of cases with benign cellular Pap smears were shown to have CIN in histopathology). [32]

Satisfactory percentage of *ASCUS* in cytology was associated with underlying CIN (SIL) lesions *(24.1%),* six cases had CIN1/LGSIL (20.7%) and one had CINII-III/HGSIL (3.4%). Different studies have reported that 12-61% of patients seen for an ASCUS Pap smear has CIN on histopathology. [8,33, 34,35]

Regarding patients having with *AGC* in cytological smears, *(33.3%)* had CIN (SIL) lesions and (66.6%) showed benign lesions in histopathology. This is in agreement with Kaferle and Malouin (2001), [36] who reported that 50-80% women with AGUS smears will have no histological abnormality on further evaluation and 20-50% are found to have significant histologic abnormalities, such as CIN, adenocarcinoma in situ or adenocarcinoma. It has been reported that the type and severity of lesions found in women with ASCUS and AGUS differ greatly. While most cases with ASCUS have reactive benign changes, AGUS is associated with a significant risk of HSIL (mimicking an endocervical glandular lesion cytologically). AGUS in young women is often managed aggressively, even when results of the colposcopic examination are normal. [37,38]

In the present study, for patients with cytologic findings of *LGSIL, 89.3%* had CIN (SIL) in biopsy, which was almost similar to that reported by Al-Alwan et al (1994) but higher than that reported by Al-Badri (2000), [5] which was 84% & 72.4% respectively. [31] Of those diagnosed with LGSIL in cytology, *14.3%* had CINII-III (HGSIL) in histopathology. This is in agreement with that reported by Al-Badri (2000), which was 14.4%. [32] It is also in agreement with studies done by Siadle and Karakostova (2000) [35] and Jones et.al (1995) [39] (although slightly lower), who found 16% and 18.6% respectively of high-grade lesions demonstrated by colposcopically directed cervical biopsy in LGSIL cytological smears. A slightly higher figure was reported by Kobelin et al (1998), which was 20%. [8] As is noted from these results, the present study showed lower incidence of high-grade lesions in relation to other studies. This could be expected regarding the low incidence of cervical cancer in our society in relation to other societies.

Minimally abnormal Pap smears revealed histologic findings ranging from normal to high-grade lesions. Patients with minimal cytologic abnormalities had CIN (SIL) in *54%.* This is slightly higher than that reported by Wright et.al (1995) [40] who noted an overall incidence of 45% of biopsy-confirmed CIN in patient with minimal Pap smear abnormalities. It is also higher than that reported by Kobelin et al (1998), [8] which was 34%. This higher rate could be due to the study design, because many of cases selected for colposcopy had repeated smears of abnormal findings. This was observed by many studies when colposcopy was performed only after repeated abnormal Pap smears. [8] It is also important to mention that only 7.9% of histologic high grade SILs in histopathology were diagnosed in patients with ASCUS and LGSIL smears in our study. This is lower than that reported by Kobelin et al (1998) [8] where histologic high-grade SIL was diagnosed in 29.1% of women with ASCUS and LGSIL smears. It was expected to have lower incidence of HGSIL in the present study because of lower incidence of cervical cancer in our society. [20]

HGSIL in cytology were significantly correlated with CIN (SIL) in histopathology. This is

in agreement with Koblein et al (1999), [8] who reported that HGSILs in cytology were significantly correlated with high-grade abnormalities or malignant histological findings. In a study done by Al-Alwan et al (1994), all cases with CINII & III in cytology showed high-grade and malignant lesions in histopathology. [31] Also Al-Alwan (2001) recorded a specificity rate of cytology in the detection of HGSIL to be 98.4%. [26]

The most common cytological findings preceding CIN I/LGSIL in histopathology in the present study, were LGSIL (70%), ASCUS (20)%, and AGC (6.7%). Al-Anbari (2002) [27] reported (92.9%, 4.7%, and 2.4% respectively). Al-Alwan et al (1994) [31] reported that 84% of CINI in histopathology was preceded by CINI in cytology. Al-Badri (2000) reported 55%. [5] These variable figures could be attributed to the number of cases and study design. The most common cytological findings preceding CIN II-III/HGSIL in histopathology in the present study were minimal Pap smear abnormalities (71.4%) then high-grade abnormalities (28.6%). This is in agreement with studies done by Kinney et al (1998) [16] and Apgar and Brotzman (2001), [21] where the minimal abnormalities were coincident with (68.6%) of cases with histologic high-grade cervical neoplasia. The most common cytologic diagnoses immediately preceding the discovery of histologic CIN II/III/HGSIL in the present study were LGSIL (57.1%), HGSIL (28.6%) and then ASCUS (14.3%). In Other studies they were ASCUS (38.8%), followed by HGSIL (31.4%), LGSIL (20%) and AGC (9.7%). [16,21] So, according to the results we recommend that all patients with HGSIL in cytological smears should be immediately referred to colposcopy, where a histologic confirmation could be obtained. On the other hand only 7.9% of histologic high grade SILs in this study were diagnosed in patients with ASCUS and LGSIL cytological smears. Different methods for management of patients, with ASCUS and LGSIL (minimal Pap smear abnormality) smears, were recommended, [7,18,40] these are:

a. Immediate referral for colposcopy. Colposcopy offers a prompt accurate diagnosis of SIL. On the other hand it is not available all over our country and it would be an excessive intervention that is not mandated for use in women following first minor cytological abnormality.

b. Cytological surveillance for (ASCUS+LGSIL) is generally safe (particularly with three-smear follow up). It is an available procedure in our country. Women with minimal Pap smear abnormalities should be referred for colposcopy if the abnormalities persist on follow up.

c. To use HPV testing. At the present time the best method recommended for assessing patients with minimal Pap smear abnormalities, especially the high-risk group, is to do HPV typing. These technologies are unavailable in our country. It is recommended to adopt these new methods to improve the sensitivity and specificity of cervical Pap smear.

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