Diagnostic Value of Cytology and Colposcopy in Patients with Abnormal Cervical Pap Smears

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ABSTRACT

Background: An optimal cancer detection system for preclinical cervical lesions should combine a cytological examination with a colposcopic follow-up examination. Detection at early pre-invasive stage provides an opportunity for treatment to prevent progression to invasive cancer.

Objective: The present study aimed at evaluation of cytology, colposcopy, and combined cytology and colposcopy in predicting histopathological diagnosis of cervical intraepithelial neoplasia/squamous intraepithelial lesion (CIN/SIL) or other neoplastic changes in patients with abnormal cervical cytological findings.

Methods: This prospective study was conducted in the Cyto-colposcopy Unit of Teaching Laboratories and Outpatient Department of Medical City Teaching Hospital over a period of one year (Sep. 2001- Sep. 2002). Eighty-one married females were included in the study. A cervical smear was taken followed by a colposcopic examination of the cervix and then a punch biopsy was taken from the suspected lesions for histopathological study. Estimation and evaluation of the validity parameters of cytology, colposcopy, and combined cytology and colposcopy were performed using different cutoff points by special statistical analysis.

Results: Sensitivity, specificity and accuracy of cytology in the diagnosis of CIN/SIL were 73%, 93.2% and 84.0% respectively. The False–negative rate was 27%. Sensitivity, specificity and accuracy of colposcopy in the diagnosis of CIN were 83.3%, 58.5% and 70.1% respectively choosing doubtful findings as a cut-off point. The combination of cytology and colposcopy gave the following results: sensitivity, specificity and accuracy were 94.6%, 61.4% and 76.5% respectively; the negative predictive value (NPV) was 93.1%. When suspicious colposcopic findings were chosen as the cut-off point, the specificity and the positive predictive value (PPV) were higher at the expense of sensitivity and NPV

Conclusion: The conventional Pap smear, a valuable tool in the evaluation of patients with abnormal cervical cytology, was found to be of relatively low sensitivity in predicting CIN/SIL. Colposcopy is a valuable tool too. However, the validity parameters showed variable figures depending on the different cut-off points applied for the diagnosis of CIN/SIL. The ideal cut-off point was when doubtful and higher-grade colposcopic lesions are considered positive. The combination of cytology and colposcopy resulted in an increased sensitivity and NPV. The specificity could be further increased or improved when the threshold was set to distinguish higher-grade lesions (suspicious lesions) from lesser abnormalities.

Key words: Colposcopy, Abnormal Pap smears, Biopsy

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Introduction

Cervical intraepithelial neoplasia (CIN) and cervical cancer remain important health problems for women worldwide with high morbidity and mortality for advanced lesions. [1] Incidence rates for cervical cancer show a wide geographic variation because of widespread differences in the availability of screening programs and the prevalence of risk factors. The lowest reported incidence rates are from the Middle East, where the incidence is particularly low among Muslims and Jews, as compared to other religious groups**.** [2]According to the latest Iraqi Cancer Registry Center records (2000), cervical cancer ranks the 10th among the most common female cancers (accounting for 2.9% of total female malignancies). [3] Incidence of cancer of the cervix is comparatively low In Iraq, as in most Muslim countries. It was found to be 1.31/100.000 of the female population (Iraqi Cancer registry board 2000).

Cytological screening, using cervical Pap smears; continue to be an effective tool for detecting cervical neoplasia in a pre-invasive state due to the long natural history of progression from low-grade dysplasia to invasion. [4,5] Still, it does not demonstrate the characteristics of an optimal screening test as it has a low sensitivity. [6] So a second screening method can compensate for this failure. This is by far the most appropriate application of colposcopy. It will enable the detection of a good percentage of abnormalities missed by cytological screening. [7] The effectiveness of the diagnostic combination of colposcopy, cytology and histopathology, in reducing cervical cancer, is evidenced by the marked decrease in the death

rate from cervical cancer during the last three decades. [8] Each diagnostic mode evaluates a different parameter and has different advantages. The cervical Pap smear examines only surface cells; these are obtained from a wide surface area of both the endocervix and ectocervix.

Although the epithelium may look grossly normal, cytological examination may reveal abnormalities. The colposcope is basically a binocular microscope on a stand, which enables an examiner to visualize the epithelium of the lower genital tract (vagina, ectocervix, and usually some of the endocervix) under magnification. Meanwhile the cervix is usually visualized under low power magnification after acetic acid and lugol's iodine application to stain the cervix temporarily [7,8] If the colposcopic examination is satisfactory (i.e., the entire transformation zone is examined and the extent of all lesions is seen) directed biopsies of lesions, especially the most severe lesions, are performed. [9,10] The first objective of colposcopic examination is to locate the source of the abnormal cells seen by Pap smear. [11] The diagnostic accuracy of cytology and colposcopy may then be checked by the histopathology results of every colposcopically suspicious lesion. [12]

Abnormal Pap smear (Epithelial cell abnormalities according to The Bethesda System terminology) is a broad term that includes Atypical Squamous Cells of Undetermined Significance (ASCUS), Atypical Glandular Cells of Undetermined Significance (AGUS), Low-Grade Squamous Intraepithelial Lesion (LGSIL), High Grade Squamous Intraepithelial Lesion (HGSIL), and malignant cells. Minimal Pap smear abnormality covers ASCUS, AGUS, and LGSIL. [12,13]

Methods

Study Design: This is a prospective study that was carried out in the Cytocolposcopic Unit belonging to the Teaching Laboratories and Outpatient Department of Medical City Teaching Hospital during the period of (September 2001 to September 2002). One of the main aims of the study was to compare the performance of cytopathology and colposcopy with histopathology, with estimation and evaluation of the validity parameters.

Patients: Eighty-one married females were included in the study, which was conducted in the Cytocolposcopic Unit in the Teaching Laboratories and Outpatient Department of Medical City Teaching Hospital during the period of (September 2001 to September 2002). Cases selected were women referred to the colposcopic unit with abnormal cervical Pap smears (epithelial cell abnormalities) or with persistent significant inflammatory changes within Pap smears. None of them was pregnant. All patients underwent a standardized interview and were asked to complete a questionnaire.

Cytological Examination: The cervical smears were obtained and stained with Papanicolaou stain and were subjected to cytopathological examination. All cytological interpretations were reported and categorized according to *The Bethesda System (TBS).*

Colposcopy: Colposcopic examination of the cervix, with the application of acetic acid and lugol's iodine solutions, was conducted. Colposcopic findings were classified into one of four categories; Unsatisfactory, Miscellaneous, Doubtful, and Suspicious lesions, which generally correspond to the international terminology put forward by the *1990 World Congress for Colposcopy and Cervical Pathology*. Condyloma is a significant lesion and included within the miscellaneous group.

Punch Biopsy and Histopathological Diagnosis: After identification of the abnormal area by colposcopy, directed punch biopsies taken by biopsy forceps.

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 The histopathological diagnosis was used as the gold standard for final diagnosis to which cytological and colposcopic findings were compared.

Statistical Analysis: To use colposcopy as a decision rule in predicting histopathological diagnosis of CIN/SIL, its four ordered categories, namely miscellaneous, condylomata, doubtful and suspicious findings were viewed as a dichotomous variable at three different cutoff values. A positive colposcopy is that with finding equals to or exceeds in grade the cutoff value. The colposcope test at these three cutoff values was tested for its validity in diagnosing SIL changes verified by histopathology.

Data were translated into codes using a specially designed coding sheet, and then interred into a computerized database structure. An expert statistical advice was sought for. Statistical analyses were done using SPSS version 7.5 computer software (Statistical Package for Social Sciences).

Test performance Characteristics: The performance characteristics of a test or criteria (validity parameters), sometimes called test operating characteristics include, among others: Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) and proportion of false positive and false negative results.

Results

The rate of positive SIL/CIN changes in histopathology; LGSIL and HGSIL, by grade of cellular findings in cytology and colposcopy are summarized in **Tables (1-2)** respectively. The sensitivity and specificity of conventional Pap smear results were 73.0% and 93.2%. The accuracy was 84.0% **Table-3**. HGSIL in cytology in the present study was associated with 100% prediction of similar changes in histopathology **Table-1**. When the cutoff point in colposcopy was used to differentiate mild changes from condylomata lesions and atypical lesions, it showed high sensitivity but low specificity (88.9% and 53.7% respectively) in predicting CIN/SIL lesions. Colposcopy test at the two lowest cutoff values of condyloma or doubtful was almost equally sensitive (88.9% and 83.3% respectively) in predicting possible SIL changes **Figure-1, Table-3**.

Its negative predictive value (NPV) therefore was moderately high (84.6% and 80% respectively) i.e., given a negative colposcopy at The False–negative rate was 27%. Sensitivity, specificity and accuracy of colposcopy in the these two low cutoff values one can exclude the presence of SIL changes by 84.6% and 80% confidence. The specificity of both was relatively low. However, it is slightly higher in doubtful findings. This shows high sensitivity in predicting SIL while retains a reasonable rate of specificity. So the results of sensitivity, specificity, PPV, NPP, and accuracy were 83.3%, 58.5%, 63.8%, 80% and 70.1% respectively. Considering colposcopy as positive only at the highest cutoff value of suspicious finding (with increasing cutoff points), sensitivity will significantly decrease while specificity will increase to reach 52.8% and 90.2% respectively. This was associated with a high PPV of 82.6%, i.e., given a positive test at a diagnosis of SIL (CIN) with 82.6% confidence **Figure-1, Table-3**.

Combining the results with that of cytology (when the subject was considered positive if showed a positive result by one test only); the sensitivity, specificity, PPV, NPP, and accuracy of combined cyto-colposcopic findings were (94.6%, 61.4%, 67.3%, 93.1%, and 76.5% respectively), when doubtful colposcopic findings were used as a cut-off value **(Table-3).**

***(Table 1)** The Rate of Positive CIN (SIL) Changes, LGSIL and HGSIL Diagnosed in Histopathology by Grade of Cellular Findings on Cytology*

Findings on Cytology	***Positive SIL(CIN)***			***P***	***Positive LGSIL***		***Positive HGSIL***	
	N	***%***	***OR***		***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**

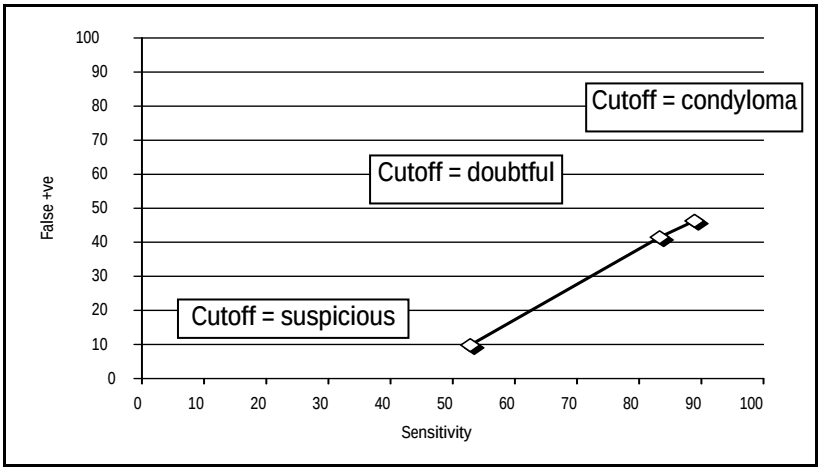
***(Table 2)** The Rate of Cin (Sil), Lgsil and Hgsil in Histopathology by Grade of Colposcopic Findings*

Colposcopical findings (n)	Positive SIL N	%	OR	P	Positive LGSIL N	%	Positive HGSIL N	%
Unsatisfactory (4)	1/4	**25.0**	1.8	0.54[NS]	1/4	25	0/4	0
Miscellaneous								
Condyloma (4)	2/4	**50.0**	5.5	0.17[NS]	2/4	50	0/4	0
(others) (26)	4/26	**15.4**	Reference		4/26	15.4	0/26	0
Doubtful (24)	11/24	**45.8**	4.6	0.02	10/24	41.7	1/24	**4.2**
Leukoplakia	1/4	**25.0**	1.8	0.73[NS]	1/4	25	0/4	0
Inconspicuous iodine	0/2	**.0**	**	0.8[NS]	0/2	0	0/2	0
Other doubtful (Fine P/M and UTZ)	10/18	**55.6**	6.9	0.004	9/18	50	1/18	5.6
Suspicious (23)	19/23	**82.6**	26.1	<0.001	13/23	56.5	6/23	**26.1**
			r=0.44 P < 0.001					

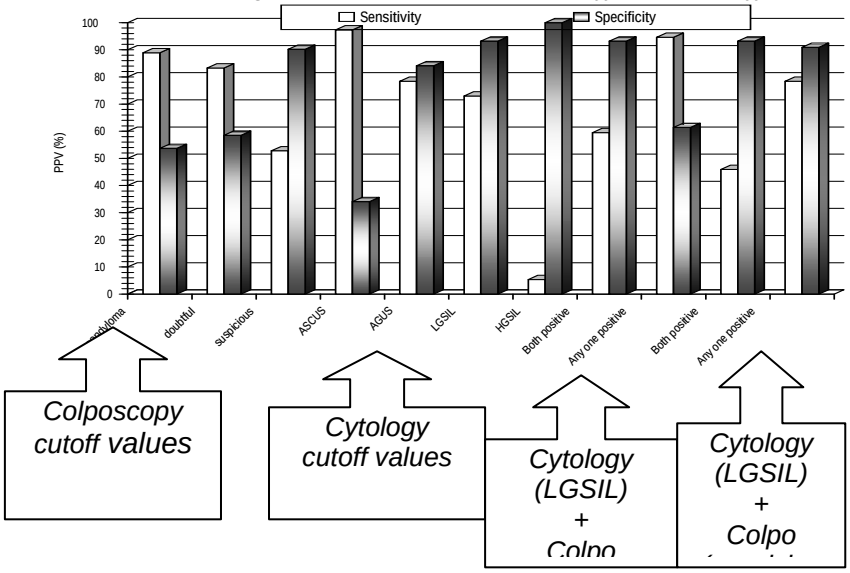
***(Table 3)** Shows the Estimated Results of Cytology, Colposcopy, and Combined Cyto-Colposcopy at Different Cutoff Points*

	Sensitivity	Specificity	PPV	NPV	False –ve	False +ve	Accuracy
Cytology-= LGSIL	73	93.2	90	80.4	27	6.8	84
Colpo = condyloma	88.9	53.7	62.7	84.6	11.1	46.3	70.1
Colpo = doubtful	83.3	58.5	63.8	80	16.7	41.5	70.1
Colpo = suspicious	52.8	90.2	82.6	68.5	47.2	9.8	72.7
Cytology (LGSIL) + Colpo (Doubtful)-both positive	59.5	93.2	88	73.2	40.5	6.8	77.8
Cytology (LGSIL) + Colpo (Doubtful) (any one positive)	94.6	61.4	67.3	93.1	5.4	38.6	76.5

***(Figure 1)** ROC (Receiver Operator Characteristics) Curve of Colposcopy at Different Cutoff Values Showing the Trade Off between Sensitivity and False +Ve (Complement of Specificity) in the Diagnosis of SIL (CIN) (Verified By Histopathology)*



***(Diagram 1)** Bar Chart Comparing the Sensitivity and Specificity of Colposcopy and Cytology Separately and In Combination at Different Cutoff Values*



Discussion

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. As more than two-thirds of the patients had late diagnoses (i.e., stages IIb, III, or IV), a feasible control strategy would be to encourage Iraqi women to seek early detection of cervical intraepithelial neoplasia. [14,15] Detection at early pre-invasive stage provides an opportunity for treatment to prevent progression to invasive cancer.[16] Much credit for these dramatic gains belongs to the effectiveness of the Papanicolaou Pap cytological test in detecting cervical precancers,to the accessibility of the cervix to colposcopy and biopsy. [17,18]

Sensitivity, specificity and accuracy of ***cytology*** in the diagnosis of CIN/SIL in the present study were 73%, 93.2% and 84.0% respectively. This is higher than that reported by Al-Badri (2000), [19] which were 69%, 73% and 71% respectively. Maiman *et al* 1998 reported comparative figures of 60%, 80%, and 96% respectively. [20] We can observe from these variable figures that the conventional Pap smears are generally of low sensitivity but of high specificity. The same was observed by other literature. In the 12 studies for evaluation of the accuracy of conventional Pap smears and new methods of Pap testing, sensitivity ranges from 30% to 87% and specificity ranges from 86% to 100%. [21,22] So that the other tests have been proposed to help improve the sensitivity of screening Pap smears, such as cervicography and colposcopy. [23] The specificity of Pap smear in the present study was 93.2%. This is in agreement with some studies, which showed specificity greater than 90% and may be as high as 99%. [21,23,24] Only HGSIL in cytology in the present study was associated with (100%) prediction of similar changes in histopathology. Al-Alwan and Al-Alwan *et al* studies (1987-1994) reported the same finding. [25, 26] Agency for Health Care Policy and Research also reported the same findings. [27]

The False–negative result in the present study was 27%. This is lower than that reported by Al-Badri (2000), [28] which was 30%, but higher than that reported by Seckin et al, (1997) who reported 20%. [29] False-negative rates in Pap smears, ranging from 6-55%, have been sporadically reported. [30] A range of 20-45% has been quoted most frequently, depending on the study design. [31] Accordingly the results are in the acceptable range. A growing literature sights the shortcoming of the Pap smear, focusing on the causes of false-negative smears and the problem of cervical cancer in the 25 to 33% of individuals who have been screened. [32]

Accuracy of cytology in the present study was 84%. Most studies of the conventional Pap tests are severely biases: the best estimates suggest that it is only moderately accurate. [22]

Al-Badri (2000), reported that the accuracy of cervical cytology was 71%. [28]

The *colposcopy* in the present study showed high sensitivity but low specificity when the cutoff point is used to differentiate mild changes from HPV and atypical lesions (88.9% and 53.7% respectively). This is within the range observed among nine studies for distinguishing normal cervix and inflammation from all other diagnoses in colposcopy. The estimated values of sensitivity in these studies were high (87%-99%), whereas those of specificity were lower (23%-87%). [33] An example of these studies is the one conducted by Cristoforoni *et al* (1995), who reported sensitivity, specificity, NPV and PPV values of 90%, 34%, 77% and 88% respectively. [34] On the other hand, when doubtful and higher-grade lesions are considered positive, there is a slightly reduction in sensitivity but with increase in specificity. This *cut-off point was considered ideal* in the present study in predicting a histopathological diagnosis of CIN/SIL by colposcopy. This shows high sensitivity in predicting SIL while retains a reasonable rate of specificity. The specificity was further increased or improved when the threshold was set to distinguish higher-grade lesions (suspicious lesions) from lesser abnormalities in the present study. This was at the expense of sensitivity, so that sensitivity and specificity will be 52.8% & 90.2% respectively. The same observation was reported by Cristoforoni *et al* (1995), [34] to be 64% & 92% respectively. Other studies confirmed that the specificity could be improved when the threshold was set to distinguish high-grade lesions and cancer from lesser abnormalities (the mean specificity was 69% versus 48%). [35] Al-Badri 2000 reported a specificity of 81%, which was slightly lower than that in the present study, and almost a similar PPV for suspicious lesions, an 85%. [28] Al-Alwan 2001 reported similar results in specificity and PPV of 95.3% and 84.2% respectively, for high-grade lesions. [14]

The combination of *cytology and colposcopy* in this study showed high sensitivity and NPV when cases were considered positive if showed a positive result by one test only (when using doubtful findings as a cut-off value). This means identifying more patients who actually have SIL, which is the main goal, at the expense of an increase in the number of false positive results. However, the latter would be further clarified by histopathological study of the punch biopsies. The results of sensitivity, specificity, and accuracy were (94.6%, 61.4%, and 76.5% respectively). Variable figures are reported in different studies. Ole et al, (1994) reported sensitivity, specificity and accuracy of 75%, 78%, and 77%.[36] Davidson *et al* 1994 reported 91%, 96%, and 98% respectively[37] .Al-Badri 2000 reported 89%, 67%, and 80% respectively. [28] The variation in figures could be due to different cutoff point values used in different studies, size of the sample, and study design.

In the present study the sensitivity of combined cytology and colposcopy was greater than the individual sensitivity of each of them, while the specificity was less than in cytology but almost equal to colposcopy. That was in agreement with Davidson et al (1994), who reported the specificity of combined cytology and colposcopy to be lower than that of cytology alone but equal to that of colposcopy. [37]

In conclusion, cervical Pap smear is a valuable test with inherent limitations, as it has a relatively low sensitivity with a rate of false negative results in diagnosing CIN/SIL cervical lesions. The combination of cytology and colposcopy showed high sensitivity when using doubtful findings as a cut-off value to identify more patients who actually have CIN/SIL.

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