ORIGINAL CONTEMPORARY STUDY

Sequential Screening with Cytology and Colposcopy in Detection of Cervical Neoplasia

[1]Malur PR,[2]Desai BR,[3]Dalal Anita, [4]Durdi Geeta, [5]Sherigar Bhavana, [6]Gupta Pallav

[1]Professor and Head, Department of Pathology, JN Medical College, Nehru Nagar, Belgaum, Karnataka, India

[2]Professor and Head, Department of Obstetrics and Gynecology, JN Medical College, Nehru Nagar, Belgaum, Karnataka, India

[3,4,5]Associate Professor, Department of Obstetrics and Gynecology, JN Medical College, Nehru Nagar, Belgaum, Karnataka India

[6]Postgraduate Student, Department of Obstetrics and Gynecology, JN Medical College, Nehru Nagar, Belgaum, Karnataka India

Correspondence: Sherigar Bhavana, Associate Professor, Department of Obstetrics and Gynecology, JN Medical College Nehru Nagar, Belgaum-590010, Karnataka, India, Phone: 09341109070, e-mail: bhavanayatin@rediffmail.com

Abstract

Background: Pap smear is the most commonly used screening test for cervical cancer, however it has disadvantage of having low sensitivity. Colposcopy has higher sensitivity as compared to Pap smear but low specificity. Sequential screening with both Pap smear and colposcopy can overcome these problems.

Aim: The study was aimed to find out the diagnostic efficacy of both Pap smear and colposcopy. It was also intended to find out the advantages of sequential use of Pap smear and colposcopy in screening for cervical cancer.

Design: It was a cross-sectional study conducted in colposcopy clinic of KLE's Dr. Prabhakar Kore Hospital and MRC, Belgaum from November 2006 to September 2008.

Material and methods: A total of 190 patients with complaints of postcoital bleeding, intermenstrual bleeding, postmenopausal bleeding, persistent vaginal discharge or those found to have an unhealthy cervix on per speculum examination were included in the study. In all the 190 cases Pap smear, colposcopic evaluation and colposcopic directed biopsy were performed.

Statistical analysis: Sensitivity, specificity, positive predictive value, negative predictive value of both Pap smear and colposcopy were calculated with histopathology as a gold standard , keeping LSIL as a disease threshold for test positivity.

Results: Pap smear was positive in 14.21% (27/190) cases, colposcopy was positive in 37.89% (72/190) cases. Biopsy confirmed LSIL and higher lesions in 31.57% cases. The sensitivity, specificity, positive predictive value and negative predictive value of Pap smear were 41.66%, 96.92%, 86.21% and 78.26% respectively and 80%, 81.54%, 66.66% and 89.83% respectively for colposcopy. Combined colposcopy and Pap smear could accurately diagnose 53/60 biopsy confirmed cases of LSIL and higher lesions with an accuracy of 88.33%.

Conclusion: Sequential use of Pap smear and colposcopy in screening for cervical cancer increases the accuracy of the test.

Keywords: Pap smear, colposcopy, screening, cervical cancer, low grade squamous intraepithelial lesions, high grade squamous intraepithelial lesions.

INTRODUCTION

Cancer of the cervix is a global health problem. An estimated 4,70,600 new cases of cervical cancer occur among women worldwide each year, the vast majority of which are in developing countries. Of the 2,33,000 women who die of cervical cancer annually, approximately 80% are from the developing countries.[1] Carcinoma of the cervix continues to be the most common genital tract cancer encountered in clinical practice in India accounting for 80% of all genital tract cancers.[2] Precancerous lesions occur more commonly in women less than forty years of age which provides opportunity for screening and early detection of cervical neoplasms.[3] Pap smear is the most commonly used screening method for early detection of cervical cancer, but it has certain disadvantages like low sensitivity (<50%) and a delay in providing immediate results.[4,5] In limited resource settings WHO has recommended once in a life time screening for early detection of cancer in all women between 35 and 40 years of age.[6] Therefore it becomes important to use an adjunctive screening test like colposcopy which has high sensitivity (64-99%)[7] and can provide immediate results for evaluation of cervical precancerous lesions. Colposcopy further helps in executing a targeted biopsy which can be useful in defining diagnosis of precancerous lesions and carcinoma of cervix.[8] We conducted a study using combination of Pap smear and colposcopy in symptomatic women to find out the advantage of using sequential testing as compared to either test when performed alone.

MATERIAL AND METHODS

The study design was a cross-sectional study. Study was carried out among the women attending the colposcopy clinic of KLE's Dr. Prabhakar Kore Hospital and MRC, Belgaum from November 2006 to September 2008. Ethical clearance for the study was obtained from the institute's ethical clearance committee.

A total of 190 patients with complaints of postcoital bleeding, intermenstrual bleeding, postmenopausal bleeding, persistent vaginal discharge or those found to have an unhealthy cervix on per speculum examination were included in the study. Pregnant women, women with active vaginal bleeding, or having a frank growth on cervix were excluded from the study. After brief explanation of the procedure, an informed consent was obtained from the patients. A structured proforma was prepared for each case which included information regarding patient's age, chief presenting complaint, menstrual history, parity, findings of per speculum and general physical examination.

PROCEDURE

Following procedures were carried out in a sequential manner:

I. Pap smear was obtained by a gynecologist from both ecto cervix and endo cervix using Ayre's spatula and cytobrush respectively.
II. Colposcopy was performed by a team of three gynecologists and the findings were recorded. Colposcopic lesions were graded using modified Reid's colposcopic index.
III. Colposcopic directed biopsies were obtained in all the cases from the abnormal areas and four quadrant biopsies were obtained from the squamo — columnar junction in those cases where lesions were not noticed.

STATISTICAL ANALYSIS

Sensitivity, specificity, positive predictive value and negative predictive value were calculated for both the Pap smear and colposcopy. Biopsy results in case of absence of lesion on colposcopy were used as reference for measuring true disease, thereby adjusting for verification bias. The criteria to be considered test positive was finding of LSIL and above lesions for both colposcopy and Pap smear.

Sensitivity and specificity were also obtained for combined colposcopy and Pap smear, to evaluate the advantages of combined screening.

RESULTS

A total of 190 women were included in the study. The youngest patient included in this study was 22 years of age and the oldest 65 years. Majority of the patients who participated in the study were 22 to 45 years of age. Most of the women (90.5%) had parity between 1-3 (Table 1). Only 2.63% patients were nullipara. The presenting complaints were white discharge per vaginum in 61.05% patients, postcoital bleeding in 4.2% patients, postmenopausal bleeding in 5.78% patients, inter menstrual bleeding in 0.52% patients and unhealthy cervix on per speculum examination in 28.4% patients. In all the 190 cases, results of Pap smear, colposcopy and biopsy were available. Biopsy confirmed LSIL in 16.3% cases, HSIL in 10% cases and carcinoma in 5.26% cases. Out of 10 cases of carcinoma cervix, nine were squamous cell carcinoma of cervix and one case was of adenocarcinoma. Further workup of the patient confirmed it to be endometrial carcinoma with extension to cervix. Majority of the cases of both LSIL (21/31) and HSIL (12/19) were seen between 30 to 49 years of age. It was interesting to note that out of 10 cases of carcinoma of cervix, five were under 40 years of age.

Table 1: Characteristics of the study population

Characteristics	*Number of women (n=190)*
Age (years)	
Range	22 to 65
Mean	38.110
Median ± SD	35 ± 9.88
Parity	
Range	0 to 6
Mean ± SD	2.39 ± 0.94

LSIL was diagnosed in 14 cases on Pap smear (Table 2). Eight of these cases were confirmed on biopsy to have LSIL whereas five cases were reported as carcinoma of cervix and one as chronic cervicitis. HSIL was diagnosed in 13 cases. Six of these cases were confirmed on biopsy whereas two cases each were reported as LSIL and carcinoma of cervix. Remaining three cases were reported as chronic cervicitis. Carcinoma was diagnosed in two cases on Pap smear which were confirmed on histopathology. Retrospective analysis of the 19 biopsy confirmed cases of HSIL showed that Pap smear could diagnose only six cases. Amongst the 10 cases of carcinoma cervix confirmed on biopsy, Pap smear showed evidence of malignancy only in two cases, LSIL in five cases, HSIL in two cases and inflammatory smear in one case. Sensitivity of Pap smear was found to be 41.66%, specificity 96.2%, positive predictive value 86.21% and negative predictive value 78.26% (Table 3) in diagnosing LSIL and above lesions.

Colposcopic diagnosis of LSIL and above lesions was made in 72/190 cases. Out of the forty-six cases of LSIL diagnosed on colposcopy 50% were confirmed to be the same on biopsy. Colposcopy overestimated the grade of lesion in 45.65% cases whereas it underestimated the grade of lesion in 4.35% cases. HSIL was diagnosed in 24 cases on colposcopy out which 14 were confirmed to be the same on biopsy. Six of these cases were diagnosed as carcinoma and one as LSIL. Remaining three cases showed features of chronic cervicitis on biopsy. Out of 19 biopsy confirmed cases of HSIL, colposcopy could accurately diagnose 14 cases. The sensitivity of colposcopy in diagnosing LSIL and above lesion was 80%, specificity 81.54%, positive predictive value 66.66% and negative predictive value 89.83% (Table 4).

Table 2: Correlation of cytology findings with histopathology (n = 190)

Cytology results	*Histopathologic results*				
	Normal	*Chronic cervicitis*	*LSIL*	*HSIL*	*Carci-noma*
Normal (12)	2	9	1	0	0
Inflammatory (146)	1	114	19	12	0
Trichomonas infection (2)	0	0	0	1	1
Candida infection (1)	0	0	1	0	0
LSIL (14)	0	1	8	0	5
HSIL (13)	0	3	2	6	2
Carcinoma (2)	0	0	0	0	2
Total (190)	3	127	31	19	10

Table 3: Diagnostic efficacy of Pap smear

Pap smear	*Histopathology positive*	*Histopathology negative*
Positive (29)	25(a)	4(b)
Negative (161)	35(c)	126(d)
Total (190)	60	130

Sensitivity = a/(a + c) = 25/25 + 35 = 41.66%
Specificity = d/(d + b) = 126/126 + 4 = 96.92 %
Positive predictive value = a/(a + b) = 25/25 + 4 = 86.21%
Negative predictive value = d/(c + d) = 126/35 + 126 = 78.26%

Table 4: Diagnostic efficacy of colposcopy

Colposcopy	*Histopathology positive*	*Histopathology negative*
Positive (72)	48(a)	24(b)
Negative (118)	12(c)	106(d)
Total (190)	60	130

Sensitivity = true positive (a)/true positive (a) + false negative (c) = 48/48 + 12 = 80.00%
Specificity = true negative (d)/true negative (d) + false positive (b) = 106/106 + 24 = 81.54%
Positive predictive value = true positive (a)/true positive (a) + false positive (b) = 48/48+24 = 66.66%
Negative predictive value = true negative (d)/true negative (d) + false negative (c) = 106/106+12 = 89.83%.

Overall there were sixty cases confirmed as LSIL and above lesions on biopsy. Both colposcopy and Pap smear were positive in 19 of these cases, colposcopy alone in 29 cases where as Pap smear alone was positive in 5 cases. In seven out of these sixty cases neither Pap smear nor colposcopy could diagnose the lesion accurately. So colposcopy and Pap smear together could accurately diagnose 88.33% (53/60) of histologically confirmed cases (Table 5).

DISCUSSION

Cervical cancer is second most common cancer among women worldwide and third leading cause of cancer related death in women.[9] Out of 233,000 women who die each year due to cervical cancer, majority are from developing countries.[10] Pap smear is the most commonly used method of cervical screening, however it has the disadvantage of having low sensitivity, often less than 50%,[4,5] high cost and a delay in providing immediate results. In developing countries many women do not return at a later date and are lost to follow-up.[11]On the other hand sensitivity of conventional colposcopy was found to be high (64-99%) but specificity was found to be low (30-93%).[7] Adjunctive testing using two tests in sequential combination assists in improving the sensitivity of the test without compromising its specificity.[12] Colposcopy is a simple OPD procedure which has an advantage of being more sensitive as compared to Pap smear in diagnosing precancerous lesions.

In the present study colposcopy and Pap smear evaluation were done in a sequential manner with histopathology as the reference standard . The sensitivity of Pap smear in diagnosing LSIL and above lesions was found to be 41.66% , far lower than colposcopy (80%). However the specificity of Pap smear (96.92%) was significantly higher as compared to colposcopy (81.54%). Positive predictive value for Pap smear and colposcopy were 86.21% and 66.66% respectively. Negative predictive values for Pap smear and colposcopy were 79.26% and 89.83% respectively.

In the present study there were 60/190 cases of biopsy confirmed precancerous and cancerous lesions of cervix. Pap smear alone could identify approximately 40% of these cases as compared to colposcopy alone which could identify 80% of these cases. However, combination of colposcopy and Pap smear was successful in identifying 88.33% cases of LSIL and higher lesions.

In view of the above results it can be concluded that combination of colposcopy and Pap smear can accurately diagnose precancerous and cancerous lesions in majority of the cases. Some studies have advocated the usefulness of combination of Pap smear and speculoscopy (PapSure); sensitivity and specificity of Pap Sure was found to be 89.5% each.[13] Another study reported sequential use of HPV DNA testing and Pap smear in screening for cervical cancer with a net sensitivity of 37.5% and net specificity of 100%.[14] However, HPV DNA testing is an expensive screening test. Our study indicates that sequential screening with Pap smear and colposcopy will have the advantage of improving accuracy without significantly compromising on specificity or sensitivity of the screening test and would also prevent loss of patients

Table 5: Cytology and colposcopy findings in histopathology positive cases (n = 60)

Colposcopy +ve Cytology –ve	Colposcopy –ve Cytology +ve	Colposcopy +ve Cytology +ve	Colposcopy –ve Cytology –ve
29	5	19	7

for further follow-up. However, colposcopy requires trained gynecologists and is an expensive screening test.

The results from the current study support the claim to perform combination screening tests as part of routine screening for cervical cancer rather than either test alone in order to detect maximum number of cases with accuracy and minimum loss of patients to follow-up. However, the study needs to be extended to a larger population group so as to gain wider experience and also to find out the cost effectiveness of various combination tests best suited to screen the patients for cervical cancer.

REFERENCES

1. Ferlay J, Bray F and Pisani P. Globocon 2000: Cancer incidence, mortality and prevalence worldwide. Version 1, IARC cancer Base No.5, IARC Press, Lyon 2001.
2. Padubidri VG, Daftary SN. Shaw's textbook of gynecology (13th ed) India: Elsevier 2005.
3. Holowaty P, Miller AB, Rohan T. Natural history of dysplasia of uterine cervix JNCI 1999;19:252-58.
4. Fahey MT, Irwig L, Macaskill P. Meta analysis of Pap test accuracy. Am J Epidemiol 1995;141:680-89.
5. Nanda K, McCrory DC and Myers ER, et al. Accuracy of Papanicolaou test in screening for and follow-up of cervical cytological abnormalities: A systemic review, Ann Intern Med 2000;132:810-19.
6. World Health Organization. National cancer control programme: Policies and managerial guidelines (2nd ed) Geneva.
7. Mitchell MF, Schottenfeld G, Luna T, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: A meta-analysis. Obstet Gynecol 1998;91:626-31.
8. Cecchini S, Bonardi L, Cipparone G, Ottaviano M, Pieroni G. Contribution of cytology, colposcopy, target biopsy and conization to the early diagnosis of precancerous and cancerous lesions of cervix uteri. Tumori 1978;64:389-98.
9. Sawaya GF, Brown AD, Washington AE and Garber AM. Clinical practice. Current approaches to cervical-cancer screening. N Eng J Med 2001;344:1603-07.
10. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB and Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. Am J Obstet Gynecol 2003;189:295-304.
11. Divall PDM, Scott BD, Middlecote and De wet JI. Cervical cytological services in the orange free state: Demographic characteristics. S Afr Med J 1989;76:615-18.
12. Ferris DG, Wright TC Jr, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Triage of women with ASCUS and LSIL on pap smear reports management by repeat Pap smear, HPV DNA testing or colposcopy. J Fam Pract 1998;46:125-34.
13. Twu Nae-fang, Chen Yi-Jen, Wang Peng-Hui, Bill Ken-Jen, Laiet chung-Ru, Chao kuan-chong, et al. Improved cervical cancer screening in premenopausal women by combination of Pap smear and speculoscopy. European journal of Obstetrics and Gynecology and Reproductive Biology 2007;133:114-18.
14. Bhatla N, Mukhopadhyay A, Kriplani A, Pandey RM, Gravitt EP, Shah KV, et al. Evaluation of adjunctive tests for cervical cancer screening in low resource settings. Indian Journal of Cancer 2007;44:51-44.