

Liquid-based Cytology vs Conventional Cytology as a Screening Tool for Cervical Cancer in Postmenopausal Women

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ABSTRACT

Aim: To evaluate and compare the efficacy of liquid-based cytology (LBC) with conventional cytology (CS) as a screening tool for cervical cancer in postmenopausal women.

Materials and methods: This was an observational cross-sectional study conducted over one year. Subjects were recruited from patients attending the outpatient department of the Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, Uttar Pradesh, India. Pap smear and LBC were taken in all subjects. In cases with suspected lesions, the discrepancy between Pap smear and LBC and colposcopy was found.

Results: Pap smear reported 14.3% inadequate smears in women with postmenopausal changes and 5% inadequate smears in women without postmenopausal changes. In contrast, LBC reported no inadequate smear. This difference was statistically significant ($p = 0.011$). Cervical neoplasia was ruled out in 53.6% cases by Pap smear and 75.8% cases by LBC. The difference was statistically significant ($p = 0.002$).

Conclusion: Liquid-based cytology offers better results in detecting cervical pathology when compared with Pap smear. Liquid-based cytology could be better as a screening method, especially in postmenopausal women in which the screening is challenging due to menopause-induced anatomical and hormonal changes.

Clinical significance: Cervical cancer is the most common genital cancer among Indian women. Postmenopausal women are at higher risk for developing cervical cancer. Low estrogenic state poses a challenge for detection of cervical cancer by CS in postmenopausal women. We investigated LBC as a better cervical cancer screening tool in this age group.

Keywords: Cervical cancer screening, Liquid-based cytology, Pap smear, Postmenopausal.

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INTRODUCTION

An estimated 4,70,000 new cases of cervical cancer are diagnosed each year worldwide, and 80% of these occur in developing countries. The rates of detection of cancer cervix have been improving steadily. From 2004 to 2008, mortality rates decreased by 2.6% per year in African-American women and have remained stable in white women. Screening programs for cervical cancer have been shown to be effective in reducing the overall mortality from the disease.

Pap smear cervical cancer screening method is a convenient, painless, and widely acceptable method. It has a sensitivity of about 68% and a specificity of about 75%. However, it is considered suboptimal because of false-positive and false-negative test results, which are largely due to poor quality sampling and preparation and to errors in detection and interpretation. Liquid-based cytology (LBC) was developed as an alternative method and gained popularity because the use reduced the incidence of inadequate cervical smears from 9 to 2.5% and increased the sensitivity.¹ Although numerous studies have compared the accuracy of two screening techniques, not much study is done specifically in postmenopausal women who are at risk of cancer cervix and thus require screening.

Postmenopausal age group poses a special challenge as far as screening by conventional Pap smear is concerned. In postmenopausal women, there is tissue atrophy due to nonestrogenic state following reduced ovarian function. This leads to decrease in the number of cells and thus increase in reporting of inadequate smears. Moreover, cervix may become smaller and vagina narrower. In elderly women, cervix may be flushed with vagina. Cervical discharge decreases in amount during menopause and may disappear completely after menopause. Thus, it may be difficult to obtain cervical smears in postmenopausal age group.² Also, the cytological patterns of the advanced atrophic menopause are influenced

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by dryness of the genital tract and scarcity of recoverable cellular material, resulting in preparations that contain relatively few cells. The dominant squamous cells are of the parabasal type; also, it is not uncommon to see a few scattered, more mature cells, evidently corresponding to nonatrophic areas of the squamous epithelium. This may result in increased reporting of low-grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASCUS) in smears, resulting in an increase in the false-positive report.

The present study was intended to include postmenopausal women who were most susceptible to cervical cancer, had never been screened in the past, and in whom Pap smear was difficult to obtain and interpret. This study aimed to evaluate and compare the efficacy of LBC with conventional cytology (CS) as a screening tool for cervical cancer in postmenopausal women.

MATERIALS AND METHODS

This observational cross-sectional study was conducted over a period of 1 year in the Department of Obstetrics and Gynecology at King George's Medical University (KGMU), Lucknow, Department of Pathology, KGMU, and Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. Ethical clearance was taken from the institutional ethical committee.

The subjects were recruited from those attending the outpatient department of the Department of Obstetrics and Gynecology, KGMU, Lucknow, Uttar Pradesh, India. The study included postmenopausal women with or without high-risk factors or with suspicion of cervical cancer. High-risk factors included women with consummation age less than 20 years, 5 or more children, history of smoking/tobacco chewing, history of sexually transmitted infections, unexplained persistent vaginal discharge, poor hygiene, low socioeconomic status, multiple sexual partners, or oral

contraceptive pills. Women not willing to take part in the study and known cases of cervical neoplasia were excluded.

Informed consent was obtained from recruited postmenopausal women about the procedure, its efficacy, and safety. The history of the subject was taken followed by a general, systemic, and gynecological examination. Pap smear and LBC were taken in all subjects and reported by Bethesda system. The Thin Prep System for LBC was from Hologic, USA. In cases with suspected lesions, or discrepancy between Pap smear and LBC, colposcopy was done. Punch cervical biopsy was done in patients with combined colposcopic Reid's score of 2 or more.

All data were tabulated and analyzed statistically using Statistical Package for Social Sciences, version 15.0 software. The values were represented in number (%) and mean \pm standard deviation. A value of $p < 0.05$ was considered to be significant.

RESULTS

In the present study, 95 postmenopausal women were included, with a mean age of 54.21 ± 8.61 years (from 40 to 78 years). Only 5 women (5.3%) were nullipara and 44 women (48.4%) of para 4 and above. The majority of subjects had healthy cervix and vagina. Totally, 35 (95%) women had postmenopausal changes on per speculum examination, like cervix flushed with vagina (19), narrowing of vagina (12), and senile vaginitis (10). It was observed that Pap smear reported 14.3% inadequate smears in women with postmenopausal changes and 5% inadequate smears in women without postmenopausal changes. On the contrary, LBC reported no inadequate smear. This difference was found to be statistically significant ($p = 0.011$). This showed that anatomical changes decrease the efficacy of Pap smear in comparison with LBC. The cytology results were reported by Bethesda system. The detail is shown in Table 1.

Table 1: Pap smear and LBC reports according to Bethesda system (n = 95)

Sl. no.	Reports	No. of subjects in Pap (percentage) n = 95	No. of subjects in LBC (percentage) n = 95	p-value
1.	Inadequate	8 (8.4)	0	0.004
2.	Negative	51 (53.68)	72 (75.8)	0.002
	Inflammation	7	13	
	Infection	1	2	
3.	Epithelial cell abnormalities (squamous)	35 (36.8%)	22 (23.1%)	0.040
	ASCUS	8 (8.4)	4 (4.2)	0.233
	ASC-H	0	0	0
	LSIL	16 (16.8)	6 (6.3)	0.023
	HSIL	8 (8.4)	7 (7.4)	0.788
	SCC	3 (3.2)	5 (5.3)	0.470
4.	Epithelial cell abnormalities – AGCUS	1 (1.1)	1 (1.1)	1.000

ASC-H: Atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; AGCUS: Atypical glandular cells of unknown significance

Totally, 51 (53.68%) reports were negative for intraepithelial lesion or malignancy by Pap smear, out of which 7 showed inflammation compared with 72 (75.8%) cases which were found to be negative by LBC, of which 13 showed inflammation. The difference was statistically significant ($p = 0.002$). Pap smear showed more epithelial cell abnormalities (36.8%) compared with LBC (23.1%). The difference was statistically significant ($p = 0.04$). Liquid-based cytology detected five cases of squamous cell carcinoma (SCC) compared with three by conventional Pap smear. The 16 cases of LSIL were reported by conventional Pap smear compared with 6 by LBC. One added advantage with LBC was the detection of two cases of bacterial vaginosis and seven cases of atrophic vaginitis. Pap smear did not report these changes.

Colposcopy was done in 70 subjects. Totally, 54 (77.1%) subjects had a low-grade lesion, 9 (12.9%) had intermediate, and 7 (10%) had a high-grade lesion in colposcopic findings according to the Modified Reid Colposcopic index. A cervical biopsy was taken in 23 subjects. There were 3 (13.04%) cases of SCC, 8 had intraepithelial neoplasia (26.08% cervical intraepithelial neoplasia [CIN] I and 8.69% CIN II/III), and 10 (43.47%) had inflammatory changes. Two women had normal histology (8.69%).

Cervical neoplasia was ruled out in 53.6% cases by Pap smear and 75.8% cases by LBC. The difference was found to be statistically significant ($p = 0.002$). In the present study, SCC was detected in five cases (5.3%) by LBC, whereas it was detected in three cases (3.2%) by Pap smear. In women with postmenopausal changes, Pap smear detected no case of SCC, while LBC detected 2.9% subjects. Liquid-based cytology showed a better detection rate of smears negative for cervical neoplasia when compared with Pap smear. This study indicated that LBC leads to better diagnosis of SCC when compared with Pap smear, especially in women with postmenopausal changes.

The efficacy of cytology was compared in different age groups. Table 2 shows the result among different age groups of women screened. Pap smear had maximum diagnostic accuracy for 51 to 60 years age group (86.2%), while LBC had maximum efficacy for age group 61 to 70 years. The diagnostic accuracy of LBC was better

compared with that of conventional Pap smear in both the pre- and postmenopausal women. In postmenopausal women, the diagnostic accuracy of LBC was 88.9% compared with 85.7% of conventional Pap smear.

DISCUSSION

The cervical cytological examination is the mainstay of screening cervical cancer. It can be carried out using either conventional Pap smear or LBC. The study was done to find the best screening method for cervical cancer in postmenopausal women who have challenges in the form of anatomical changes, less number of cells, and fewer secretions. Various studies have shown that there are fewer unsatisfactory results with LBC, which occur primarily due to obscuration by inflammation or blood and mucus or due to inappropriate spreading and fixation of cells. With increasing age, especially in postmenopausal women, tissue atrophy occurs due to decline in estrogen levels leading to a poor yield of cells, ultimately increasing the unsatisfactory cytology smears. A recent study conducted in the United States found that women who had unsatisfactory cytology results were older, menopausal, and/or posthysterectomy than those who did not have unsatisfactory results.³ Various studies like those by Ronco et al⁴ and Fremont-Smith et al⁵ proved that LBC reduces inadequate reports in comparison to Pap smear. Sykes et al⁶ also concluded the same results with 9.1 vs 2.7% inadequate slides in Pap smear and LBC respectively. In the present study, this difference between the two techniques was found to be statistically significant. Singh et al⁷ carried out a study to assess the diagnostic accuracy of LBC vs conventional Pap smear and found that LBC technique showed a significant reduction in unsatisfactory samples, had better clarity, uniform spread of smears, and lesser time for screening.

The ASCUS is an intriguing, often confusing cytological entity in the management of cervical cancer. The false reporting of ASCUS is increased with the use of Pap smear due to misinterpretation of inflammatory and reparative processes as ASCUS in smears. Postmenopausal changes result in an increase in the reporting of ASCUS. Extensive inflammation, parabasal cells with

Table 2: Comparison of diagnostic accuracy of conventional Pap smear and LBC for different age groups (n = 90)

Sl. no.	Age groups	Conventional Pap smear					Liquid-based cytology				
		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
1	40–50 ^[4]	20	91.9	25	89.5	83.3	33.3	92.5	25	94.9	88.4
2	51–60 ^[5]	66.7	88.5	40	95.8	86.2	66.7	89.7	40	96.3	87.5
3	61–70 ^[0]	0	100	–	85.7	85.7	0	100	–	88.9	88.9
4	>70 ^[3]	–	50	0	100	50	–	50	0	100	50

^[1] Incorporates positive cases in corresponding age group

organophilic cytoplasm, nuclear variations secondary to drying, and degeneration associated with atrophic vaginitis may result in cellular changes that are falsely interpreted as ASCUS. This leads to overdiagnosis and overtreatment and follow-up of the subjects. Vassilakos et al⁸ detected that use of thin-layer method reduced the reporting of ASCUS. Ronco et al⁴ and Klinkhamer et al⁹ also concluded that the thin prep system had reduced detection rate of ASCUS when compared with conventional smear. A study done by Stabile et al¹⁰ to compare two oncotic cervical cytology techniques, the CS and the LBC, in low-risk patients for uterine cervical cancer found that LBC had a better performance to diagnose atypical cells, and the cytohistologic concordance was higher than in CS. Hussein et al¹¹ carried out a study to compare the performance of LBC and CS in the high prevalence setting of colposcopy clinic. A study by Simion et al¹² aimed to analyze the diagnosis, correlations, and differences between CS and LBC. They found that LBC resulted in the diagnosis of some entities missed in CS (ASCUS, ASCUS associated with atypical glandular cells not otherwise specified, high-grade squamous intraepithelial lesion [HSIL] associated with adenocarcinoma in situ). Liquid-based cytology also provided the identification of a higher number of cases of associated lesions. In this study, LBC reported 9.0% postmenopausal women to have ASCUS. The difference between the two was not statistically significant ($p = 0.624$). However, LBC decreases reporting of ASCUS, thus leading to decrease in false-positive results and that the agreement between Pap and LBC was 77%. In this study, the agreement between the two techniques was observed as 76.8% in normal/ASCUS, 16.7% in LSIL, and 66.67% in HSIL/SCC. The overall agreement is 71.3% between the two techniques and the difference is also statistically significant ($p < 0.001$).

The sensitivity of Pap smear and LBC was found to be the same (25%) in this study. This is similar to a study by Sykes et al⁶ who reported a similar sensitivity of the two methods in the detection of any epithelial abnormality. Ronco et al⁴ reported same sensitivity between two methods for detection of CIN II or CIN III. However, a study by Hussein et al¹¹ found very high sensitivity of LBC when compared with CS. In the present study, specificity of LBC (94.9%) is better when compared with Pap smear (91.5%). Similar findings of high specificity were also reported by Sherwani et al¹³ and Ferenczy et al¹⁴. On the contrary, the findings by Bergeron et al¹⁵ and Hussein et al¹¹ reported lower specificity of LBC when compared with Pap smear. The sensitivity of CS is more in general population, as shown in a study done by Sherwani et al.¹³ They found that conventional Pap smear is 53.7% sensitive and 50% specific for screening purpose. Chinaka et al¹⁶ in their study carried out to compare the accuracy of CS

and LBC for primary screening of cervical cancers found that sensitivity and specificity of LBC were 100%, whereas that of CS was 86 and 97% respectively. In this study, the positive predictive value (PPV), negative predictive value, and diagnostic accuracy of LBC are found to be better when compared with Pap smear, similar to the studies of Hussein et al¹¹ and Fremont-Smith et al.⁵ On the contrary, the study conducted by Castle et al¹⁷ concluded that LBC did not perform better than the conventional Pap tests in terms of relative sensitivity and PPV.

This study proved that LBC correlates with colposcopic and biopsy findings with significant statistical association when compared with Pap smear. The diagnostic accuracy of LBC in subjects with postmenopausal changes was also better when compared with Pap smear (91.2 vs 86.7%). So, LBC is a better method for screening women with advanced age groups in which there is difficulty in collection and interpretation of smears.

This study demonstrates that LBC performs better than conventional Pap in postmenopausal women. Nevertheless, more comparative studies are needed in the postmenopausal group to evaluate these two cytological techniques. The strength of the study is the efficacy of LBC in an age group, which requires being addressed, especially in Indian scenario where routine cytology screening is not the norm. The main weakness of the study was the lesser number of subjects recruited.

CONCLUSION

Liquid-based cytology offers better results in detecting cervical pathology when compared with Pap smear. Another advantage is the possibility of using the same sample for testing for human papillomavirus and for other molecular tests.

Consequently, LBC could be better as a screening method, especially in postmenopausal women in which the screening is challenging due to menopause-induced anatomical and hormonal changes.

CLINICAL SIGNIFICANCE

Cervical cancer is the most common genital cancer among Indian women. Postmenopausal women are at higher risk for developing cervical cancer. Low estrogenic state poses a challenge for detection of cervical cancer by CS in postmenopausal women. We investigated LBC as a better cervical cancer screening tool in this age group.

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