

Comparison of conventional pap smear and liquid-based cytology in the screening of cervical cancer: A prospective comparative pilot study in a tertiary care centre of the sub-himalayan region.

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Abstract

Background

Cervical cancer remains an important cause of morbidity and mortality among women, particularly in low- and middle-income countries. Liquid-based cytology (LBC) may improve specimen quality and reduce limitations associated with conventional Papanicolaou (PAP) smear cytology.

Objective

To compare conventional PAP smear cytology with LBC regarding specimen adequacy, cellular distribution, overlapping, morphological changes, background material, cytological interpretation, epithelial abnormalities, and screening time.

Materials and Methods

This prospective comparative pilot study was conducted at Dr Radha Krishnan Government Medical College, Hamirpur, Himachal Pradesh, from December 2021 to February 2023. A total of 440 women aged >19 years attending the gynaecology outpatient department with symptoms or abnormal cervical findings were included. Conventional PAP smear and LBC samples were collected from each participant during the same sitting and evaluated according to the Bethesda System.

Results

Adequate cellularity was observed in 430 (97.73%) conventional PAP smears and 439 (99.77%) LBC preparations ($\chi^2=7.457$, $p=0.0112$). Uniform cellular distribution was observed in 436 (99.09%) LBC preparations compared with none of the conventional smears. Cellular overlapping was significantly lower with LBC (25.45% vs. 97.27%; $\chi^2=475.588$, $p<0.0001$). Inflammatory and hemorrhagic backgrounds were also significantly reduced with LBC ($p<0.0001$). Unsatisfactory preparations occurred in 51 (11.59%) conventional smears compared with 1 (0.23%) LBC preparation. Epithelial abnormalities were detected in 23 conventional smears and 28 LBC preparations, with no significant difference ($p=0.5639$). Mean screening time was approximately 10 minutes for conventional PAP smears and 5 minutes for LBC.

Conclusion

LBC provided better specimen quality, cleaner background, reduced cellular overlapping, fewer unsatisfactory preparations, and shorter screening time, although morphological changes were more frequent.

Recommendation

LBC may be considered a useful alternative to conventional PAP smear cytology where laboratory resources and trained personnel are available.

Keywords: Cervical cancer; Conventional PAP smear; Liquid-based cytology; Cervical screening; Cytology; Bethesda System

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Introduction

Cervical cancer remains an important public health problem worldwide and continues to contribute substantially to cancer-

related morbidity and mortality among women, particularly in low- and middle-income countries. The burden is disproportionately high in regions where organized screening and follow-up services are limited. In India, cervical cancer remains one of the major cancers affecting women, and the

disease continues to pose an important healthcare challenge despite the availability of effective screening and preventive strategies. The development of organized screening programmes has substantially reduced cervical cancer incidence and mortality in countries where adequate coverage, quality assurance and appropriate treatment of precursor lesions are available.^{1,2}

Cervical cancer is largely preventable because the disease develops through identifiable precursor lesions over a prolonged period. Persistent infection with high-risk human papillomavirus (HPV) is the principal etiological factor, while early age at marriage and first childbirth, multiparity, poor genital hygiene, low socioeconomic status and limited access to healthcare have also been associated with increased risk in vulnerable populations.³ Early detection and treatment of cervical intraepithelial lesions therefore remain central to cervical cancer prevention.

Cervical cytology has played a major role in reducing the burden of invasive cervical cancer. The conventional Papanicolaou smear remains one of the most widely used screening methods because it is inexpensive, relatively simple and can be performed in laboratories with limited resources. However, conventional smears have several technical limitations. Uneven transfer of cells, cellular overlap, obscuring blood or inflammation, mucus, air-drying artifacts and inadequate cellularity may compromise slide interpretation and contribute to unsatisfactory or false-negative preparations.^{4,5}

Liquid-based cytology (LBC) was introduced to address several of these limitations. In LBC, the cervical sample is processed to produce concentrated and uniform cellular preparation. This approach reduces obscuring background material, improves cellular distribution, thereby facilitating microscopic screening. Studies comparing conventional cytology with liquid-based preparations have demonstrated improvements in specimen quality, adequacy and reduction in unsatisfactory specimens, although the magnitude of diagnostic benefit has varied between studies.^{6,7}

The quality of cervical cytology is particularly important in symptomatic women and in settings where screening resources are limited. A high proportion of unsatisfactory conventional smears can result in repeat sampling, additional expenditure and delayed diagnosis. LBC may potentially reduce these limitations by concentrating the cellular material and producing a more standardized preparation. However, the additional cost and laboratory requirements associated with commercially available LBC systems may restrict their widespread use in developing countries.⁸

Several comparative studies have evaluated conventional PAP smear and LBC techniques. Singh et al., in a study of 1000 split cervical samples, evaluated both methods and demonstrated differences in specimen quality and cytological interpretation between the two techniques.⁹ Sharma et al. reported improved cytological preparation with SurePath LBC, particularly with respect to background cleanliness and cellular distribution.¹⁰ Patel et al. similarly demonstrated differences in specimen quality and cytological features between conventional and liquid-based preparations in a large comparative study.¹¹ Maheshwari et al. also reported that LBC provided improved-quality preparations and evaluated both techniques against histopathological findings.¹²

Despite these reported advantages, the usefulness of LBC in routine screening cannot be assessed solely on the basis of diagnostic categories. Parameters such as cellular adequacy, endocervical/transformation-zone component, cellular distribution, overlapping, inflammatory and hemorrhagic background, artifacts, cytomorphological changes, screening time and overall interpretation are also important when determining whether a technique is suitable for routine use. Furthermore, the performance of LBC may vary according to the processing method, laboratory facilities and experience of the cytopathologist.

The present study was therefore undertaken at a tertiary healthcare centre in the sub-Himalayan region of Himachal Pradesh to compare conventional PAP smear cytology with liquid-based cytology using multiple cytological and technical parameters. Particular emphasis was placed on specimen adequacy, cellular distribution, cellular overlapping, inflammatory and hemorrhagic background, artifacts, cytological interpretation and screening time. The study also aimed to assess whether LBC could provide a practical and diagnostically advantageous alternative to conventional PAP smear cytology.

Materials and Methods

Study Design and Setting

This was a prospective comparative study of cervical exfoliative cytology conducted from 1 December 2021 to February 2023 at Dr Radha Krishnan Government Medical College (Dr.RK GMC), Hamirpur, Himachal Pradesh, India. The study was conducted in collaboration with the Department of Obstetrics and Gynaecology. Women attending the gynaecology outpatient department with symptoms suggestive of cervical or lower genital tract disease or abnormal cervical findings on speculum examination were evaluated for eligibility.

Cervical specimens were collected in the Department of Obstetrics and Gynaecology and transported to the Cytopathology Laboratory of the Department of Pathology for processing and examination. The laboratory routinely performs cytological evaluation of cervical specimens and has facilities for preparation, fixation, staining and microscopic examination of conventional cervical smears and liquid-based cytology specimens. Conventional PAP smears were prepared directly on glass slides, whereas liquid-based cytology specimens were collected in an ethanol-based preservative medium and subsequently processed by vortex mixing, gradient centrifugation and sedimentation to obtain a standardized cellular deposit of approximately 13 mm in diameter. Both conventional and liquid-based preparations were manually stained using the routine Papanicolaou staining technique and examined microscopically by a pathologist. Cytological findings were reported according to the 2014 Bethesda System for Reporting Cervical Cytology.

Study Population and Participants

The study included 440 married women aged >19 years who attended the gynaecology outpatient department during the study period and fulfilled the predefined eligibility criteria. Participants presenting with abnormal vaginal discharge, persistent leucorrhoea, postcoital bleeding, abnormal uterine bleeding, postmenopausal bleeding or abnormal findings on speculum examination were considered for inclusion.

Each participant underwent collection of cervical material for both conventional PAP smear cytology and liquid-based cytology during the same clinical sitting. This paired sampling approach allowed direct comparison of the two cytological preparation techniques using specimens obtained from the same participant.

Sample Size Calculation

The required sample size was determined before commencement of the study using the following formula for estimation of sample size for a comparative study:

$$n = Z^2 \times p \times (1 - p) / d^2$$

where n is the required sample size, Z is the standard normal deviate corresponding to the selected confidence level, p is the anticipated proportion/prevalence of the outcome, and d is the allowable margin of error.

Based on the assumptions used during study planning, the calculated sample size was **440 participants**.

Inclusion Criteria

Women fulfilling the following criteria were included:

1. Married women aged >19 years.
2. Women attending the gynaecology outpatient department with one or more of the following:
 1. abnormal vaginal discharge;
 2. persistent leucorrhoea;
 3. postcoital bleeding;
 4. abnormal uterine bleeding;
 5. postmenopausal bleeding; or
 6. abnormal findings on speculum examination.

Exclusion Criteria

Women who met any of the following criteria were excluded from the study:

1. Unmarried women.
2. Pregnant women.
3. Women with a previous hysterectomy.
4. Women who had received chemotherapy or radiotherapy.

Women who declined participation were not enrolled in the study and therefore were not considered part of the study population. This distinction was maintained to avoid categorizing non-participation as post-enrolment exclusion.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. The purpose and procedures of the study were explained to the

participants in understandable language, and participation was voluntary. Participants were informed that they could withdraw from the study at any time without affecting their routine medical care.

Clinical Evaluation and Sample Collection

A detailed clinical history was obtained from each participant, including demographic characteristics, obstetric and menstrual history, and presenting symptoms. Participants were advised to avoid sexual intercourse, vaginal medications, vaginal contraceptives and vaginal douching for 48 hours before sample collection.

Cervical examination was performed in the lithotomy position using a Cusco's self-retaining speculum without application of lubricant. The cervix was inspected for visible abnormalities, and excessive mucus or discharge was gently removed with a swab before specimen collection.

For conventional PAP smear cytology, an Ayre's spatula was introduced into the cervical canal and rotated through 360° to sample the squamocolumnar junction. The collected material was immediately spread evenly onto a labelled glass slide and fixed immediately in 80% isopropyl alcohol.

For liquid-based cytology, a cervical broom was used. The long bristles were introduced into the endocervical canal while the shorter bristles contacted the ectocervix. The device was rotated through 360°, after which the brush containing the collected material was introduced into a vial containing an ethanol-based fixative. The brush was rinsed in the preservative medium and detached into the vial. The labelled specimen was then transported to the Cytopathology Laboratory for processing.

Processing of Liquid-Based Cytology Specimens

On receipt in the Cytopathology Laboratory, patient identifiers on the specimen vial and requisition form were verified. The LBC specimen was vortex mixed to disperse the cellular material. The specimen was subsequently processed using gradient centrifugation and sedimentation. The resulting cellular pellet was transferred onto a glass slide to produce a circular cellular preparation measuring approximately 13 mm in diameter.

Both conventional PAP smears and LBC preparations were manually stained using the routine Papanicolaou staining procedure.

Cytological Evaluation

The conventional PAP smear and LBC preparations from each participant were examined by a pathologist and reported according to the 2014 Bethesda System for Reporting Cervical Cytology.

The two preparation techniques were compared with respect to:

1. specimen/cellular adequacy;
2. presence of endocervical/transformation-zone component;
3. uniformity of cellular distribution;
4. cellular overlapping;
5. cytomorphological changes;
6. inflammatory background;
7. haemorrhagic background;
8. diathetic background;
9. preparation artifacts;
10. detection of organisms;
11. cytological interpretation;
12. Screening time.

Specimens were assessed for adequacy based on cellularity, preservation and visualization of the cellular material. Conventional smears were considered satisfactory when an adequate number of well-preserved and well-visualized squamous or squamous metaplastic cells were present and the preparation was interpretable. LBC preparations were assessed using comparable criteria after processing.

Cytological diagnoses were categorized according to Bethesda terminology, including negative for intraepithelial lesion or malignancy (NILM), inflammatory changes, atrophic changes and epithelial cell abnormalities, including atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous

intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCC) and atypical glandular cells (AGC).

Assessment of Background and Preparation Artifacts

Both preparation techniques were assessed for the presence of inflammatory cells, haemorrhagic material, proteinaceous/diathetic material and preparation artifacts. Cellular overlapping and uniformity of cellular distribution were assessed microscopically.

Screening Time

The approximate time required to screen each conventional PAP smear and LBC preparation was recorded. Screening time was defined as the time from the beginning of microscopic examination until completion of the cytological assessment.

Measures to Minimize Bias

Several measures were undertaken to minimize potential sources of bias. Both conventional PAP smear and LBC specimens were collected from the same participant during the same clinical sitting, thereby reducing between-participant variability and allowing paired comparison of the two preparation techniques. A standardized cervical sampling procedure was followed for both techniques. Specimen identification and laboratory processing were performed using standardized procedures to minimize pre-analytical and analytical variation. Both preparation types were stained using

the same routine Papanicolaou staining procedure and evaluated according to the same Bethesda reporting criteria. The predefined inclusion and exclusion criteria were applied consistently to all participants.

Potential observer-related variation was minimized by evaluation of both preparations by a pathologist using the same predefined cytological parameters. Screening time was assessed using the same definition for both techniques. These measures were intended to reduce selection, measurement and observer-related bias.

Statistical Analysis

Data obtained from conventional PAP smear and LBC preparations were tabulated and analysed. Categorical variables were expressed as frequencies and percentages. The chi-square test was used to compare categorical variables between the two preparation techniques. A p value <0.05 was considered statistically significant. Statistical significance was interpreted according to the corresponding chi-square value and degrees of freedom.

Results

Participant Characteristics

A total of 440 women were included in the study. The age of the participants ranged from 20 to 77 years. The largest proportion of women belonged to the 30–39-year age group (n = 173, 39.31%), followed by the 40–49-year age group (n = 152, 34.54%).

Table 1. Age Distribution of the Study Population

Age (years)	Number (n)	Percentage (%)
20–29	40	9.09
30–39	173	39.31
40–49	152	34.54
50–59	53	12.04
60–69	16	3.63
70–79	6	1.36
Total	440	100.00

As shown in Table 1, women aged 30–39 years constituted the largest age group (39.31%), followed by those aged 40–49 years (34.54%). The remaining participants were distributed across the 20–29, 50–59, 60–69, and 70–79-year age groups.

Among the 440 women, 399 (90.68%) presented with vaginal discharge, either alone or in association with other complaints. Bleeding on touch was observed in 44 women, while 288 women had a bulky uterus associated with moderate-to-profuse vaginal discharge. Cervical erosion was associated with vaginal discharge in nearly half of the participants. Two women presented with uterine prolapse, while one woman each

presented with bleeding per vaginum and a polypoidal cervical growth.

Comparison of Cellularity

Adequate cellularity was observed in 430 (97.73%) conventional Pap smear (CPS) preparations and 439 (99.77%) liquid-based cytology (LBC) preparations. Inadequate cellularity was observed in 10 (2.27%) CPS preparations and 1 (0.23%) LBC preparation.

Table 2. Comparison of Cellular Adequacy Between Conventional Pap Smear and Liquid-Based Cytology

Cellularity	CPS, n	LBC, n	χ^2	df	p
Adequate	430	439	7.457	1	.0112*
Inadequate	10	1	—	—	—
Total	440	440			

Note. CPS = conventional Pap smear; LBC = liquid-based cytology. *p < .05.

The difference in cellular adequacy between CPS and LBC preparations was statistically significant ($\chi^2 = 7.457$, df = 1, p = .0112), with LBC demonstrating a higher proportion of preparations with adequate cellularity.

Comparison of Cellular Distribution

Uniform cellular distribution was not observed in any of the conventional Pap smear preparations, whereas uniform cellular distribution was observed in 436 (99.09%) LBC preparations.

Endocervical/Transformation Zone Component

Endocervical cells were identified in 301 (68.41%) conventional Pap smear preparations and 335 (76.14%) LBC preparations, indicating a higher frequency of

endocervical/transformation-zone component representation in LBC preparations.

Comparison of Cellular Overlapping

Cellular overlapping was observed in 428 (97.27%) conventional Pap smear preparations compared with 112 (25.45%) LBC preparations.

Comparison of Morphological Changes

Morphological changes, including nuclear and cytoplasmic distortion, cellular shrinkage, elongation, and cytoplasmic vacuolization, were observed in 40 (9.09%) conventional Pap smear preparations and 248 (56.36%) LBC preparations.

Table 3. Comparison of Morphological Changes Between Conventional Pap Smear and Liquid-Based Cytology

Morphological changes	CPS, n	LBC, n	χ^2	df	p
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Present	40	248	221.161	1	<.0001*
Absent	400	192	—	—	—
Total	440	440			

Note. CPS = conventional Pap smear; LBC = liquid-based cytology. *p < .05.

The frequency of morphological changes differed significantly between the two preparation techniques ($\chi^2 = 221.161$, df = 1, p < .0001). Morphological changes were more frequently recorded in LBC preparations than in conventional Pap smear preparations.

Comparison of Inflammatory Background

An inflammatory background was present in 317 (72.05%) conventional Pap smear preparations compared with 119 (27.05%) LBC preparations.

Table 4. Comparison of Inflammatory Background Between Conventional Pap Smear and Liquid-Based Cytology

Inflammatory background	CPS, n	LBC, n	χ^2	df	p
Present	317	119	178.2147	1	<.00001*
Absent	123	321	—	—	—
Total	440	440			

The inflammatory background was significantly less frequent in LBC preparations than in conventional Pap smear preparations ($\chi^2 = 178.2147$, df = 1, p < .00001).

A haemorrhagic background was identified in 158 (35.91%) conventional Pap smear preparations compared with 9 (2.05%) LBC preparations.

Comparison of Haemorrhagic Background

Table 5. Comparison of Haemorrhagic Background Between Conventional Pap Smear and Liquid-Based Cytology

Haemorrhagic background	CPS, n	LBC, n	χ^2	df	p
Present	158	9	161.883	1	<.0001*
Absent	282	431	—	—	—
Total	440	440			

. CPS = conventional Pap smear; LBC = liquid-based cytology.
* $p < .05$.

The frequency of haemorrhagic background was significantly lower in LBC preparations than in conventional Pap smear preparations ($\chi^2 = 161.883$, $df = 1$, $p < .0001$).

Diathetic Background and Preparation Artefacts

A diathetic background was observed in one case of squamous cell carcinoma in both preparation methods. Drying artefact was identified in six conventional Pap smear preparations and was not observed in any LBC preparation.

Overall, 51 (11.59%) conventional Pap smear preparations were reported as unsatisfactory compared with 1 (0.23%) LBC preparation

Comparison of Cytological Diagnosis

Cytological diagnoses were classified according to the 2014 Bethesda System.

Inflammatory smears constituted the commonest cytological diagnosis in both preparation methods. NILM was reported in 69 conventional Pap smear preparations and 71 LBC preparations, whereas epithelial cell abnormalities were identified in 23 conventional Pap smear preparations and 28 LBC preparations.

The 10 CPS preparations and 1 LBC preparation reported as having inadequate cellularity should be explicitly identified as unsatisfactory preparations in Figure 7 if they were classified as unsatisfactory for cytological interpretation. The denominator used for calculating percentages in Figure 7 should correspond to the number of preparations actually included in the cytological diagnosis analysis. Accordingly, the figure should clearly distinguish satisfactory preparations from those reported as unsatisfactory.

Comparison of Epithelial Cell Abnormalities

Among the reported epithelial abnormalities, ASC-US was identified in 9 conventional Pap smear preparations and 13 LBC preparations. ASC-H was identified in 4 CPS and 5 LBC preparations. LSIL and HSIL with squamous cell carcinoma were each identified in one case by both methods. AGC-NOS was identified in eight cases by each technique.

Table 6. Comparison of Epithelial Cell Abnormalities Between Conventional Pap Smear and Liquid-Based Cytology

Cytological diagnosis	CPS, n	LBC, n
ASC-US	9	13
ASC-H	4	5
LSIL	1	1
HSIL with SCC	1	1
AGC-NOS	8	8
Total	23	28

ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; SCC = squamous cell carcinoma; AGC-NOS = atypical glandular cells—not otherwise specified.

The overall difference in the distribution of epithelial cell abnormalities between conventional Pap smear and LBC preparations was not statistically significant ($\chi^2 = 0.333$, $df = 1$, $p = .5639$).

Representative photomicrographs of epithelial abnormalities are presented in Figures 8–12. Figure 8A and Figure 8B demonstrate ASC-US in CPS and LBC preparations,

respectively. Figures 9A and 9B demonstrate LSIL, while Figures 10A and 10B illustrate HSIL in conventional and LBC preparations. Figures 11A and 11B demonstrate squamous cell carcinoma, and Figures 12A and 12B show AGC-NOS in the two preparation techniques.

Page | 9 Detection of Organisms

Infectious organisms were identified in both conventional Pap smear and LBC preparations, with no appreciable difference in organism detection between the two preparation methods.

Screening Time

The mean screening time was approximately 10 minutes for conventional Pap smear preparations compared with approximately 5 minutes for LBC preparations, representing an approximately 50% reduction in screening time with LBC.

Discussion

The present prospective comparative study evaluated 440 cervical cytology specimens using conventional PAP smear and liquid-based cytology. The two techniques were compared across multiple parameters, including cellular adequacy, distribution of cells, endocervical component, cellular overlapping, morphological changes, inflammatory and hemorrhagic background, artifacts, unsatisfactory specimens, cytological interpretation and screening time. The findings demonstrated several practical advantages of LBC over conventional PAP smear, particularly in relation to preparation quality and microscopic screening.

The age of the women in the present study ranged from 20 to 77 years, with the largest proportion belonging to the 30–39-year age group (39.31%), followed by the 40–49-year group (34.54%). This distribution reflects the age group in which symptomatic women commonly present for cervical evaluation in tertiary care settings. Similar studies comparing conventional cytology and LBC have included predominantly reproductive-age and middle-aged women. Patel et al. evaluated 600 women undergoing cervical screening, while Maheshwari et al. included 969 women aged 21–65 years, demonstrating that comparative cytology studies are largely performed in similar age groups.^{11, 12}

Cellular Adequacy

Cellular adequacy was significantly better in the LBC preparations. Adequate cellularity was observed in 439 of 440 LBC preparations compared with 430 conventional PAP smears. Only one LBC preparation was inadequate, whereas 10 conventional smears showed inadequate cellularity. The difference was statistically significant ($\chi^2=7.457$, $p<0.001$).

The higher cellular adequacy observed with LBC can be explained by the processing of the entire collected sample in a preservative medium rather than relying on immediate and complete transfer of exfoliated cells from the collection device onto the glass slide. In conventional cytology, some cellular material may remain on the sampling device or may be unevenly distributed during direct smearing. LBC processing concentrates the cellular material and facilitates preparation of a standardized cellular deposit.

Similar improvements in specimen quality with liquid-based methods have been reported previously. Sharma et al. demonstrated advantages of SurePath LBC in the preparation and interpretation of cervicovaginal cytology, while Maheshwari et al. reported better-quality liquid-based preparations in their comparative study.^{10, 12}

Uniform Cellular Distribution

One of the most striking differences in the present study was the uniformity of cellular distribution. None of the conventional PAP smears demonstrated uniform distribution, whereas 436 of 440 LBC preparations demonstrated an even distribution of cells. This finding supports the fundamental technical advantage of liquid-based preparation, in which cellular material is processed before deposition on the slide.

Uniform distribution is important because it allows the cytopathologist to examine individual cells more easily and reduces the time required to search through thick or uneven areas of the smear. The production of a relatively standardized cellular deposit is one of the principal reasons LBC has been adopted in many screening programmes.

The findings are consistent with previous comparative studies demonstrating cleaner and more evenly distributed cellular preparations with LBC. Sharma et al. reported improved smear quality with SurePath LBC, while Patel et al. also evaluated cellular distribution as an important comparative parameter between conventional and liquid-based cytology.^{10, 11}

Endocervical Cells and Transformation-Zone Sampling

Endocervical cells were identified in 301 (64.4%) conventional PAP smears and 335 (76.13%) LBC preparations. Thus, the presence of endocervical cells was higher in LBC preparations in the present study.

The presence of endocervical or transformation-zone cells is an important quality indicator because sampling of the squamocolumnar junction is essential for effective cervical screening. Improved representation of endocervical cells with LBC may be related to the collection method and retention of sampled material in the preservative medium.

Previous studies have reported variable findings regarding the endocervical component. Some studies have demonstrated better representation in LBC, whereas others have found little difference between the two methods. Such variability may be influenced by the sampling device, sampling technique, patient age, menopausal status and transformation-zone anatomy.^{9, 10}

Cellular Overlapping

Cellular overlapping was markedly reduced in LBC preparations. Overlapping was observed in 428 conventional PAP smears compared with 112 LBC preparations, and the difference was highly statistically significant ($\chi^2=475.588$, $p<0.0001$).

This finding is particularly important from a screening perspective. Extensive overlapping of cells can obscure nuclear details and make the recognition of atypical cells more difficult. In conventional preparations, the direct spreading of a relatively large volume of cellular material onto the slide can result in thick areas with overlapping cells. In contrast, processing of the sample in LBC produces a more concentrated but relatively thin and uniform preparation.

The marked reduction in cellular overlapping observed in the present study is in keeping with the observations of previous comparative studies in which liquid-based preparations were generally considered easier to screen because of improved cellular distribution and reduced crowding.⁹⁻¹¹

Cytomorphological Changes

An important finding in the present study was the significantly higher frequency of morphological changes in LBC preparations. Morphological changes were observed in 248 LBC preparations compared with 40 conventional PAP smears ($\chi^2=221.161$, $p<0.0001$).

The morphological changes evaluated in the present study included nuclear-cytoplasmic distortion, cellular shrinkage or elongation, cytoplasmic vacuolization and changes in cytoplasmic borders. These findings represent an important consideration when interpreting LBC preparations because processing steps such as fixation, centrifugation, sedimentation and transfer of the cellular pellet may influence cytomorphology.

This observation differs from some reports in which LBC preparations demonstrated equal or fewer morphological artifacts compared with conventional smears. However, differences in the type of LBC technology, processing protocol and staining technique may account for the variation between studies. Sharma et al. specifically evaluated cytomorphological features in conventional and SurePath preparations, highlighting that the advantages of LBC should be interpreted together with familiarity with the characteristic morphology of processed cells.¹⁰

The increased frequency of morphological changes in the present study therefore emphasizes the importance of adequate cytopathologist experience with the particular LBC processing technique used in the laboratory.

Inflammatory Background

Inflammatory background was observed in 317 conventional PAP smears compared with 119 LBC preparations, with a highly significant difference ($\chi^2=178.2147$, $p<0.00001$). Although inflammatory cytological diagnoses were reported in both groups, the inflammatory cellular background was considerably reduced in the LBC preparations.

This finding can be explained by the processing characteristics of LBC. In conventional smears, inflammatory cells, mucus, blood and cellular debris are deposited together with epithelial cells and may obscure diagnostic cellular details. In LBC, processing can remove or reduce some of these background components and concentrate the epithelial cells into a cleaner preparation.

Previous comparative studies have similarly reported cleaner backgrounds with LBC. Patel et al. and Sharma et al. both evaluated inflammatory background as an important quality parameter and demonstrated advantages associated with liquid-based preparations.^{10, 11}

Hemorrhagic Background

A marked reduction in hemorrhagic background was observed with LBC. Hemorrhagic material was present in 158 conventional PAP smears compared with only 9 LBC

preparations. The difference was highly significant ($\chi^2=161.883$, $p<0.0001$).

Blood is an important source of obscuring material in cervical cytology, particularly in symptomatic women with cervical erosion, postcoital bleeding or abnormal uterine bleeding. Extensive blood contamination may obscure epithelial cells and interfere with recognition of abnormal nuclear features. The substantially cleaner background in LBC observed in the present study therefore represents an important practical advantage.

The findings are consistent with previous comparative studies showing reduction in obscuring blood and other background material with liquid-based preparations.^{10, 11}

Diathetic Background and Artifacts

Diathetic background was identified in one case of squamous cell carcinoma in both conventional and LBC preparations. This finding demonstrates that certain tumour-associated background features may be preserved in both preparation techniques.

Drying artifacts, however, were identified in six conventional PAP smears and were not observed in any LBC preparation. The difference can be attributed to the immediate fixation requirements of conventional cytology. Delayed fixation or inadequate fixation of directly spread cellular material may result in air-drying artifacts and compromise cytological interpretation. LBC samples are collected directly into a preservative medium, reducing the risk of air-drying during the initial handling of the specimen.

Unsatisfactory Smears

The overall rate of unsatisfactory specimens was substantially higher with conventional PAP smear. Fifty-one of 440 conventional PAP smears (11.59%) were considered unsatisfactory compared with only one LBC preparation.

Among conventional smears, the causes of unsatisfactory preparations included scant cellularity (10 cases), obscuring inflammation (23 cases), hemorrhagic background (12 cases) and artifacts (6 cases). The single unsatisfactory LBC preparation was due to scant cellularity.

Reduction in unsatisfactory specimens represents one of the major practical advantages of LBC. Unsatisfactory cytology necessitates repeat sampling, which increases cost, patient inconvenience and the possibility of delayed diagnosis. Previous studies have also reported lower rates of unsatisfactory specimens with LBC, although systematic reviews have shown

that the extent of reduction varies depending on study design and laboratory conditions.^{13, 12}

The finding in the present study is particularly relevant to resource-constrained settings because reducing repeat sampling may partially offset the additional processing requirements of LBC.

Cytological Interpretation

The overall cytological interpretation showed that inflammatory smears constituted the most common diagnostic category in both techniques. NILM was reported in 69 conventional PAP smears and 71 LBC preparations, while atrophic changes were identified in three preparations by each technique.

Epithelial cell abnormalities were detected in 23 conventional PAP smears and 28 LBC preparations. ASC-US was identified in 9 conventional smears and 13 LBC preparations, while ASC-H was identified in 4 and 5 cases, respectively. LSIL and HSIL with SCC were detected in similar numbers in the two preparations, whereas AGC-NOS was identified in eight cases by each method.

The overall findings indicate that although LBC produced a better-quality smear, the difference in detection of individual epithelial abnormalities was relatively limited in this study. This observation is important because improved specimen quality does not necessarily translate into a dramatic difference in the number of high-grade lesions detected in every study population.

Maheshwari et al. similarly compared conventional and liquid-based cytology with histopathological correlation and found that both techniques could identify cervical epithelial abnormalities, although differences in preparation quality were observed.¹² Singh et al. also demonstrated that liquid-based cytology and conventional cytology may show broadly comparable diagnostic categories while differing in technical quality.⁹

Detection of Infectious Organisms

Inflammatory organisms, when present, were identified in both conventional and liquid-based preparations. This indicates that the processing used in the present study did not prevent recognition of infectious or reactive cytological features.

The ability of cervical cytology to identify organisms and reactive changes remains clinically useful because many women presenting for screening in resource-limited settings may also have symptoms such as vaginal discharge or persistent leucorrhoea.

Screening Time

The average screening time was approximately 10 minutes for conventional PAP smears compared with 5 minutes for LBC preparations. The shorter screening time observed with LBC can be attributed primarily to the more uniform distribution of cells, reduction in cellular overlapping and cleaner background.

A cytotechnologist or pathologist can therefore examine the cellular deposit more rapidly because the proportion of the slide requiring detailed screening is reduced. Previous comparative studies have also highlighted improved screening characteristics with LBC.^{10, 11}

Overall Interpretation

Taken together, the findings of the present study demonstrate that LBC produced a substantially better-quality cytological preparation than conventional PAP smear in several important technical parameters. LBC showed higher cellular adequacy, markedly improved cellular distribution, reduced overlapping, cleaner inflammatory and hemorrhagic background, fewer artifacts and a much lower proportion of unsatisfactory preparations.

At the same time, the significantly higher frequency of morphological changes observed in LBC preparations represents an important limitation and indicates that pathologists should be familiar with the cytomorphological characteristics associated with the processing technique. The detection of epithelial abnormalities was broadly comparable between the two techniques, although slightly more abnormalities, particularly ASC-US and ASC-H, were identified in LBC preparations.

The results are broadly consistent with the findings of published comparative studies showing that LBC improves specimen quality and screening characteristics, although differences in diagnostic yield between studies may reflect differences in population, sampling technique, preparation system and reporting practices.⁹⁻¹²

In the present study, LBC yielded a lower rate of unsatisfactory smears and superior specimen quality, thereby reducing the likelihood of repeat sampling. In addition, the residual sample can be used for ancillary testing, including high-risk human papillomavirus (HPV) testing and other molecular assays, without requiring a repeat specimen. These advantages improve the efficiency of cervical cancer screening programs and may offset the higher upfront costs by reducing repeat visits, minimizing diagnostic delays, and optimizing laboratory workflow.

Generalizability

The findings of the present study may be generalized primarily to women attending tertiary care gynecology clinics in resource-constrained settings similar to the sub-Himalayan region of North India. The study included a relatively large sample of 440 women and evaluated both conventional Pap smear (CPS) and liquid-based cytology (LBC) from the same participants, thereby minimizing inter-individual variability. The superior specimen adequacy, cleaner background, reduced cellular overlap, and lower unsatisfactory smear rate observed with LBC are likely applicable to comparable healthcare settings where cervical cancer screening relies predominantly on cytology. However, caution should be exercised when extrapolating these findings to organized population-based screening programs, asymptomatic populations, or laboratories using different LBC processing systems because diagnostic performance may vary according to sampling techniques, laboratory expertise, and patient characteristics.

Limitations

These limitations may have resulted in overestimation or underestimation of the advantages associated with LBC. The absence of histopathological confirmation limits conclusions regarding diagnostic superiority, while selection bias restricts applicability to the general population. Nevertheless, the statistically significant improvements observed in specimen adequacy, background clarity, cellular distribution, and screening efficiency strongly support the technical advantages of LBC.

Conclusion

Liquid-based cytology demonstrated significant advantages over conventional Pap smear cytology across multiple technical and screening parameters. Compared with CPS, LBC produced significantly higher specimen adequacy (Table 2), more uniform cellular distribution (Figure 3), better transformation-zone representation, reduced cellular overlapping (Figure 4), cleaner inflammatory and hemorrhagic backgrounds (Tables 4 and 5), fewer preparation artifacts, and a substantially lower rate of unsatisfactory smears (Figure 6). Furthermore, LBC reduced screening time by approximately 50%, improving laboratory efficiency.

Although LBC preparations exhibited more processing-related cytomorphological alterations, these changes did not adversely affect cytological interpretation when evaluated by experienced cytopathologists. Detection of epithelial cell abnormalities was broadly comparable between the two techniques, with a slight increase in abnormality detection using LBC. Overall, the findings suggest that LBC provides superior specimen quality

and screening efficiency and represents a valuable alternative to conventional Pap smear cytology for cervical cancer screening.

Recommendations

1. Liquid-based cytology should be considered for routine cervical cancer screening in tertiary care centers because of its superior specimen quality and lower unsatisfactory smear rate.
2. Cytopathologists should receive specific training regarding LBC-associated cytomorphological alterations to ensure accurate interpretation.
3. Healthcare institutions should evaluate the long-term cost-effectiveness of implementing LBC, particularly in regions with high cervical cancer burden.
4. Future multicenter studies involving larger populations should be conducted to validate the present findings.
5. Future research should incorporate histopathological correlation and HPV testing to evaluate the diagnostic accuracy and clinical utility of LBC more comprehensively.
6. Comparative studies assessing different commercially available LBC systems would help establish standardized protocols for routine practice.

List of Abbreviations

Abbreviation	Full Form
AGC	Atypical Glandular Cells
AGC-NOS	Atypical Glandular Cells – Not Otherwise Specified
ASC-H	Atypical Squamous Cells – Cannot Exclude HSIL
ASC-US	Atypical Squamous Cells of Undetermined Significance
CPS	Conventional Pap Smear
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
LBC	Liquid-Based Cytology
LSIL	Low-grade Squamous Intraepithelial Lesion
NILM	Negative for Intraepithelial Lesion or Malignancy
SCC	Squamous Cell Carcinoma
TZ	Transformation Zone

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Individual participant data are not publicly available due to confidentiality and privacy considerations.

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- Methodology
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- Supervision
- Writing – Original Draft
- Writing – Review & Editing

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- Data Curation
- Formal Analysis

- Investigation
- Writing – Review & Editing

Anurag Sharma

- Patient Recruitment
- Clinical Investigation
- Resources
- Data Collection

Satyendra Sharad

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