

Can LBC Completely Replace Conventional Pap Smear in Developing Countries

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Received: 7 November 2017 / Accepted: 16 April 2018 / Published online: 18 May 2018
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Abstract

Background A number of screening techniques have been developed to reduce the incidence of cervical cancer, most

common of which is conventional Pap smear (CPS) being overtaken by liquid-based cytology (LBC) in most of the developed countries. There are a number of studies with conflicting results, and no method has been shown superior in terms of all parameters. LBC was introduced in our hospital in 2014, and we planned to do a study and compare results of the two techniques. This study aims to compare the two methods in terms of sensitivity, specificity, positive predictive value and negative predictive value, turnover time, cost-effectiveness, sample adequacy. This study has been done in 100 women with unhealthy cervix to increase the output.

Method This was a prospective observational study. A total of 100 women fulfilling the inclusion criteria were subjected to screening test. In first 50 cases, first

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conventional Pap smear was taken and then LBC, and in remaining 50 cases, first LBC and then conventional Pap smear were taken; this was done to remove bias.

Results The number of unsatisfactory slides was reduced with LBC, and turnover time was less for LBC. The detection of ASCUS was increased with LBC, but the detection of higher-grade lesions (HSIL and SCC) was equal with both tests.

Conclusion The superiority of LBC with respect to reduction in the number of unsatisfactory slides and less turnover time is being offset with increased detection of low-grade lesions subjecting women to further testing increasing the cost of programme and anxiety among women. It is difficult to say that it can completely replace conventional Pap smear in low-resource settings.

Keywords Liquid-based cytology · ASCUS · HSIL · LSIL · SCC · AGUS

Introduction

Cervical cancer is the fifth most common cancer in humans, the third most common cancer worldwide and the second most common cancer in India [1]. Cervical cancer is the commonest cancer causing death among women in developing countries [2]. Mortality due to cervical cancer is also an indicator of health inequities as 86% of all deaths due to cervical cancer occurs in developing, low- and middle-income countries [3]. The worldwide incidence of cervical cancer is approximately 510,000 new cases annually with approximately 288,000 deaths worldwide. Every year in India 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. India has population of 432.2 million aged 15 years and older who are at high risk of developing this cancer [ICO information Centre on HPV and cancer (Summary report 2014-08-22)]. The projected number of new cervical cancer cases in 2025 is 203,757. The projected number of cervical cancer deaths in 2025 is 11,517 (WHO cervical cancer summary report update, September 2010). The fact that cervical cancer is 100% treatable and preventable makes it an important area of action. The incidence of cervical cancer has decreased dramatically in many developed countries since cytology began to be used for cervical cancer screening in 1960s. The sensitivity of conventional cytology has been estimated to be between 30 to 87% and its specificity between 86 to 100%, but the rate of false negative may be as high as 25 to 50%. It is estimated that in UK, 80% of all cases of cervical cancer are prevented by the cervical cancer screening programme.

Yet, despite this success, there have been problems. First challenge was high percentage of inadequate smears, up to

15% in some centres. A smear reported to be inadequate generates severe anxiety in women and burdens the system by requiring a repeat. Second concern was occurrence of truly negative smears in women who are subsequently found to have abnormalities. Nearly 30% of new cancer cases each year occur among women who underwent Pap testing. Errors of sampling, fixation, interpretation or follow-up may be responsible for the missed cases.

The idea for liquid-based cytology started to be developed in 1970s; at that time, it was part of desire to automate the process of cervical cytology. The automation aspect was unsuccessful at that time, largely because of the inadequate processing power of the contemporary computers; however, the idea for LBC continued to be developed. LBC could produce sample which was fully representative of material removed and potentially easier to screen. Liquid-based thin-layer preparations of cervical specimens are characterized by excellent fixation, homogenous thin-layer dispersal of cellular material, crisp cellular detail and a clear background. Evidence is insufficient, however, to confirm that LBC is more accurate than CPS. The present study incorporating 100 women with unhealthy cervix aimed to compare conventional cytology with LBC, and data was analysed.

Materials and Methods

The study was conducted in a tertiary level hospital. A total of 100 women who had come to visit gynaecology OPD and had unhealthy cervix on per speculum examination were selected. The incidence of abnormal smear is 1.5–5%, and the sample size of 100 is calculated with 1.5% being cutoff. Informed written consent was taken. In first 50 cases, first CPS was taken followed by LBC and in next 50 cases first LBC and then CPS were taken; this is to reduce bias due to cell collection technique. These samples were sent to laboratory. For LBC SurePath method of cell collection was followed; that is, after taking the smear the brush head along with the sample was detached and kept in the solution containing preservative liquid. LBC sample was further processed in a nanocyte machine. Both slides were stained by Papanicolaou stain. The slides of conventional Pap smear were read by one pathologist, slides of LBC were read by another pathologist, and both of them were blinded from the results. The data were collected from them, and results were analysed. The sensitivity of two techniques was evaluated with histopathology as gold standard. ASCUS and LSIL were considered as low-grade lesions, and for histopathology CIN 2 and 3 were considered as high grade. All lesions of ASCUS and the above were subjected to colposcopy, and guided biopsy was taken. CIN 2 was taken as end point to compare the two methods.

Results

Out of 100 women, maximum were in age group of 30–39 years, i.e. 42 and the rest were in perimenopausal group (40–49 years). Mean age of study population was 41.4. Age range was 25–75 years. Five cases were nulliparous, and the rest were multiparous. Majority of unhealthy cervix was in form of cervical erosion, 37 cases had both hypertrophy and erosion, four had congestion, five had cervical descent, and four had cervical polyp. Of 100 cases evaluated with CPS, 93 had satisfactory smears for evaluation and seven were unsatisfactory, whereas for LBC only 1 smear was unsatisfactory for evaluation and that was due to scanty cellularity. Out of 100 cases, 28 underwent colposcopy and guided biopsy; 25 cases were detected to have epithelial abnormality of ASCUS and the above and three cases underwent colposcopy because of clinical suspicion. Out of 100 cases, in CPS, 39 were found to have no e/o intraepithelial malignancy (NILM), 28 were inflammatory, 7 cases had ASCUS, four cases had ASCH, four cases had HSIL, two cases had AGUS, five had atrophic smears, two were detected to have candida, and two were detected as squamous cell carcinoma. In LBC, 56 were found to have no e/o intraepithelial malignancy (NILM), 18 were inflammatory, 12 cases had ASCUS, one case had ASCH, four cases had HSIL, four had atrophic smears, and two were detected as squamous cell carcinoma (Table 1). The time required to read LBC slides was significantly less as compared to conventional Pap smear (Table 2).

All women with epithelial abnormality of ASCUS and the above were subjected to colposcopy. Primary end point was histopathologically confirmed CIN 2 or more. Out of 28 cases subjected to colposcopy, two cases had chronic cervicitis, the rest were diagnosed to have epithelial abnormality. A total of 17 cases of epithelial abnormality

Table 2 Comparison of time required for reading slides by the two methods

| | Conventional pap | Liquid-based cytology | P value |
|-----------------|------------------|-----------------------|---------|
| Time in minutes | 400 | 200 | 0.004 |

were detected by conventional Pap smear, and two cases were detected to have SCC. Out of remaining nine cases of epithelial abnormality diagnosed by cervical biopsy, two were unsatisfactory for evaluation and remaining seven were reported as normal. Out of 19 cases of epithelial abnormality, seven were detected as ASCUS, four as HSIL, four as ASCH, two as AGUS and two as squamous cell carcinoma (Table 3).

Out of seven cases reported as ASCUS, four had CIN 1 on histopathology, two had CIN 2, and one had chronic cervicitis.

Out of 28 cases who underwent colposcopically guided biopsy, only one was unsatisfactory for evaluation on LBC and seven were reported as normal. A total of 17 cases of epithelial abnormality were detected by LBC, and two were detected to have SCC. Out of 19, 12 were reported as ASCUS, one as ASCH, four as HSIL, and two as SCC. Out of 12 cases reported as ASCUS, seven were diagnosed to have CIN 1, four were diagnosed as CIN 2, and one as CIN 3. Out of four HSIL cases, one was diagnosed as CIN 2 and three as CIN 3. Two cases of SCC were confirmed on biopsy. Comparing Tables 3 and 4, higher-grade lesion was missed more by LBC. Major drawback of conventional Pap smear was the number of unsatisfactory smears (Table 4).

Figure 1 compares both conventional Pap smear and LBC in one of the slides of SCC among two and shows disorganized clusters with marked pleomorphism, hyperchromasia. Background of conventional Pap smear shows

Table 1 Comparison of cytology findings of both tests as per sampling method used

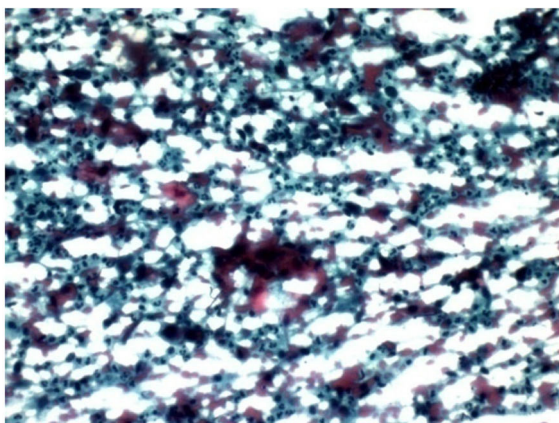
| Cytology findings | First 50 samples | | Next 50 samples | |
|-------------------|------------------|-----|-----------------|-----|
| | CPS | LBC | CPS | LBC |
| Unsatisfactory | 04 | 01 | 03 | 00 |
| NILM | 19 | 26 | 20 | 30 |
| Inflammatory | 13 | 10 | 15 | 08 |
| ASCUS | 04 | 07 | 03 | 05 |
| ASCH | 02 | 00 | 02 | 01 |
| HSIL | 02 | 02 | 02 | 02 |
| AGUS | 01 | 00 | 01 | 00 |
| SCC | 01 | 01 | 01 | 01 |
| Atrophic | 03 | 02 | 02 | 02 |
| Candida | 01 | 01 | 01 | 01 |
| Total | 50 | 50 | 50 | 50 |

Table 3 Correlation of CPS with histopathology report ($n = 28$)

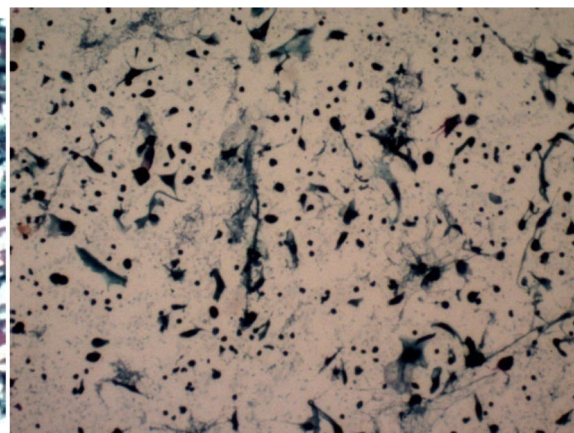
| Cytology findings | Histopathology | | | | | Total |
|-------------------|--------------------|-------|-------|-------|-----|-------|
| | Chronic cervicitis | CIN 1 | CIN 2 | CIN 3 | SCC | |
| Unsatisfactory | – | 02 | – | – | – | 02 |
| NILM | 01 | 03 | 03 | – | – | 07 |
| ASCUS | 01 | 04 | 02 | – | – | 07 |
| ASCH | – | – | 04 | – | – | 04 |
| AGUS | – | – | – | 02 | – | 02 |
| HSIL | – | – | 01 | 03 | – | 04 |
| SCC | – | – | – | – | 02 | 02 |
| Total | 02 | 09 | 10 | 05 | 02 | 28 |

Table 4 Correlation of liquid-based cytology with histopathology ($n = 28$)

| Cytology findings | Histopathology | | | | | Total |
|-------------------|--------------------|-------|-------|-------|-----|-------|
| | Chronic cervicitis | CIN 1 | CIN 2 | CIN 3 | SCC | |
| Unsatisfactory | – | 01 | – | – | – | 01 |
| NILM | 02 | 01 | 04 | 01 | – | 08 |
| ASCUS | – | 07 | 04 | 01 | – | 12 |
| ASCH | – | – | 01 | – | – | 01 |
| HSIL | – | – | 01 | 03 | – | 04 |
| AGUS | – | – | – | – | – | – |
| SCC | – | – | – | – | 02 | 02 |
| Total | 02 | 09 | 10 | 05 | 02 | 28 |



Conventional pap smear



Liquid based cytology

Fig. 1 Slide of SCC comparing both conventional Pap smear and LBC

tumour diathesis. Morphology of cells is better with conventional Pap smear.

Figure 2 shows the HSIL slide encountered in the study comparing both LBC and conventional pap smear, LBC showing thick and irregular nuclear membrane, the biopsy of above case shows features suggestive of CIN3 (Fig. 3).

Out of nine cases of CIN 1, as per conventional Pap smear, four (44.44%) were reported as ASCUS, three as normal, and two were unsatisfactory for evaluation. As per LBC, 1 was unsatisfactory for evaluation, one was normal, and seven (77.77%) were reported as ASCUS. Thus, LBC was more sensitive in detecting cases of CIN 1.

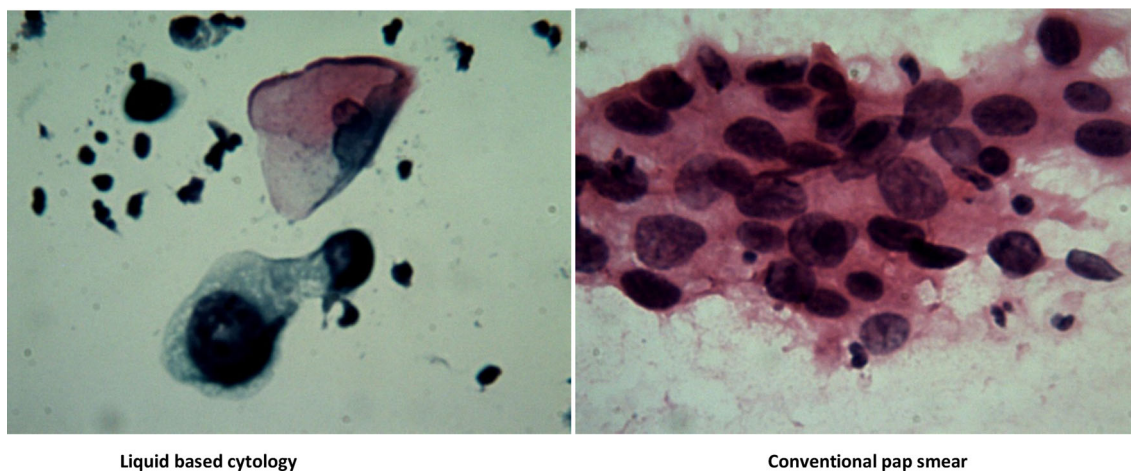
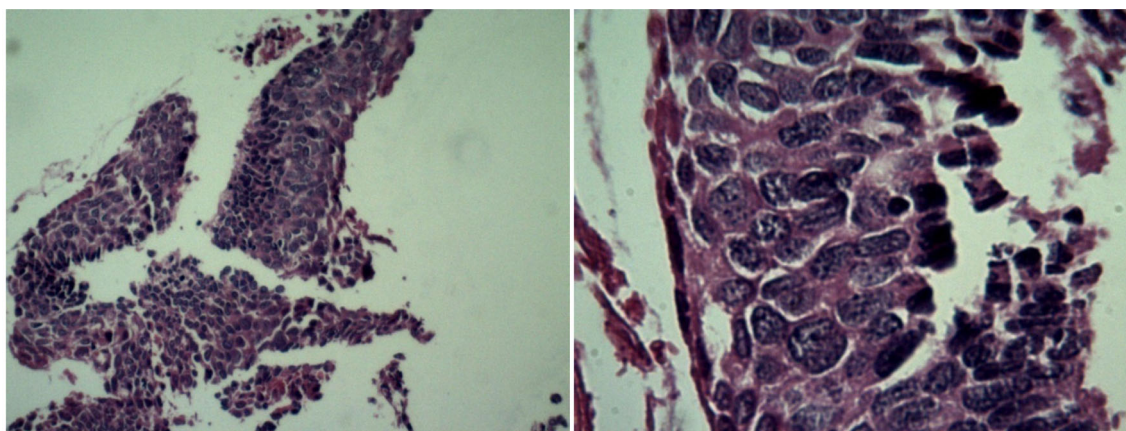


Fig. 2 Slide of HSIL comparing both conventional Pap smear and LBC



Biopsy showing f/s/o CIN3(low power) High power view

Fig. 3 Corresponding biopsy of the above case showing HSIL in both smears

Out of ten cases of CIN 2, as per conventional Pap smear, three were normal, two were detected as ASCUS, four as ASCH, and one as HSIL (70%). As per LBC, four were normal, four as ASCUS, one as ASCH, and one as HSIL (60%). Thus, conventional Pap smear was more sensitive in detecting CIN 2. Out of five cases of CIN 3, as per conventional Pap smear, three were reported as HSIL and two as AGUS (100%). As per LBC, one was reported as normal, one as ASCUS, and three as HSIL (80%). Thus, conventional Pap smear was more sensitive in detecting CIN 3 (Table 5). Even though the number of epithelial abnormality detected by both methods is exactly 17, when correlated with histopathology, conventional Pap smear was more sensitive in detecting higher-grade lesions. The corresponding cytology on LBC of five missed higher-grade lesions (ASCH and AGUS) was ASCUS [4] and 1 NILM.

Out of two cases of squamous cell carcinoma, both conventional Pap smear and LBC reported as SCC. But in

conventional morphology of cells was more clear and sheets of malignant cells could be seen. In LBC, morphology was less clear with scanty cellularity.

Thus, the number of unsatisfactory smears was definitely reduced by LBC (from 7 to 1%). Conventional Pap smear was more sensitive in detecting high-grade epithelial abnormalities. LBC was more sensitive in detecting low-grade malignancy (ASCUS).

Taking CIN 2 as the end point, the sensitivity of conventional Pap smear was better as compared to liquid-based cytology (Table 6).

Discussion

The conventional Pap smear has been utilized for cervical cancer screening for more than 50 years. Despite being credited with a 70% reduction in mortality for cervical cancer screening, the false negative rate is still a cause for

Table 5 Correlation of conventional Pap smear, liquid-based cytology and histopathology

| Histopathology | Conventional Pap smear | | | | | | | Liquid-based cytology | | | | | | |
|-----------------------------|------------------------|------|-------|------|------|------|-----|-----------------------|------|-------|------|------|------|-----|
| | U | NILM | ASCUS | ASCH | AGUS | HSIL | SCC | U | NILM | ASCUS | ASCH | AGUS | HSIL | SCC |
| CIN 1 (9) | 2 | 3 | 4 | – | – | – | – | 1 | 1 | 7 | – | – | – | – |
| CIN 2 (10) | – | 3 | 2 | 4 | – | 1 | – | – | 4 | 4 | 1 | – | 1 | – |
| CIN 3 (5) | – | – | – | – | 2 | 3 | – | – | 1 | 1 | – | – | 3 | – |
| Chronic cervicitis (2) | – | 1 | 1 | – | – | – | – | – | 2 | – | – | – | – | – |
| Squamous cell carcinoma (2) | – | – | – | – | – | – | 2 | – | – | – | – | – | – | 2 |
| Total (28) | 2 | 7 | 7 | 4 | 2 | 4 | 2 | 1 | 8 | 12 | 1 | – | 4 | 2 |

Table 6 Comparison between LBC and conventional Pap smear

| Parameters | Conventional Pap smear (%) | LBC (%) |
|---------------------------|----------------------------|---------|
| Sensitivity | 82.35 | 70.58 |
| Specificity | 93.97 | 91.56 |
| Positive predictive value | 73.68 | 63.15 |
| Negative predictive value | 96.29 | 93.82 |

concern. Liquid-based cytology has been introduced to overcome the shortcomings of conventional Pap smear, but still there is concern if it can replace conventional Pap smear in screening of cervical cancer due to conflicting results in various studies [4–8].

In our study, satisfactory smears on SurePath LBC were 99% as compared to 93% on conventional Pap smear. Quite similarly various studies have reported an increased number of satisfactory smears (72.2 to 92%) on liquid-based cytology than conventional Pap smears [9, 10]. This improvement for SurePath liquid-based cytology is related to the fact that 100% of collected sample is transferred to the fluid vial and that the cell enrichment process reduces obscuring material such as blood, mucus and inflammatory cells.

The time needed for LBC slides screening is also less as reported previously by various studies [11, 12]. This is due to multiple factors, including the 13-mm circle of stained cells, a smaller screening area than that found in conventional Pap smear; the optimal preservation and staining of cellular material, eliminating the additional screening time required with conventional smears due to air drying artifacts and the reduction or elimination of obscuring factors. This improvement in quality of slides is supported by various studies. In our study, the time to read 10 slides of CPS was about 40 min as compared to 20 min with LBC. The time required to read LBC slides is significantly less as compared to conventional Pap.

It has been reported by earlier studies that endocervical cells were detected less frequently with LBC as compared to conventional Pap smear [13]. The present study

supported this finding, where groups of endocervical cells (honeycomb appearance) were seen prominently in conventional Pap smear; in LBC very few glandular and endocervical cells were seen. The only two cases reported as AGUS were by conventional Pap smear. Out of these, one was reported as NILM and other as ASCUS by LBC. On histology both cases had severe dysplasia (CIN 3).

The most striking result of present study is the increase in detection of ASCUS cases with liquid-based cytology compared to CPS with no significant difference in detection of higher-grade cytologic lesions. This increased detection of low-grade cytologic lesions is supported by many studies [14, 15].

Several reviews and metaanalysis of performance of liquid-based cytology based on nonrandomized studies have been published but have reached conflicting conclusions. A recent systematic review on liquid-based cytology found one small randomized controlled trial only. The same review identified only five “high-quality” studies. Such studies did not show increased accuracy with liquid-based cytology in agreement with our results. The relative frequency of atypical cells of undetermined significance (ASCUS) varied between studies, but overall in high- and medium-quality studies more were classified as atypical cells by liquid-based cytology than by conventional cytology [15].

In this study, out of 12 cases reported as ASCUS by LBC as compared to seven by conventional Pap smear, seven were histologically confirmed as CIN 1. It is estimated that more than half of these abnormalities will regress to normal. The increased detection of low-grade cytological lesions by LBC might result in higher rates of further testing with HPV testing and colposcopic guided biopsy. This adds more burden in terms of cost apart from increased cost of LBC itself. However, patients who develop invasive cervical carcinoma in spite of their participation in the screening programme repeatedly show milder lesions (LSIL or ASCUS) in these preceding smears; this demonstrates the importance of cytological stringency. Thus, increased cost might be justified at the

cost of detecting low-grade cytological lesions, subjecting them to further testing which might pick up invasive lesions which otherwise might have been missed. Long-term studies are required for this. In the present study, the sensitivity of conventional Pap smear was higher (82.38 vs 70.58%) compared to LBC. The specificity of the two techniques was comparable, 93.97% for conventional Pap smear vs 91.56% for LBC. Conventional Pap smears demonstrated a tendency to be more accurate when histopathology was used as gold standard. Approximately 93% of high-grade readings in Pap smears corresponded with high-grade lesions in histopathology compared with 83% for LBC in one of the studies [15]. In our study, the detection of HSIL and SCC was equal with both tests. Due to small sample size, difference of 4–5 cases has dramatically decreased the sensitivity of LBC, though in most studies both methods have almost equal sensitivity.

The Australian Health Technology Advisory Committee Report and the Canadian Co-ordinating Office for Health Technology Assessment concluded that LBC would increase the detection of cervical abnormalities and decrease the number of unsatisfactory samples, but decided that the relative improvement in the sensitivity was not sufficient to mandate universal introduction of the technique.

On the basis of this analysis the main advantage of liquid-based cytology is reduction in the rate of unsatisfactory slides. Other established advantages are the shorter time needed for interpretation and the possibility of using the same sample for testing for human papilloma virus and other molecular tests.

We have not gone for cotesting with HPV. When decision regarding ASCUS and LSIL cases has to be taken, cotesting with high-risk HPV may be beneficial. In such scenario, we recommend LBC for screening. But in low-resource countries like India, conventional cervico-vaginal cytology may still hold a better option as compared to LBC since the detection of higher-grade lesions is better with conventional Pap smear.

In a study by Suba Eric et al., he recommends conventional cervical cytology as the primary screening tool. The study states that Papanicolaou screening services with or without HPV or visual screening services must be implemented without further delay in any setting where cervical screening is appropriate but unavailable with consideration given to HPV vaccination after, rather than before, full coverage of target demographic groups by screening services has been achieved or possibility has been excluded that HPV vaccination may be ineffective for cervical cancer prevention.

In low-resource settings, conventional cervical cytology may still be better option as compared to LBC. LBC is definitely recommended to decrease the number of

unsatisfactory smears, and cotesting with HPV may improve the detection of higher-grade lesions.

Conclusion

The number of unsatisfactory slides was reduced with liquid-based cytology. The turnaround time for LBC was less as compared to conventional Pap smear. The endocervical cells and glandular cells were seen better with conventional Pap smear. The detection of ASCUS was increased with LBC as compared to conventional Pap. The detection of higher-grade cytologic lesions (HSIL and SCC) was equal with both tests. Increased detection of low-grade lesions might increase the cost of the programme with further testing.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution.

Informed consent Informed consent was obtained from all the individual patients involved in the study.

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