



Liquid Based Cytology versus Conventional Cytology for Evaluation of Cervical PAP Smear

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The cervix is the narrow inferior segment of the uterus which projects into the vaginal vault. Conventional cervical cytology is a simple, cost effective method that has been in use for more than 50 years and is still a highly effective cervical cancer screening procedure. Liquid-based, thin-layer preparation of cervical cytology specimens was a subsequent modification in technique. The present study was split-sample study was to compare Thin Prep Liquid-based Cytology with Conventional Pap Smear, relying on a laboratory with long term experience of the former. In our study most of the Conventional preparations showed cell overlapping, inflammatory cells, blood and mucus that obscure the epithelial cell morphology which was much reduced in Liquid based preparations.

Keywords: Cervix; cervical cancer; pap smear; thin prep liquid-based cytology.

1. INTRODUCTION

Cytology is a branch of science that deals with the study of cells. Two main branches of cytology are: Aspiration cytology and Exfoliative cytology.

1.1 Exfoliative Cytology [1]

Exfoliative cytology is the study of normal and disease altered desquamated cells from various sites. The rate of desquamation varies with each tissue, its function, and metabolic capacities.

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Some of these desquamated cells accumulate in natural cavities and its recesses.

There are two types of cellular exfoliation:

1.2 Natural Spontaneous Exfoliation

The physiologically desquamated cells will often show, besides the normal changes of natural ageing the pathological changes as well. Vaginal cells in the vaginal pool secretion in the posterior vaginal fornix and mesothelial cells in the effusions of the pleural and abdominal cavities are studied by spontaneous exfoliation.

1.3 Artificial Exfoliation (Surface Microbiopsy)

Surface of the mucosa is scraped or tissue is aspirated with a needle and viable cells are traumatically exfoliated before their natural time of shedding. The study of exfoliative cytology was first described in the middle of the nineteenth century [2,3,4].

The Pap test is considered by many to be the most cost effective cancer reduction program ever devised [5]. Credit for its conception and development goes to George N. Papanicolaou, an anatomist and Greek immigrant to the United States. In 1928 he reported that malignant cells from the cervix can be identified in vaginal smears [6]. Later, in collaboration with the gynecologist Herbert Traut, who provided him with a large number of clinical samples, Papanicolaou published detailed descriptions of preinvasive cervical lesions [6]. Pathologists and physicians initially greeted this technique with skepticism, but by the late 1940s Papanicolaou's observations had been confirmed by others. The Canadian gynaecologist J. Ernest Ayre suggested taking samples directly from the cervix with a wooden spatula rather than from the vagina with a pipette as originally described by Papanicolaou [7].

Eventually, cytologic smears were embraced as an ideal screening test for preinvasive lesions, which, if treated, would be prevented from developing into invasive cancer. The first cervical cancer screening clinics were established in the 1940s [8]. Cervical cytology became the standard screening test for cervical cancer and premalignant cervical lesions with the introduction of the Papanicolaou (Pap) smear in 1941 [9].

Liquid-based, thin-layer preparation of cervical cytology specimens was a subsequent modification in technique. Terminology for reporting cervical cytology was standardized by the Bethesda System in 1988 [10]. This system has been revised several times, and the current system was developed in 2014 [11,12,13]. Liquid-based cytology is a technique that enables cells to be suspended in a monolayer and thus better morphological assessment is possible. It includes the preparation and evaluation of cells collected in a liquid fixative. It is being introduced in developed countries to improve the sensitivity of the Pap test. During recent years, it has also been used for non-gynecologic cytology, e.g. in breast cytology. Two technologies - Thin Prep (Cytoc Corp.) and SurePap (Tripath imaging, Inc.) have been more widely used [14].

The advantages of liquid-based cytology include improved sensitivity and specificity since fixation is better and nuclear details are well preserved. Singh et al. (2018) proved that LBC performed much better by showing more sensitivity, specificity and accuracy than the conventional method of cytology to detect recurrence of squamous cell carcinoma [15]. Abnormal cells are not obscured or diluted by other epithelial or inflammatory cells. There is, therefore, a lower rate of unsatisfactory cervical cytology samples.

The residual cell suspension can be used to make further cytological preparations or used for other tests like detection of human papilloma virus (HPV) DNA. Many researchers have endorsed that Liquid based cytology is able to work in a variety of adjunctive tests [16- 19]. Other ancillary techniques like immunocytochemistry can also be performed on the residual sample. The more widely used technologies for liquid-based cytology require expensive equipment [20-25].

2. MATERIALS AND METHODS

This study was conducted in the Department of Pathology, Sree Balaji Medical College and Hospital during October 2015 and September 2017. In our study we proposed to conduct a comparative analysis of cervical cytology by using CPS with ThinPrep LBC.

Samples were collected from patients attending the inpatients and outpatients Department of Gynaecology, Sree Balaji Medical College and Hospital after obtaining consent. Patients aging 18 years and above were randomly selected on the basis of complaints like bleeding per vaginum, irregular menses, pain in lower

abdomen, post coital bleeding. Totally 100 samples were studied. It is a prospective study design.

After a detailed history and thorough clinical examination, pap smears were taken from the cervix with an endocervical cytobrush and slides prepared. Smears were screened independently by observer and results were compared. The Bethesda system for reporting cervical cytology was used in both groups.

2.1 Method of Collection of PAP Smear

2.1.1 Patient Preparation

- ✓ Abstinence from coitus for 24 hours prior to the procedure.
- ✓ No intravaginal medication for one week.
- ✓ No lubricants should be used during the procedure.

2.1.2 Collection of PAP Smear

For collecting the cervical pap smear, patient was put in the lithotomy position. Vulva was inspected for lesions. After inspecting and stabilizing the cervix, a brush-like device, Cervex-brush, was used to scrape the cervix. The manufacturer's instructions, viz. insertion of long bristles into endocervical canal, short bristles against the ectocervix and five full 360° rotations in clockwise direction only were followed. After obtaining material, it was divided into parts. First CPS was prepared and immediately kept in Coplins jar containing 95% alcohol for fixation. After that, the same brush head was detached and suspended into a vial containing 20 ml of preservative fluid- PreservCyt Solution. Slides were prepared using the ThinPrep 2000 automated slide processor (Hologic, USA), fixed in 95% ethanol for 15 minutes and stained by standard Pap method following manufactures instructions.

2.2 Statistical Analysis

The data was statistically analysed using Microsoft Excel 2016 and IBM SPSS version 23. Chi square test was used to analyse the data and p value was calculated whenever required; P-value of 0.05 or less ($P \leq 0.05$) was considered as statistically significant and P-value above 0.05 ($P \geq 0.05$) was considered not significant. The contingency table provides following information: the observed cell totals, the expected cell totals in '()' and the chi square statistics for each cell in

3. RESULTS

Split samples (CPS and LBC samples from the same patient) were reported on cytology according to TBS 2014. Most common age group affected was 41-60 years.

(Table 1 & Chart 1) Most common presenting complaint was discharge per vaginum.

Of the 100 cases, adequate cellularity was found in 100 cases (100%) of LBC smears & 99 cases (99%) of CPS. 1 case (1%) of CPS was not adequate. (Table 2 & Chart 2).

Of 100 cases, clean background was seen in 44 (44%) cases of LBC preparations but 20 (20%) cases of the CPS showed clean background. The results revealed that there was statistically significant difference between the two procedures (p -value is < 0.01). (Table 3 & Chart 3)

Uniform distributions of cells were found in 63 (63%) cases of LBC smears whereas it was observed in only 5 (5%) cases of CPS. This shows significant statistical difference between two methods (p -value is < 0.01). (Table 4 & Chart 4)

Of 100 cases, cellular overlapping was seen in 45 (45%) cases of LBC preparations and 98 (98%) cases of CPS. The results revealed that cell overlapping was seen more in CPS, which was statistically very significant (p - value is < 0.01). (Table 5 & Chart 5).

Of 100 cases, inflammatory background was seen in 40 (40%) cases of LBC preparations & 85 (85%) cases of CPS. The results revealed that the inflammatory background in CPS was statistically differed with the LBC procedure (TABLE 6 & CHART 6). Cytoplasmic distortion was seen in 10 (10%) & 20 (20%) cases of LBC and CPS slides respectively, which was statistically significant (p -value is < 0.05). (Table 7 & Chart 7).

The nuclear distortion was seen in 10 (10%) & 20 (20%) cases of LBC and CPS slides respectively, which was statistically significant (p -value is < 0.05). (Table 8 & Chart 8). In LBC method 26 (26%) of cases were reported as Normal Smear & 28 (28%) of cases were reported as Inflammatory Smear. In CPS, 16 (16%) cases were reported as Normal Smear & 38 (38%) cases were reported as Inflammatory Smear respectively.

8 (8%) cases & 10 (10%) of cases reported as LSIL by CPS & LBC method respectively. 4 (4%) & 2 (2%) of cases reported as ASCUS by CPS & LBC method respectively. 2 (2%) of cases were reported as Inflammatory Smear with reactive changes; 1 (1%) of cases were reported as Inflammatory smear with occasional atypia; 2 (2%) of cases were reported as Inflammatory smear with squamous metaplasia; 1 (1%) of cases were reported as reactive atrophic smear; 8 (8%) of cases were reported as atrophic smear; 1 (1%) of cases were reported as Atrophic smear with acute inflammation; 1 (1%) of cases were reported as Atrophic smear with HSIL ; 2 (2%) of cases were reported as Squamous metaplasia of endocervical cells; 3 (3%) of cases were reported as Bacterial vaginosis; 2 (2%) of cases were reported as

Trichomonas vaginalis infection; 4 (4%) of cases were reported as Candidiasis; 1 (1%) of cases were reported as atypical glandular cells; 4 (4%) of cases were reported as HSIL; 1 (1%) of cases were reported as HSIL with dense inflammation in both methods. 1 (1%) of cases were reported as repeat smear in both methods. P value is 0.999, hence, interpretation of results by the two procedures were not statistically significantly (P>0.05). (Table 9 & Chart 9).

Table 1. Age wise distribution of cases

Age Groups	No of cases
<=20	0
21-40	35
41-60	53
61-80	12

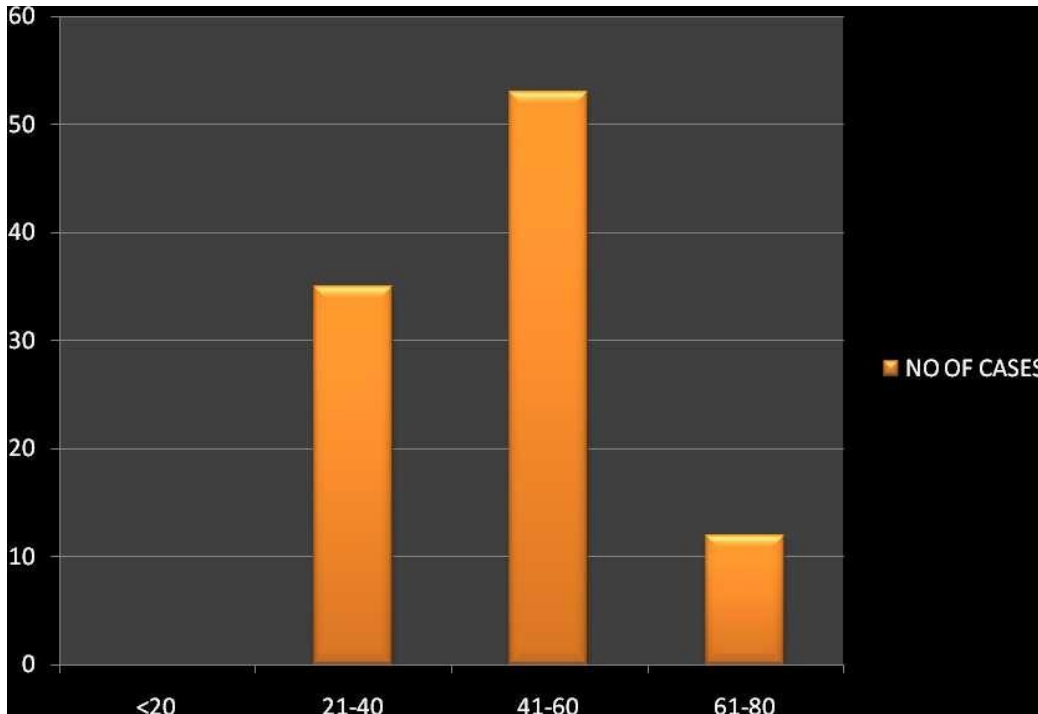


Chart-1. Age wise distribution of cases

Table 2. Comparison of cellularity

Cellularity	CPS	LBC
Adequate	99	100
Not adequate	1	0

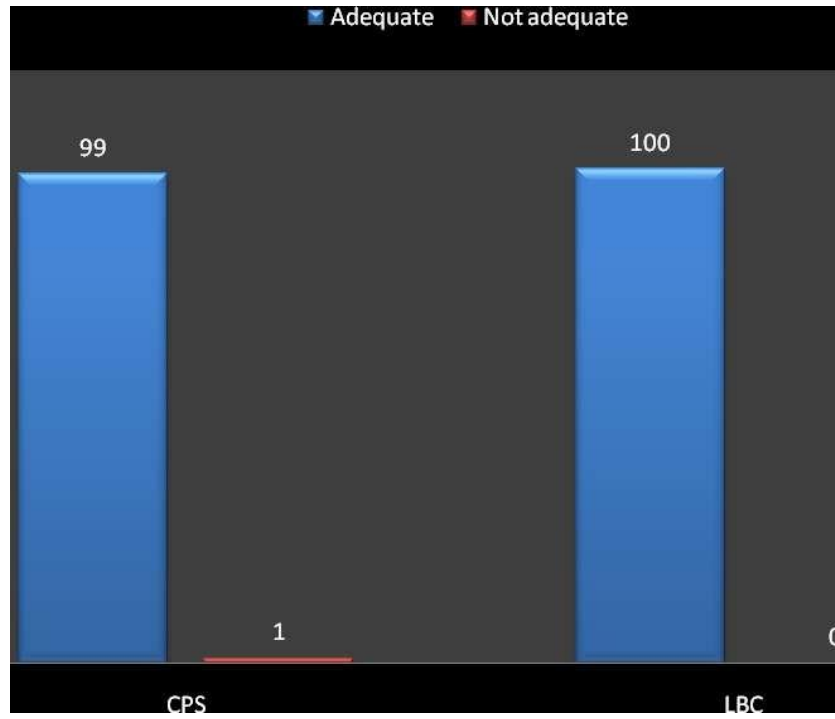


Chart 2. Comparison of Cellularity

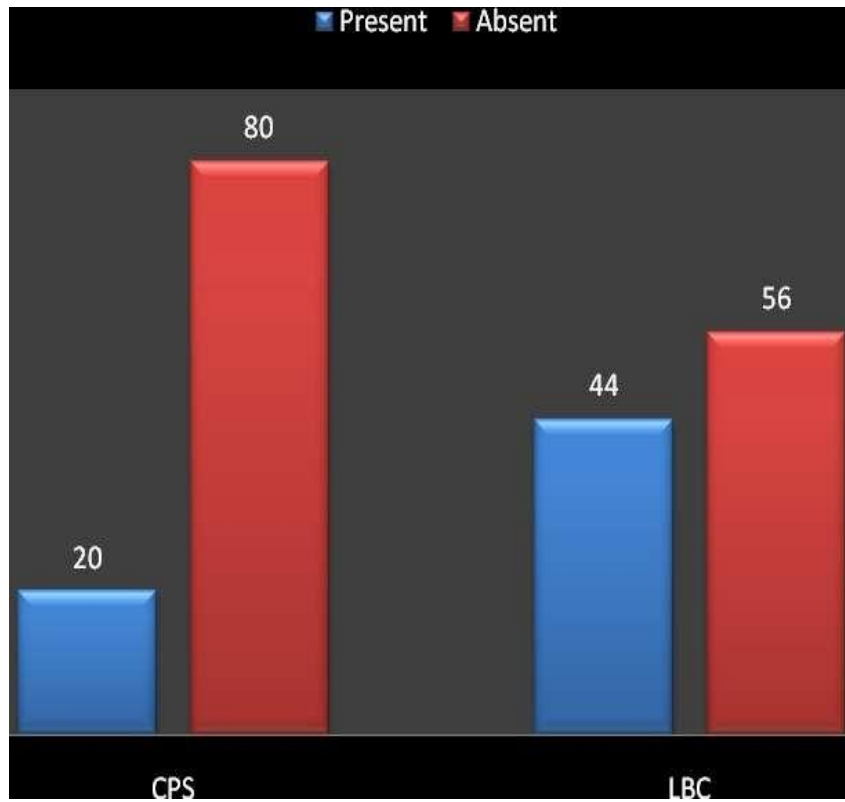


Chart 3. Comparison of clean background

Table 3. Comparison of clean background

Clean back Ground	CPS	LBC	Total	X2	p-value
Present	20 (32.00) [4.50]	44 (32.00) [4.50]	64	13.2353	0.000275
Absent	80 (68.00) [2.12]	56 (68.00) [2.12]	136		
Total	100	100	200		

p-value is <0.01 (Significant)

Table 4. Comparison of uniform distribution of cells

Uniform distribution of cells	CPS	LBC	TOTAL	X2	p-value
Present	5 (34.00) [24.74]	63 (34.00) [24.74]	68	74.9554	<0.00001
Absent	95 (66.00) [12.74]	37 (66.00) [12.74]	132		
Total	100	100	200		

p-value is <0.01 (Significant)

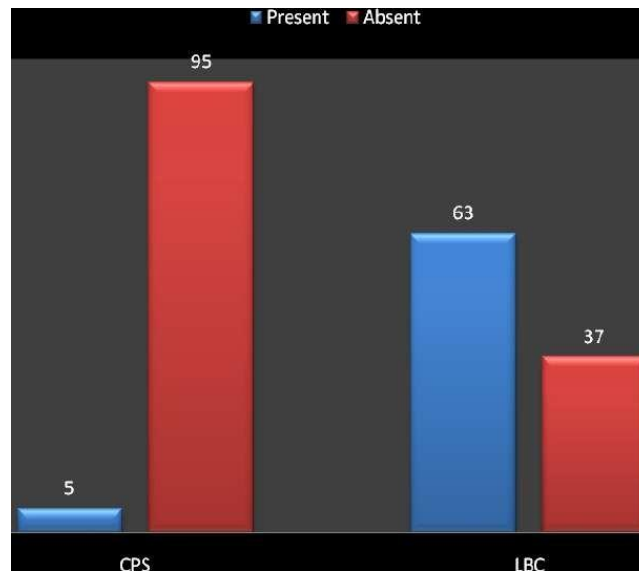


Chart 4. Comparison of uniform distribution of cells

Table 5. Comparison of cell overlapping

Cell overlapping	CPS	LBC	Total	X2	p-value
Present	98 (71.50) [9.82]	45 (71.50) [9.82]	143	68.9241	<0.00001
Absent	2 (28.50) [24.64]	55 (28.50) [24.64]	57		
Total	100	100	200		

p-value is <0.01 (Significant)

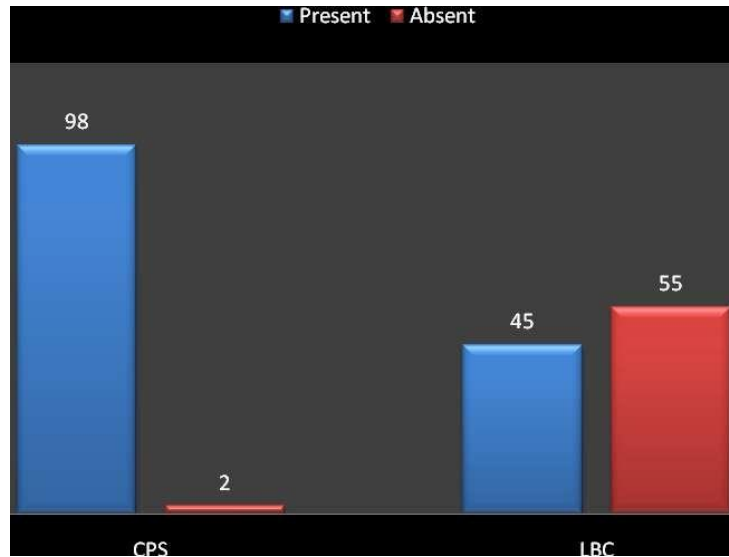


Chart 5. Comparison of cell overlapping

Table 6. Comparison of inflammatory cells in the background

Inflammatory cells in Background	CPS	LBC	Total	X2	p-value
Present	85 (62.50) [8.10]	40 (62.50) [8.10]	125		
Absent	15 (37.50) [13.50]	60 (37.50) [13.50]	75	43.2	<0.00001
Total	100	100	200		

p-value is <0.01 (Significant)

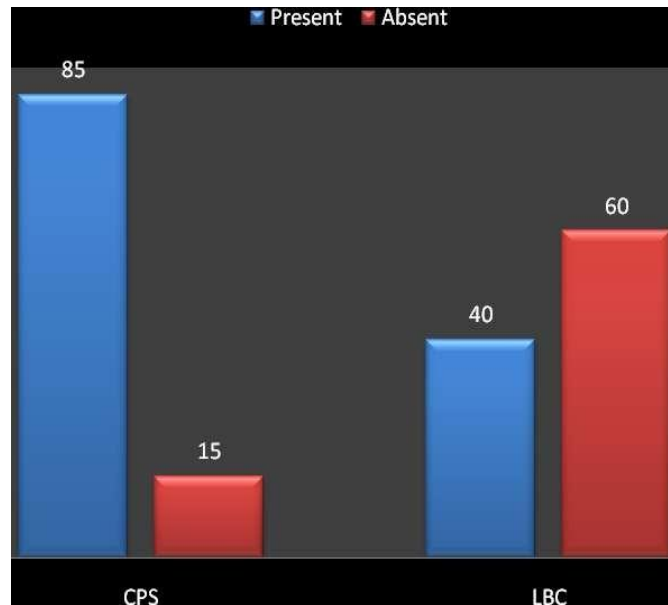


Chart 6. Comparison of inflammatory cells in background

Table 7. Comparison of cytoplasmic distortion

Cytoplasmic distortion	CPS	LBC	Total	X2	p-value
Present	20 (15.00) [1.67]	10 (15.00) [1.67]	30	3.9216	0.04767
Absent	80 (85.00) [0.29]	90 (85.00) [0.29]	170		
Total	100	100	200		

p-value is <0.05 (Significant)

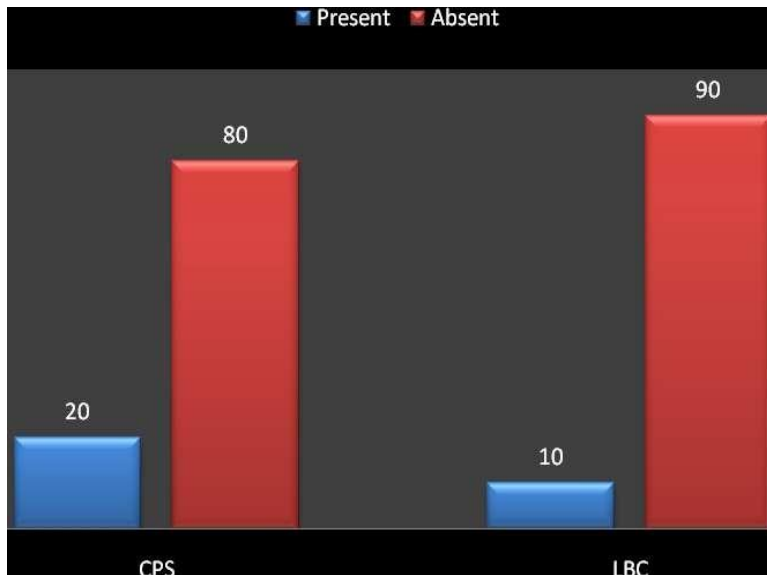


Chart 7. Comparison of cytoplasmic distortion

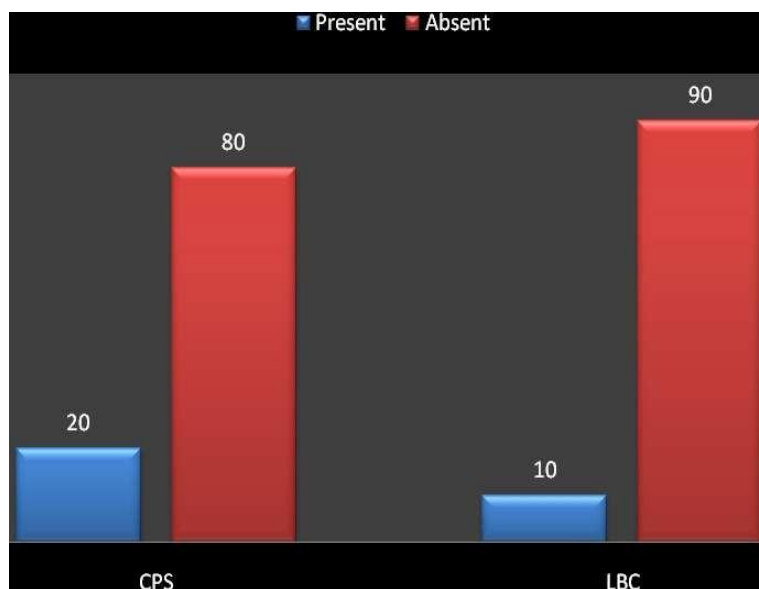


Chart 8. Comparison of nuclear distortion

Observation and Results

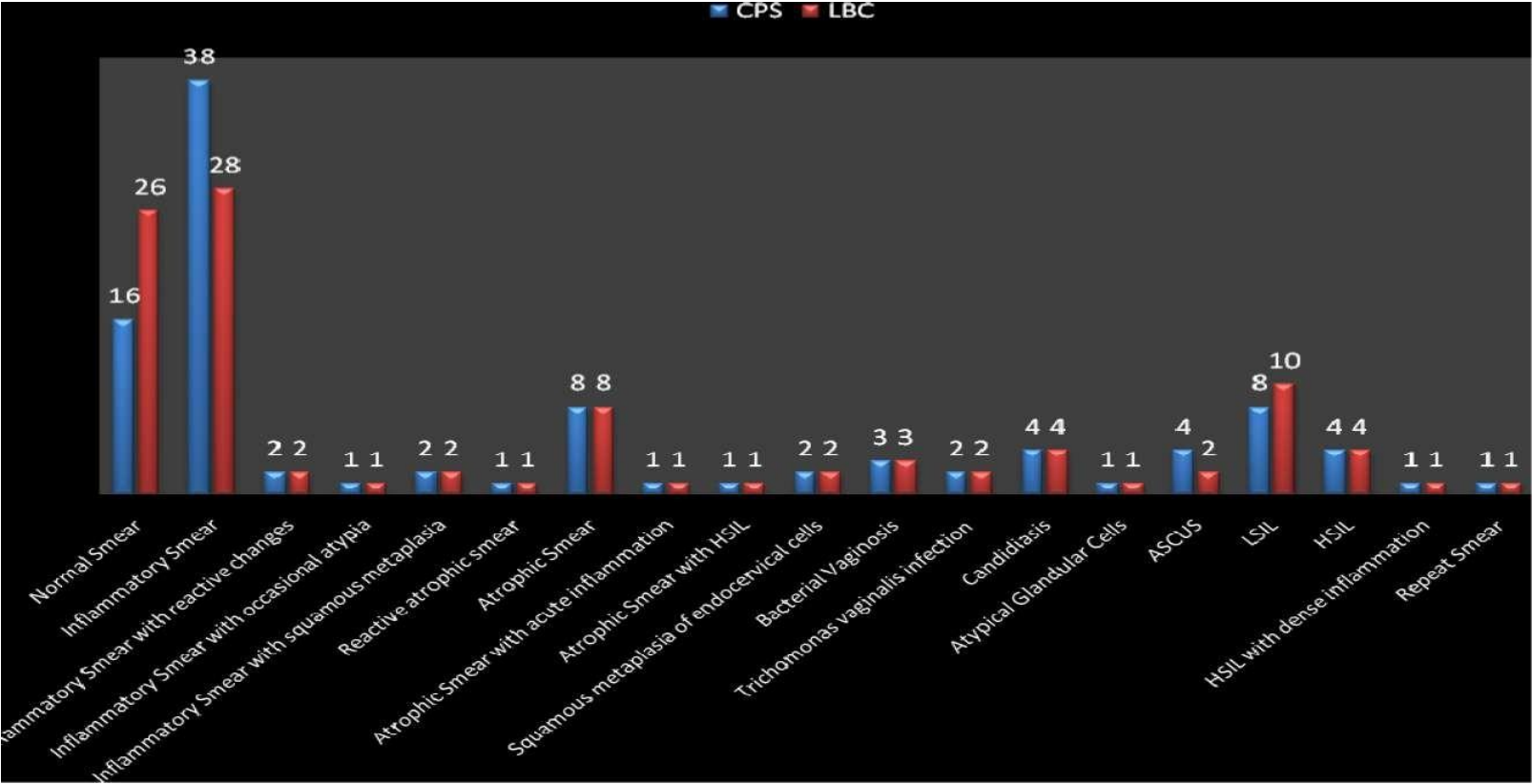


Chart 9. Comparison of interpretation

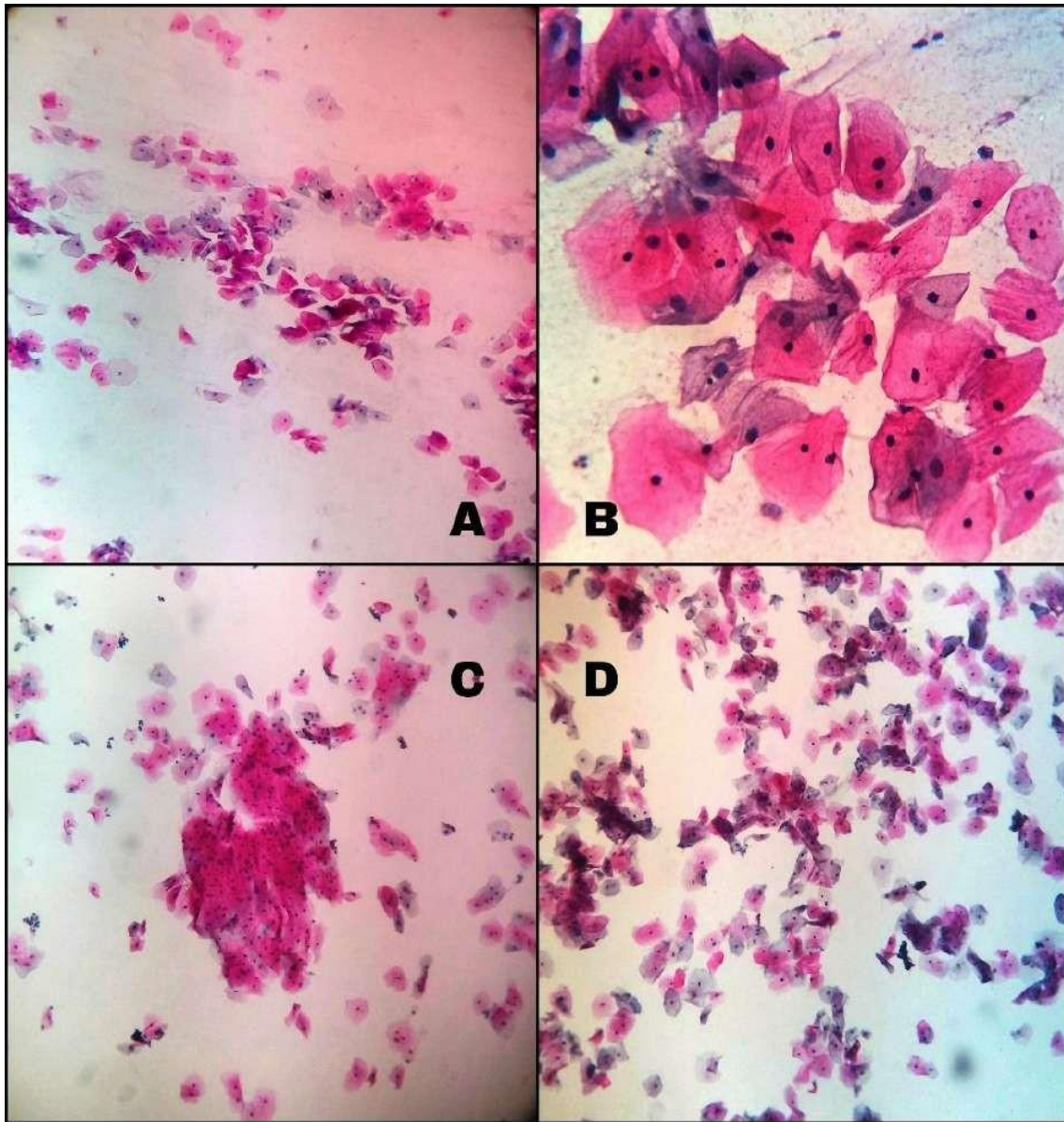


Fig. 1. Normal smear

- A. Superficial and Intermediate cells in a clean background (10x) (CPS) .
- B. Predominantly superficial and Intermediate cells in a clean background (40x) (CPS) .
- C. Superficial and Intermediate cells with endocervical cell cluster in a clean background (10x) (LBC) .
- D. Superficial and Intermediate cells in a clean background (10x) (LBC) .

Table 8. Comparison of nuclear distortion

Nuclear distortion	CPS	LBC	Total	X2	p-value
Present	20	10	30		
Absent	80	90	170	13.2353	0.000275
Total	100	100	200		

p-value is <0.05 (Significant)

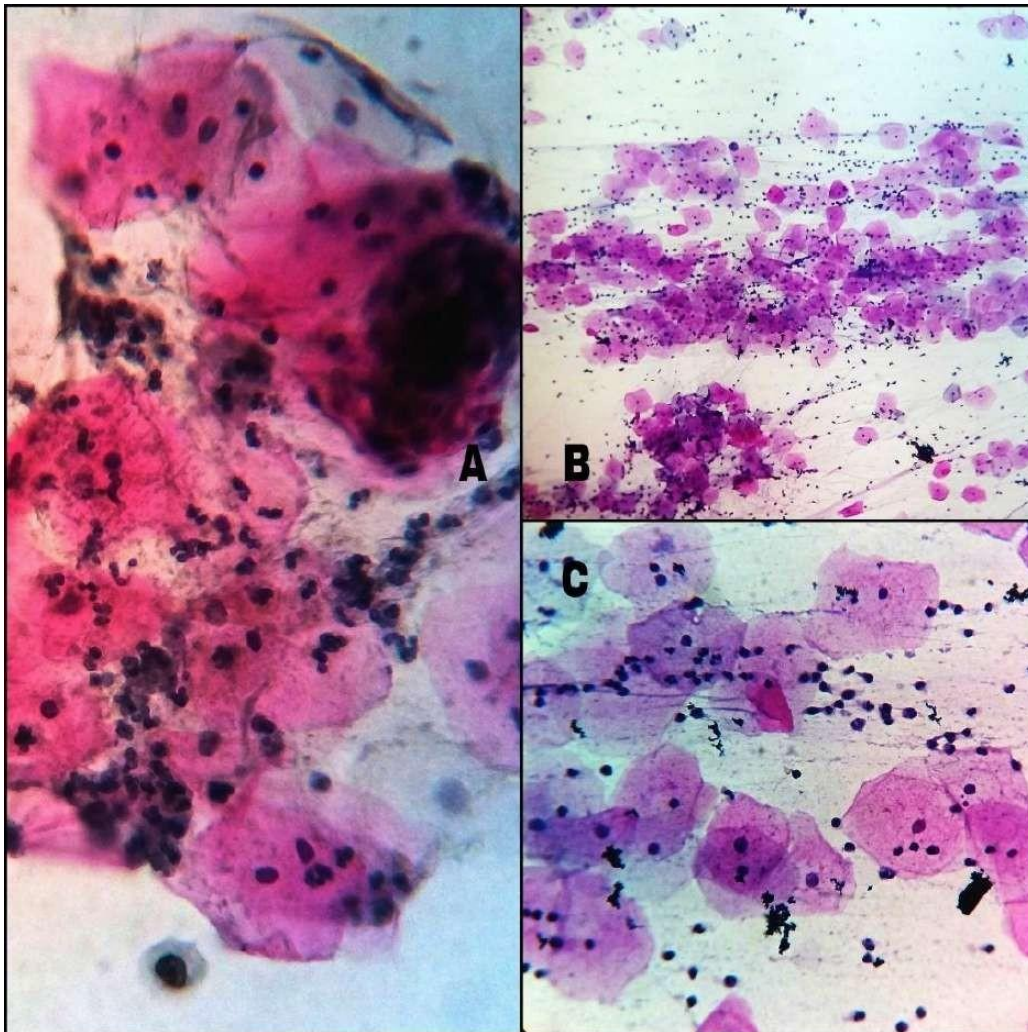


Fig. 2. Inflammatory smear

- A. Predominantly superficial and few intermediate cells in a background of neutrophils (40x) (LBC) .**
- B. Predominantly superficial and few intermediate cells in an inflammatory background (10x) (CPS) .**
- C. Predominantly superficial and few intermediate cells in an inflammatory background (40x) (CPS) .**

Table 9. Interpretation of results of CPS versus LBC

Interpretation	CPS	LBC
Normal Smear	16	26
Inflammatory Smear	38	28
Inflammatory Smear with reactive changes	2	2
Inflammatory Smear with occasional atypia	1	1
Inflammatory Smear with squamous metaplasia	2	2
Reactive atrophic smear	1	1
Atrophic Smear	8	8
Atrophic Smear with acute inflammation	1	1
Atrophic Smear with HSIL	1	1

Interpretation	CPS	LBC
Squamous metaplasia of endocervical cells	2	2
Bacterial Vaginosis	3	3
Trichomonas vaginalis infection	2	2
Candidiasis	4	4
Atypical Glandular Cells	1	1
ASCUS	4	2
LSIL	8	10
HSIL	4	4
HSIL with dense inflammation	1	1
Repeat Smear	1	1

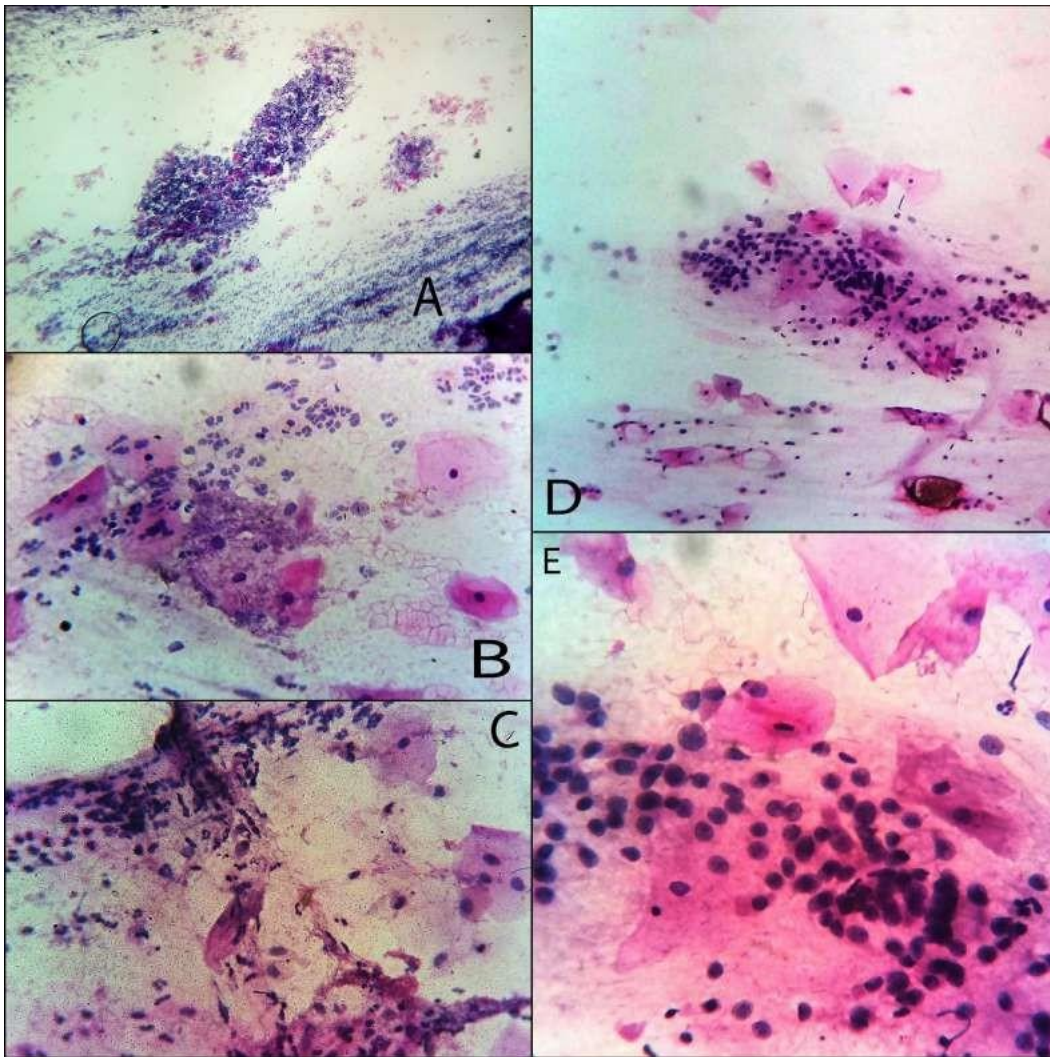


Fig. 3. Inflammatory smear with reactive change

- A. Superficial and intermediate cells in an inflammatory background (10x) (CPS) .**
- B. Superficial and intermediate cells with squamous metaplastic cells in a background of neutrophils (40x) (CPS) .**
- C. Superficial and intermediate cells in an inflammatory background (40x) (CPS) .**
- D. Superficial and intermediate cells in an inflammatory background (10x) (LBC) .**
- E. Superficial and intermediate cells in an inflammatory background (40x) (LBC) .**

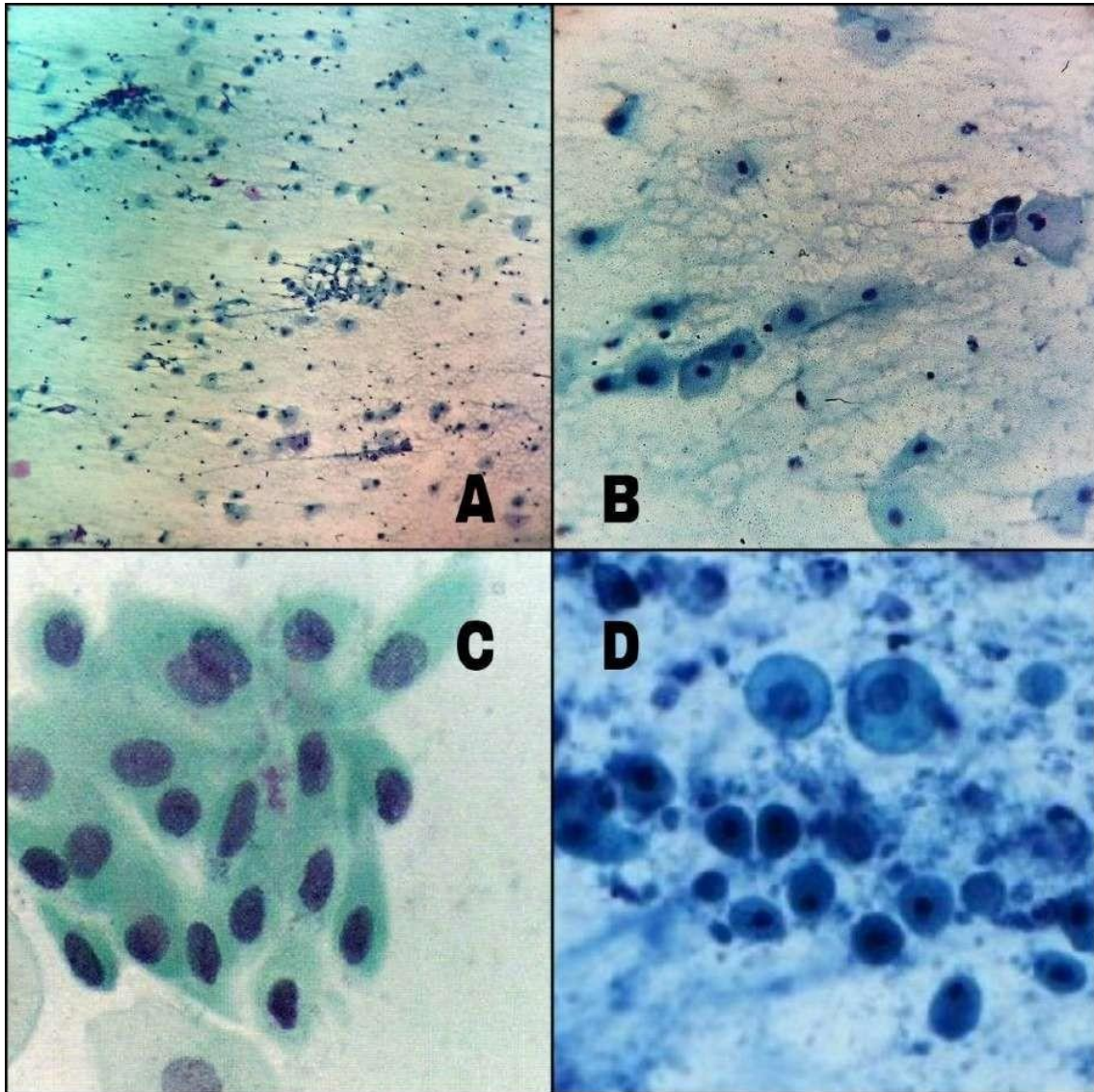


Fig. 4. Atrophic smear

- A. Parabasal and basal cells in a clean background (10x) (CPS) .**
- B. Parabasal and basal cells in a clean background (40x) (CPS) .**
- C. Parabasal and basal cells in a clean background (40x) (LBC) .**
- D. Parabasal and basal cells in a clean background (40x) (LBC) .**

4. DISCUSSION

Pap smear is one of the best available screening methods for early detection of cervical precancerous lesions. LBC is an alternate technique for processing the cervical sample collected. Most Western countries have switched over from CPS to LBC, even though the sensitivity and specificity is almost similar in

various comparison studies. The reason for this may be consistently reduced rates of unsatisfactory results on LBC, clarity of microscopy, improved sample processing, and small area to be screened. Furthermore, the potential for performing additional tests, including HPV testing on the residual sample, probably underpins the acceptability of LBC among gynecologists, colposcopists and pathologists

[26]. The cost of this test is high, but there is increase in detection of pre invasive lesions and decrease in the number of indeterminate results such as ASC (Limaye et al 2003) [27] (Trench 2000) [28].

In present study, we compared cervical smears prepared by LBC with the CPS. The smears are compared on the morphological parameters such as cellular adequacy, clean background, uniform distribution, cell overlapping, cytoplasmic distortion, nuclear distortion, inflammatory background and finally interpretation of results was done based on TBS 2014. In present study, the most common presenting complaint was discharge per vaginum. The most common presenting complaint in one of study was discharge per vaginum (42.5%) [29]. In present study, 53 cases studied belonged to 41 -60 years of life, followed by 35 cases to 21 -40 years of life. The minimum age of patient screened was 25 years and maximum was 70 years. In one study, 77 (48.1%) cases studied belonged to fourth decade of life, followed by 50 (31.2%) cases in the third decade. The minimum age of patient screened was 21 years and maximum was 63 years. LSIL and HSIL were found in 27 (64.4%) cases in patient 's aged between 21-40 years [29].

In present study, 100 cases were satisfactory for evaluation in LBC whereas 1 case was unsatisfactory for evaluation in CPS. In one of the study, 133 (83.1%) cases were satisfactory for evaluation on Pap spin whereas 51 (31.9%) cases were satisfactory on CPS. 6 cases (3.7%) were unsatisfactory for evaluation on Pap spin and 8 cases (5%) on CPS. There were only 21 cases (13.2%) which were satisfactory for evaluation but limited by factor like air drying artifact, obscuring blood and inflammation, cytolysis or absent endocervical component on Pap spin whereas 101 (63.1%) cases in the same category on CPS. The most common cause of unsatisfactory smear on Pap spin was scant cellularity in 3 cases (1.9%) and on CPS, thick smear was the commonest cause in similar percentage of cases [29].

In another case study, the unsatisfactory rate was reduced from 4.3% to 1.7% in LBC smears in the present study. The most common reason for unsatisfactory was low cellularity in both categories. There was no inadequate LBC sample due only to excess blood or obscuration by polymorphs/ mucus or other technical artefacts. Therefore, the samples with

excess blood are better handled by LBC [26,30,31].

Inadequate samples were observed in 0.3% of LBC samples versus 0.7% of Pap smears (P =.002)[32] in another study. There were 0.1% and 1.7% inadequate smear cases in the LBC method and CP, respectively, in the Tuncer et al study [33,34,35]. In the Kirschner et al. study, inadequate cases were 2.3% and 0.3% in the LBC and CP respectively [36].

The results of Yousefi et al. showed that inadequate cases were 1 case (0.3%) with CP and 14 cases (1%) with the LBC method [35]. In a study by Zafari et al., the number of inadequate smears in the CP technique was 11 cases (9.2%) and in the thin layer technique there were 5 cases (4.2%), while inadequate cases due to lower cellularity in the CP constituted 10 cases (8.3%) and in the thin layer there were 2 cases (1.7%) (P = 0.008)[34]. The National Institute for Clinical Excellence in UK showed lower proportions of unsatisfactory smears from 9% in conventional cytology to 1.6% in LBC[36].

5. CONCLUSION

The study was conducted to compare LBC with Conventional cytology for evaluation of cervical pap smears. Conventional cervical cytology is a simple, cost effective method that has been in use for more than 50 years and is still a highly effective cervical cancer screening procedure. It is widely used because of easy method of preparation of slides and interpretation of results [37].

Comparison of morphological details and results of cervical cytology smears showed that LBC provides more representative sample with reduced obscuring material which allows better morphological evaluation and better handling of haemorrhagic and inflammatory smears. LBC also generated higher number of satisfactory smears compared to conventional smears. LBC provides cytology smears with clean background that do not have inflammatory cells in any of the slides. Our study highlights that LBC may improve the sample's quality and provides better cytomorphological features compared to Conventional smear. LBC offered better clarity, uniform spread of smears, less time for screening and better handling of hemorrhagic and inflammatory samples.

Liquid based cytology is strongly advocated in the best interest of public health, by improving the quality of the sample and reducing the likelihood of false negative cytology results. Thus it will significantly improve early detection and treatment of cervical lesions.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The present study was conducted after getting the approval of the Ethical Committee of Sree Balaji Medical College and Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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