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Comparison of liquid based cytology vs conventional pap smear in cervical cancer screening in low resource setting

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Abstract
Cervical screening is the process of detecting and removing abnormal tissue or cells in the cervix before cervical cancer develops. By aiming to detect and treat cervical neoplasia early on, cervical screening aims at secondary prevention of cervical cancer. In low-resource countries like India, decisions regarding cervical screening are made based upon available resources and thus it is often not possible to offer cervical screening as frequently. The greatest impact on cervical cancer reduction appears to result from screening women aged 30-39 years, so resources may be directed to this age group. In this study, comparison of Conventional pap smear (CPS) and Liquid based cytology (LBC) will be studied and how it will aid in cervical screening in low resource setting.

Keywords: Cervical screening, liquid based cytology (LBC), conventional pap smear (CPS), ectropion, discharge per vaginum

Introduction

The uterine cervix

The cervix, lower fibromuscular portion of the uterus, measures 3-4 cm in length and 2.5 cm in diameter; however, it varies in size and shape depending on age, parity and menstrual status of the woman.
The cervix consists of 2 parts: ectocervix, endocervix

1. Ectocervix

It is the most readily visible portion of the cervix covered by a pink stratified squamous epithelium, consisting of multiple layers of cells. The histological architecture of the squamous epithelium of the cervix reveal the bottom single layer of round basal cells with a large dark-staining nuclei and little cytoplasm, attached to the basement membrane. The basal cells divide and mature to form the next few layers of cells called parabasal cells, which also have relatively large staining nuclei and greenish-blue basophilic cytoplasm. Further, differentiation and maturation of these cells leads to the intermediate layers of polygonal cells with abundant cytoplasm and small round nuclei. These cells form a basket-weave pattern. With further maturation, the large and markedly flattened cells with small, dense, pyknotic nuclei and transparent cytoplasm of the superficial layers are formed. Overall, from the basal to the superficial layer, these cells undergo an increase in size and a reduction of nuclear size. The intermediate and superficial cell layers of squamous epithelium contain glycogen.

2. Endocervix

It is largely invisible and lies proximal to external os. It is lined by reddish columnar epithelium (sometimes referred to as glandular epithelium) consisting of a single layer of tall cells with dark-staining nuclei close to the basement membrane. The boundary between squamous and columnar epithelium is called the squamocolumnar junction (Figure 2). The location of squamocolumnar junction in relation to the external os varies depending upon age, menstrual status, and other factors such as pregnancy and oral contraceptive use. Before puberty and after menopause this junction is not found on the ectocervix. Instead, in post-menopausal women the epithelium becomes atrophic, causing the junction to migrate up into the cervical canal [1].
Squamous metaplasia in the cervix refers to the physiological replacement of the everted

columnar epithelium on the ectocervix by a newly formed squamous epithelium from the subcolumnar reserve cells. The region of the cervix where squamous metaplasia occurs is referred to as the transformation zone. In fertile women squamous metaplasia is common in this junction [2]. The metaplastic epithelium of the TZ is thin, which makes the basal cells anchored to the basement membrane sensitive to infectious agents with a potential for malignant transformation [3, 4].

Etiology

Persistent infection of the cervix with high-risk types of human papillomavirus (HPV) has been established as a necessary (but not sufficient) cause for the development of cervical cancer [5]. Evidence suggests that HPV infection precedes the development of cervical cancer by several decades and that persistent infection with HPV is necessary for the development and progression of pre-cancerous lesions of the cervix, either to higher grades of pre-cancerous disease or to invasive cancer – a process that can take 10–30 years [6]. HPV is a very common sexually transmitted infection that is usually acquired soon after the initiation of sexual activity. Most HPV infections clear spontaneously within 1–2 years, but persistent infections with high-risk types of HPV (particularly HPV16 and HPV18) may progress to precursors of and ultimately to invasive cervical cancer [7]. High-risk types of HPV are identified in nearly all cancers of the cervix, and the expression of HPV oncoproteins is necessary to maintain the cancer phenotype. The International Agency for Research on Cancer evaluated the following 12 HPV types as carcinogenic to humans: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV16 and HPV18 are responsible for about 70% of cervical cancer cases worldwide [8].

Risk factors

- Immaturity, low production of mucus, and ectopy of the cervix have been described as biological conditions that favor the acquisition of HPV in young women [9].
- Multiparity and younger age of having first child is associated with cervical cancer [10].
- Oral contraceptive usage had more incidence of invasive cancer than the IUD's [11].
- Cervical cancer is associated with long duration smoking [12].
- Genetic susceptibility for cervical cancer is related to HLA class II, HLA B7 and DQB116 [13].

Aim and Objectives

Aim

- To study the effectiveness of liquid based cytology vs conventional PAP smear in cervical screening

Objective

- To evaluate the diagnostic efficacy of liquid based cytology compared with conventional Pap Smear in cervical screening and confirming it with biopsy in suspected cases.

Material and Methods

The present cross-sectional study was conducted among 200 patients in the department of Obstetrics and Gynecology Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar over the period of 1 year (1st January to 31st December 2019).

Inclusion criteria

As per Hospital Guidelines, patients were selected randomly between the age group of 35-55 years presented with following complaints;

1. Irregular menses
2. Postcoital bleeding
3. Discharge per vaginum
4. Pain lower abdomen.
5. Dyspareunia

Exclusion criteria

1. Sexually not active (nuns, virginal women)
2. Local cervical lesion causing BPV like cervical polyp, trauma
3. Women who are pregnant.

Method of collection of data

The samples were taken as part of routine hospital screening of patients for cervical epithelial lesions. Firstly patient was explained the procedure and verbal consent was obtained. Then patient was made to lie in dorsal position with knees flexed. Speculum is inserted without cleaning the local area with an antiseptic. The samples were taken with cervix brush which is broom like device and divided into two part (split–sample technique).

First, conventional Pap smear is prepared and immediately alcohol –fixed. After that smear brush will be detached and suspended in Liquid based cytology (LBC) vial containing preservative fluid, which is transferred to the pathology laboratory for further processing. Both liquid based cytology and conventional pap smear were carried out on the same patient using this split method.

LBC uses a sedimentation process whereby samples are enriched to remove debris, followed by centrifugation to generate a pellet, a portion /subset of which is then applied to the slide for analysis. The automatic slide preparation is carried out by the Cell solution F50 processor to generate a thin-layer cell sample. Then both LBC smear and conventional Pap smear were subjected to papanicolaou staining following which both slides will be analyzed by the pathologist [17].

Bethesda Classification [15] was used for reporting and biopsy was carried out to make confirmatory diagnosis in case of intraepithelial lesion or malignancy.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA).

Descriptive statistics included computation of percentages, means and standard deviations were calculated. Statistical test applied for the analysis was chi-square test. The level of confidence interval and *p*-value were set at 95% and 5%.

Results and Observations

Table 1: Distribution of cases according to age

Age in years	Number of subjects	Percentage
35-39	51	25.5%
40-44	78	39.0%
45-49	47	23.5%
>49	24	12.0%

Majority of the patients 78 (39.0%) were in the age group of 40-44 years followed by 51 (25.5%) 35-39 years, 47 (23.5%) and rest 24 (12.0%) >49 years of age.

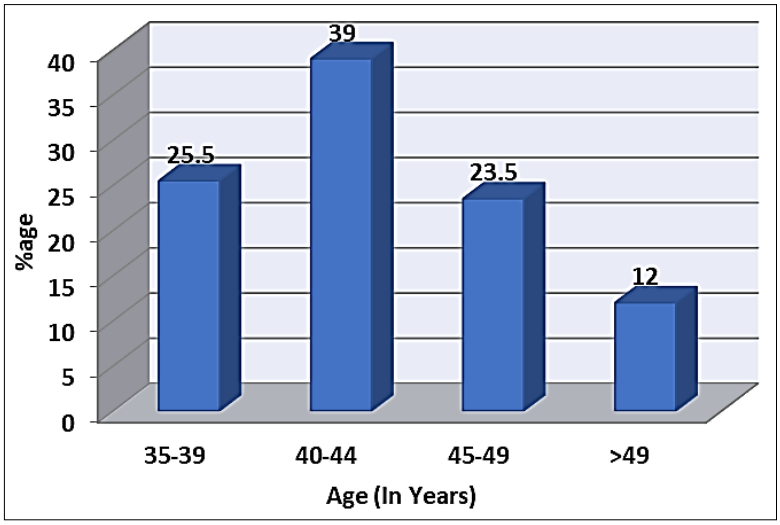


Fig 1: Age wise distribution

Table 2: Distribution of cases according to age and duration of marriage

Age of marriage	Number of subjects	Percentage	Duration of marriage	Number of subjects	Percentage
<20 years	44	22%	<10 years	34	17%
>20 years	156	78%	≥10 years	166	83%
Total	200	100.0%	Total	200	100.0

The age of marriage in majority of the patients 156 (78.0%) was found above 20 years and rest 44 (22.0%) patients got married at age less than 20 years.

The duration of marriage in majority of the patients 166 (83%) was found ≥ 10 years and rest 34 (17%) patients were found married for ≤10 years.

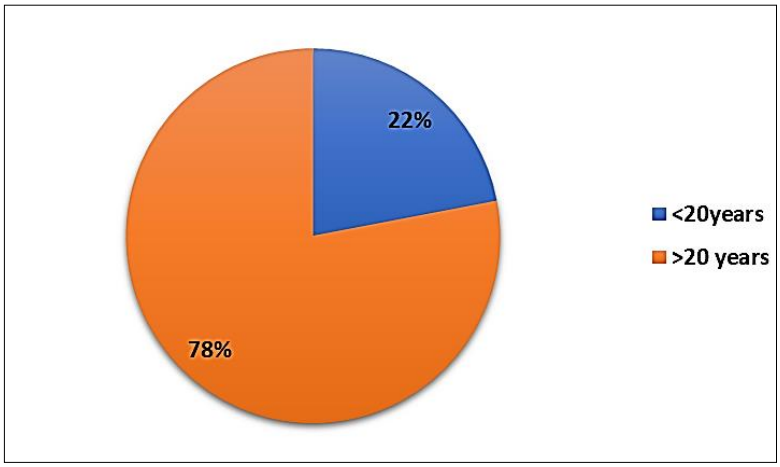


Fig 2a: Age of marriage

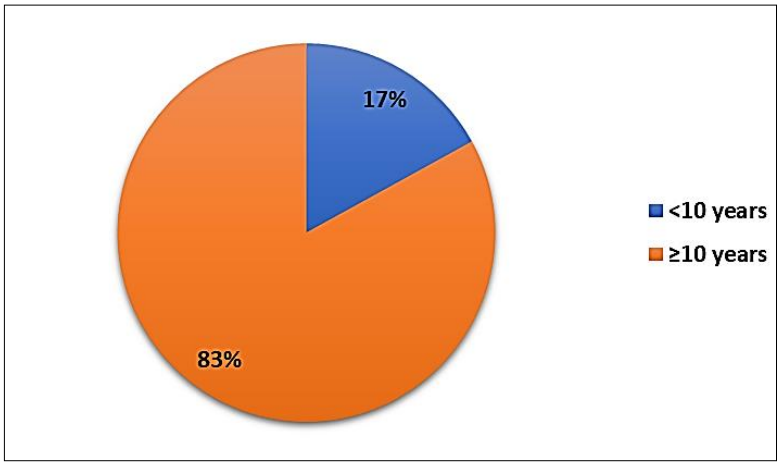


Fig 2b: Duration of marriage

Table 3: Distribution of cases according to parity

Parity	Number of subjects	Percentage
P1	20	10.0
P2	18	9.0
P3	33	16.5
P4	102	51.0
P5	12	6.0
>P5	15	7.5
Total	200	100.0%

Out of total 200 cases majority 102 (51.0%) were Para-4 followed by 33 (16.5%) P-3, 20 (10.0%) P-1, 18 (9.0%) P-2, 23 (13.5%) ≥P-5

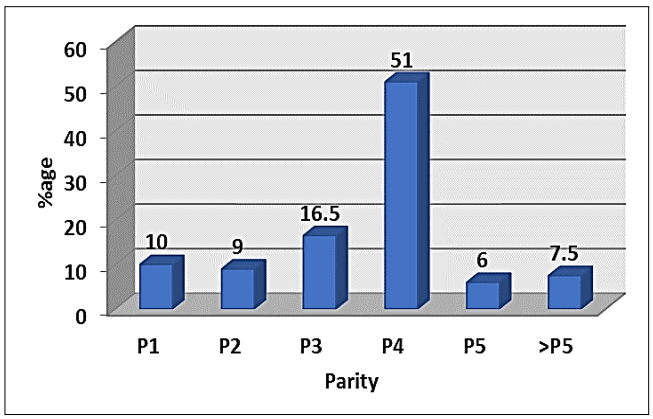


Fig 3: Distribution according to parity

Table 4: Distribution of study population according to presenting complaints

Complaints	Number of subjects	Percentage
Discharge Per Vaginum	96	48.0%
Pain Lower Abdomen	56	28.0%
Irregular Bleeding per vaginum	30	15.0%
Intermenstrual Bleeding	10	5.0%
Postcoital Bleeding	4	2.0%
Dyspareunia	4	2.0%
Total	200	100.0%

Majority of the cases presented with complaint of discharge per vaginum 96 (48.0%) followed by pain in lower abdomen 56 (28.0%), irregular bleeding per vaginum 30 (15.0%), intermenstrual bleeding 10 (5.0%), postcoital bleeding 4 (2.0%) and dyspareunia 4 (2.0%) cases.

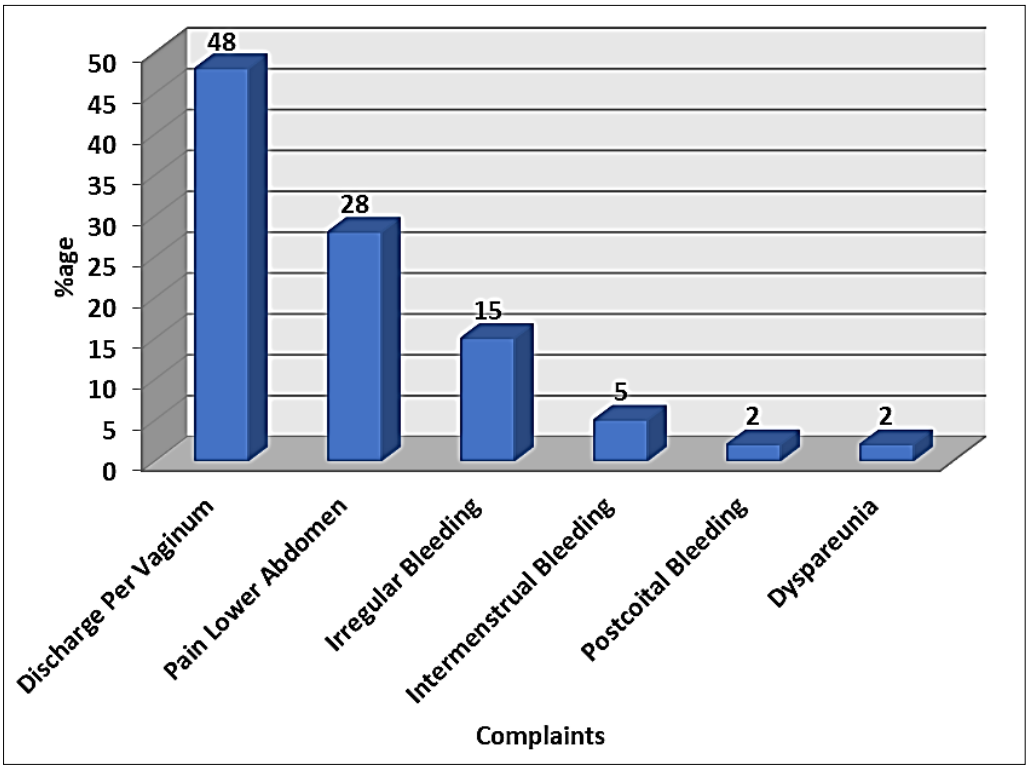


Fig 4: Distribution of presenting complaints

Table 5: Distribution of cases according to types of discharges

Types of discharges	Number of subjects	Percentage
White Discharge	52	26.0%
Greenish Discharge	9	4.5%
Yellowish Discharge	24	12.0%
Blood Stained	11	5.5%

White discharge was found prevalent in 52 (26.0%) cases followed by yellowish discharge 24 (12.0%), blood stained discharge 11 (5.5%) and greenish discharge 9 (4.5%) cases.

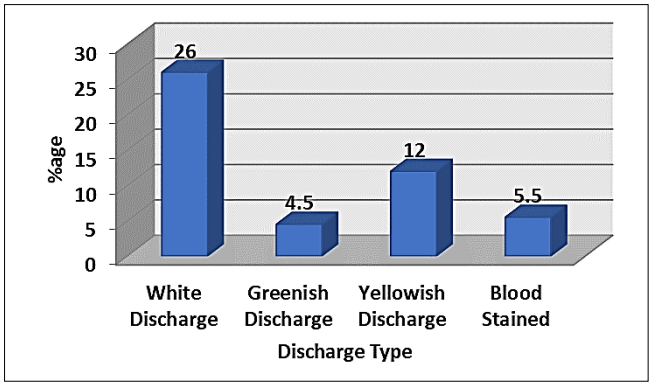


Fig 5: Distribution of types of discharges

Table 6: Distribution of cases according to clinical appearance of cervix

Clinical appearance of cervix	Number of subjects	Percentage
Normal cervix	98	49.0
Ectropion cervix	27	13.5
Hypertrophied cervix	57	28.5
Cervix flushed with vagina	18	9.0
Total	200	100.0

Out of total 200, hypertrophied cervix was observed in 57 cases (28.5%) and ectropion cervix in 27 cases (13.5%).and cervix flushed with vagina was found in 18 cases (9.0%)

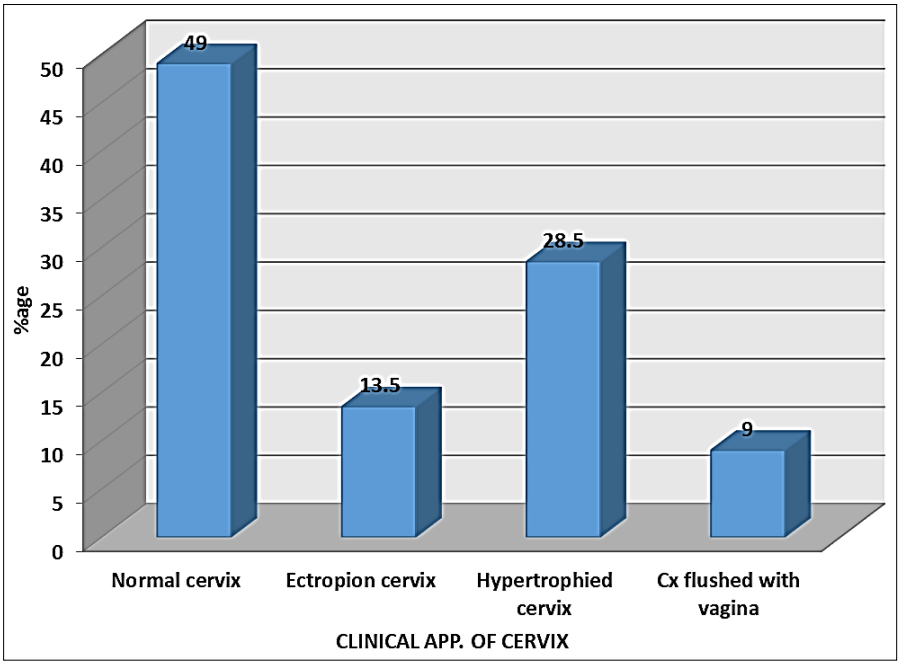


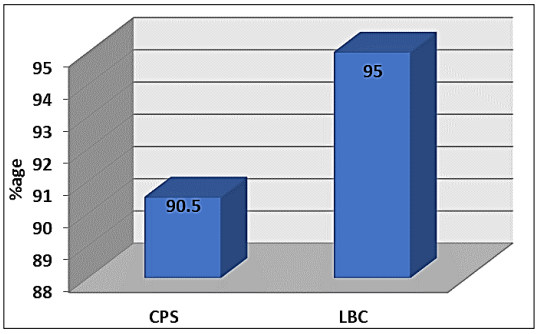
Fig 6: Distribution of cervix appearance

Table 7a: Specimen adequacy in conventional pap versus LBC

Satisfactory smears	CPS	%	LBC	%
	181	90.5%	190	95%
p-value	0.041 (Sig.)			

Test applied chi-square test

Out of the 200 cases, 181 cases (90.5%) were found satisfactory for evaluation in conventional PAP smear whereas 190 cases (95%) were found satisfactory in LBC, this difference is statistically significant (p=0.041)



Graph 7a: Satisfactory smears

Table 7b: Unsatisfactory smears and its causes

Causes	CPS	%	LBC	%
Absent endocervical cells	2	1.0	4	2.0
Low cellularity	2	1.0	6	3.0
Inflammation	8	4.0	0	0
Hemorrhage	6	3.0	0	0
Mucin	1	0.5	0	0
Total	19	9.5	10	5.0

Out of 200 cases, 19 were found unsatisfactory in CPS and 10 unsatisfactory in LBC. Unsatisfactory cases in both CPS and LBC were due to scanty or absent endocervical cells (2%, 1%), low cellularity (1.0 %, 3%), inflammation in background (4.0%, 0), hemorrhage in background (3%, 0%) and mucin in background (1%, 0).

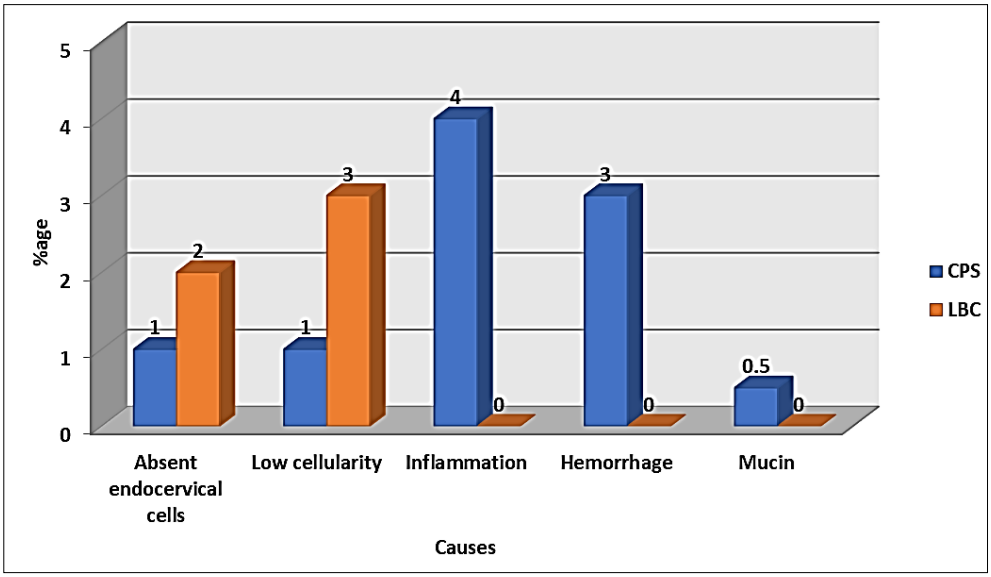


Fig 7b: Unsatisfactory smears

Table 8: Distribution of cases between CPS and LBC

Findings	CPS	%	LBC	%
Normal	7	3.5	10	5.0
NILM (Inflammatory)	170	85.0	165	82.5
Atrophic Smear	10	5	9	4.5
ASCUS	3	1.5	5	2.5
LSIL	0	0	2	1.0
HSIL	1	0.5	1	0.5
Carcinoma in Situ	-	-	-	-
Unsatisfactory	19	9.5	10	5.0
Total	200	100.0	200	100.0

Out of 200 cases in PAP; NILM was found in 170 cases, atrophic smear 10 cases (5%), ASCUS in 3 (1.5%) cases, LSIL in 0 cases and 1 (0.5%) HSIL. In LBC; NILM were seen in 165 cases, atrophic smear in 9 cases (4.5 %), ASCUS 5 (2.5%) cases, LSIL 2 (1.0%) cases and 1 (0.5%) HSIL case.

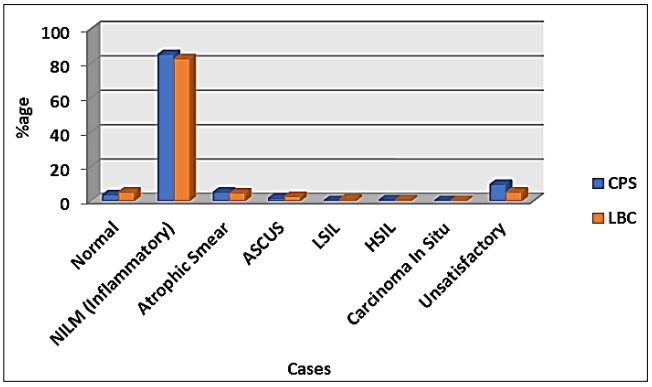


Fig 8: Distribution between CPS and LBC

Table 9: Comparison of cytology with biopsy

	CPS/LBC	CPS/LBC	CPS/LBC	CPS/LBC	
Biopsy	**Normal**	**Inflammatory**	**LSIL**	**HSIL**	**Total**
Normal cervix	3/3	3/3	-	-	6
Cervicitis	-	-	-	-	-
CIN-I	-	1/1	- /2	-	3
CIN-II	-	-	-	-	-
CIN-III	-	-	-	1 /1	1

Out of 200 cases, biopsy was done in 10 cases. Out of which, 3 patients had normal cytology (both CPS and LBC) but patients had persistent foul-smelling discharge. Biopsy in these patients was found normal. (true negative)

We did biopsy in 4 inflammatory smear patients (including those in CPS and LBC) but with complaints of post-coital bleeding and unhealthy cervix (hypertrophic cervix and ectropion) which showed normal report in 3 cases (true positive) and CIN-I in 1 cases. (false negative)

Total of 2 cases of LSIL on LBC were subjected to biopsy were found to be CIN-1. (true positive)

1 case of HSIL on CPS and LBC both was subjected to biopsy and was found to be CIN-III. (true positive)

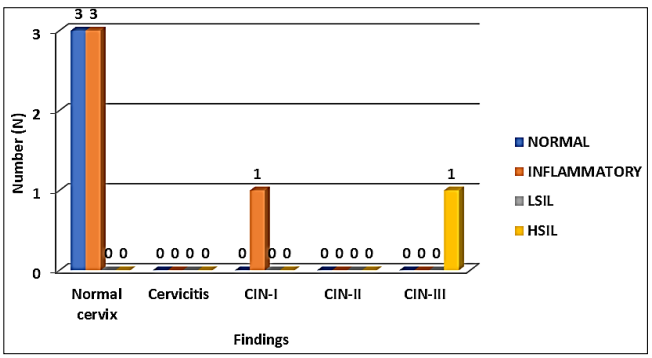


Fig 9a: CPS vs Biopsy

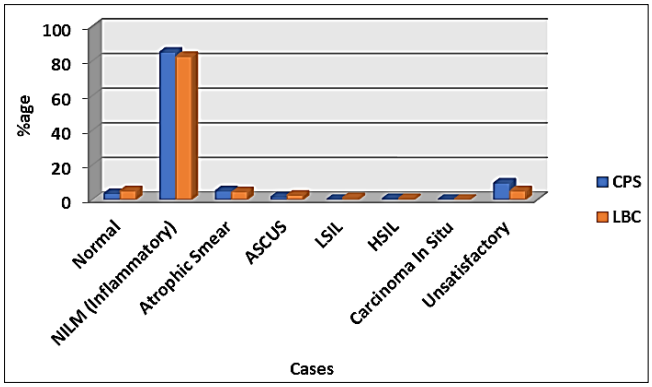


Fig 9b: Distribution between CPS and LBC

Table 10: Comparison of sensitivity and specificity of PAP and LBC with biopsy

Statistic	PAP	LBC
Sensitivity	80.00%	85.71%
Specificity	100.00%	100.00%
Accuracy	87.50%	90.00%

Sensitivity of PAP and LBC in comparison to biopsy was observed as (80% and 85.71%), specificity of PAP and LBC in comparison to biopsy (100%, 100%) and diagnostic accuracy of PAP and LBC was (87.50% and 90%).

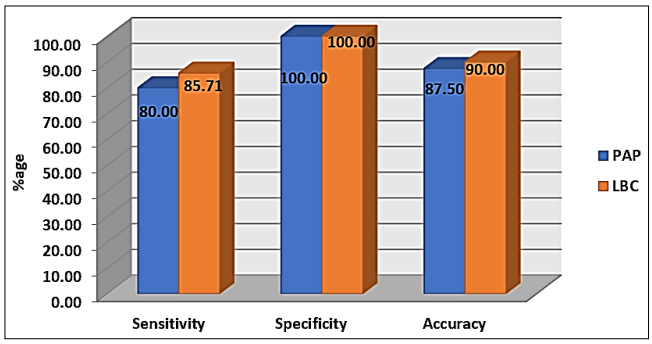


Fig 10: Distribution between PAP and LBC

Discussion

The uterine cervix, like other organs can be affected by both inflammation and malignancy. Chronic cervicitis is a very common condition in adult females, at least at the microscopic level. It affects preferentially the squamocolumnar junction and the endocervix and is often accompanied by metaplastic changes in the epithelium. On the other hand, cancer of the cervix has been recognized as the leading cause of cancer in women in India [14]. Medical literature is replete with studies in which cytology screening has resulted in a reduction of the cervical cancer burden in women and cancer cervix is considered to be an ideal malignancy for screening, aimed at detecting premalignant conditions before they progress to invasive cancer [15, 16].

In the present study majority of the patients 78 (39.0%) were in the age group of 40-44 years followed by 51 (25.5%) 35-39 years, 47 (23.5%) 45-49 years and rest 24 (12.0%) >49 years of age. This was similar to the study by Kasem *et al.* [17] in which almost two-thirds of the cases were within 26 to 45 years. Tofazzal *et al.* [18] found highest incidence of years in age group closely followed by 30 to 40 years, where the age of occurrence of invasive cervical cancer was 40 to 45 years. World Health Organization also suggested the priority age group as 35 to 45 years for the screening of CIN [19].

Parker noted that lower socio-economic status women had marriage at a younger age and child birth. Latest WHO report shows that 70% of cases are from the lower socio-economic status due to lack of access to screening programs and late detection of diagnosis and treatment [20]. Nigerio SE *et al.* [21]. postulated that illiteracy, poverty, nonuse of screening methods and lack of communication after referral among lower socio economic status persons were responsible for the increased number of dysplasia among these persons.

Duration of marriage and duration of exposure to sexual intercourse had a distinct role in genesis of cervical dysplasia. In our study, the incidence of cervical dysplasia was higher in women which were married for >10 years, and less among women who were married for ≤10 years. Kushtagi and Fernandez had demonstrated the severity of underlying cervical dysplasia increased with increase in the duration of marital life and hence the increase in the duration of sexual intercourse [22].

Regarding parity, our study showed, increased incidence of cervical dysplasia among multiparous women with 51.0% were para 4, 16.5% were para 3 and 13.5% were para 5 or more. Similar study by Shalini *et al.* [23] showed the mean parity was 4.2 in patients with invasive cancer. Kushtagi and Fernandez showed the prevalence of cervical dysplasia was significantly higher in parity of more than 2 [65]. Vaidya and Olaniyan showed more positive cases of cervical dysplasia were found with parity more than 4. This might be attributed to hormonal and nutritional changes that occur in pregnancy, immunosuppression during pregnancy, and cervical trauma during vaginal delivery [24].

Among the complaints, majority of women (48.0%) complained of excessive white discharge per vaginum. Excessive vaginal discharge playing a role in contributing to the development of cervical dysplasia was also proved to be a risk factor in the study conducted by Vaidya and Olaniyan. In their study, 24% had vaginal discharge [67].

In the study by Garg *et al.* [25], commonest complaint was white discharge (58.5%) followed by pelvic pain (24%) amongst all symptomatic women, 16% had complaint of Inter menstrual bleeding, 10% had menorrhagia, 6% had postcoital bleeding and rest 06% had complaint of itching vulva.

Malur PR *et al.* [26], in his study also observed the similar results with white discharge being the most common complaint i.e. 61.05%.

Sherwani *et al.* [60]. Kenneth and Yao [27], Nigerio SE *et al.* [64]. and Sharma P *et al.* [62] also had patients with similar complaints. Kenneth and Yao noted that white discharge was associated with neoplastic changes so patient with white discharge were sampled in our study.

In a study done by Robert ME *et al.* [28]. Post coital bleeding was noted in many patients and all these had dysplasia (66.7%) and carcinoma (33.3%). Only 4 cases in this study had this complaint. Study done by M. Tarney *et al.* [29] also had a greater number of patients with complaints of post coital bleeding.

Out of the 200 cases, 181 cases (90.5%) were found satisfactory for evaluation in conventional PAP smear whereas 190 cases (95%) were found satisfactory in LBC, this difference is statistically significant (p=0.041). Unsatisfactory cases in both CPS and LBC were due to scanty or absent endocervical cells (2%, 1%), low cellularity (1.0 %, 3%), inflammation in background (4.0%, 0), hemorrhage in background (3%, 0%) and mucin in background (1%, 0) found similar to Monsanego *et al.* [30]. According to Sherwani *et al.* [60]. in Liquid based cytology cytolysis and drying artifact is minimal or absent due to immediate fixative in a liquid fixative and lesser limited factors

such as inflammatory cells, blood and mucus and in Conventional PAP is due to thick smear.

In our study number of smears diagnosed as ASCUS was more in Liquid based cytology compared to Conventional PAP smear. Similar to that of Davey *et al.* [31]. İlter E *et al.* [32]. O Abulafia *et al.* [33]. Bolick *et al.* [34] and Weintraub *et al.* [35] showed that LBC was a better test for diagnosis of ASCUS but contrast to studies by Zhu J *et al.* [36] and Diaz Rosario *et al.* [37].

In the present study number of LSIL increased from 0% in Conventional PAP to 1% in LBC. Other studies with similar results are Sherwani RK *et al.* [60]. Hutchinson *et al*. [40] 199248, Diaz-Rosario *et al.* [80] and Beerman *et al.* [38].

Overall sensitivity and specificity

In the present investigation Sensitivity of PAP and LBC in comparison to biopsy was observed as (80% and 85.71%), specificity of PAP and LBC in comparison to biopsy (100%, 100%) and diagnostic accuracy of PAP and LBC was (87.5% and 90%). Other studies which shows higher sensitivity of LBC Sheets *et al.* [39]. Sherman *et al.* [40]. Roberts *et al.* [41]. Papillo *et al.* [42]. Guidos and Selvaggi [43] and Macharid *et al.* [44] similar to our study.

Conclusion

Our study concluded that though conventional pap smear (CPS) is a simple and cost- effective method of cervical screening which has been in use for more than 50 years, false negative rate is an important disadvantage. So, we compared both these methods in our study and compared it with the biopsy result. LBC provided more representative samples and morphology of the cells were better visualized due to less obscuring materials. LBC generated a greater number of satisfactory smears and intraepithelial lesions were detected more in LBC. Sensitivity and specificity were more in LBC than CPS. LBC showed better correlation with biopsy than CPS statistically.

To conclude, in a country where a greater number of people belong to lower socio – economic status and with higher incidence of cervical cancer, screening plays an important role in prevention. So, awareness should be created about the screening programs and government should take adequate measures to improve the quality of the screening procedures by introducing improved methods like LBC, since cervical cancer is preventable by early detection and intervention.

In Rural India where screening methods are not freely available and also rural population is unaware of the need of cervical screening due to lack of knowledge, illiteracy, lack of awareness and lack of facilities like local examination and knowledge about warning signs, it is need of the hour that Government works in this area to decrease the incidence of cervical cancer.

Although LBC is better than conventional Pap smear but in rural area if women could get conventional pap done or LBC any of these, it will be of great help.

It is our duty as clinician to take measures to provide pap smear or LBC to rural India. And even conventional pap smear will serve a lot for humanity. All this is possible if there are Government schemes to work on this subject.

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