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Original Research Article

Pap Smears and its Clinical Correlation

Cytological Spectrum of Pap Smears according to the Bethesda System and its Clinical Correlation in a tertiary care centre

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Abstract: Uterine Cervix is an easily accessible site for various infections, inflammations, and malignancies. Cervical cancer is considered to be the fourth leading cause of death in women worldwide; therefore, it needs to be detected and treated early for better survival. The primary aim of cervical PAP smear screening is to screen and identify neoplastic lesions in the early stage, as cervical cancer can be cured if diagnosed at an early stage and treated promptly. In various pap smear studies, the frequency of non-neoplastic lesions and infections of the cervix is very common. The study aimed to describe the cytomorphological spectrum of lesions of the Uterine Cervix, its clinical correlation, and the categorization of the lesions according to the Bethesda System of Classification 2014. The study's objective was to determine the preference of age and parity in different lesions of the Uterine Cervix to correlate and compare the cytological findings with histomorphological findings. The observation study included 505 women aged 21-65 attending gynecological OPD who underwent conventional pap smears from Dec 2020 to Nov 2022. Out of 505 pap smears studied, most utero-cervical lesions screened were in the 4th decade (43.56%) and parity three (32.87%). The most common presenting clinical symptom was leucorrhoea (45.9%), the most common infection was bacterial vaginosis (59.036%), and the most common abnormal epithelial cell lesion was HSIL (4.55%) (high-grade squamous intraepithelial lesion). Out of 505 pap smear cases, in 97 cases, histopathological correlation was done. The sensitivity of the pap smear was 83.33%, specificity :97.05%, Positive predictive Value :97.22%, and Negative predictive value :82.50%. Most cervical lesions are benign, but it is a site of shades of grey lesions, that includes cervical dysplasia to malignancy. Thus, a pap smear is an easy, cost-effective OPD procedure for the early detection of lesions of the uterine cervix.

Keywords: Pap smear, cervical cytology, Bethesda system, premalignant lesion, squamous cell carcinoma

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1. INTRODUCTION

Two types of epithelium line the Uterine Cervix. The uterine, the outer ectocervix comprising of squamous epithelium and the inner endocervix mucin-secreting columnar epithelium, has a squamous columnar junction in between.[1] It is an easily accessible site for various infections, inflammations, and malignancies, in which chronic cervicitis is the most common.[2] It is typical to observe inflammatory infiltrates in the transition zone. Inflammatory responses are triggered by endogenous bacterial flora, injury, and infections. Columnar cells are replaced by squamous metaplastic cells, which clog crypt apertures and cause mucus to accumulate and worsen inflammation.[3] Lesions predominantly detected through cervical pap smear screening are premalignant, malignant, infectious, and inflammatory lesions. Cancer initiates in the squamocolumnar junction between the ectocervix's squamous epithelium and the endocervix's columnar epithelium. This region faces continuous metaplastic changes throughout women's lifecycles.[4] This cancer is unique since the malignant transformation is caused by the infection of HPV (Human Papilloma Virus), predominantly by the HPV 16,18 strain. An HPV infection remains inert at its initial phase and takes 10-20 years to develop cancer. Persistent HPV infection is essential, but not sufficient for the development of cervical cancer. Several cofactors and molecular events are involved in the progression of the disease .[4] Women living with HIV are 6 times more likely to develop cervical cancer as compared to women without HIV.[5] Vaccination against HPV, and screening and treatment of pre-cancer lesions is a cost-effective way to prevent cervical cancer.[6] Cervical cancers are curable if diagnosed at an early stage and treated promptly.[7] Cervical cancer is one of the major health problems and causes of mortality in women worldwide.[3] It is the fourth leading cause of cancer death in women worldwide. In India, it is far more alarming and is the second most common cancer in women. Every year, 122844 women in India are diagnosed with cervical cancer, and 67,477 women die from the disease.[4] Several socio-economic factors such as low age of marriage, lack of personal hygiene, multiple sex partners, and overall unawareness of gynecological health may be the common reason for the high incidence and mortality rate in India. A higher incidence rate at older age also indicates a lack of screening. Despite being curable if detected early, cervical cancer has taken a devastating form in India.[5] Dr. G. Papanicolaou introduced the pap test for screening malignant and premalignant lesions, which has been used globally since 1941. It can detect early epithelial cell abnormalities and early stages of invasive cancer.[3] The sensitivity of the pap test is 50-80%, and the specificity is 98-99%.[6] It is a simple, easy, cost-effective routine OPD procedure; hence, a large population can be screened. The combined approach of HPV DNA (Human Papilloma Virus) and Pap test can improve the sensitivity in all categories of epithelial abnormalities. Because of screening programs, there has been a significant reduction in mortality from cervical cancer in developed countries.[6] The present study aims to evaluate the spectrum of different lesions of the cervix at different age groups, different parity, its clinical-cytological evaluation, and its histopathological correlation.

2. MATERIALS AND METHODS

This study was conducted in a tertiary care center in East Uttar Pradesh after due approval from the ethical committee (HIMS/IEC/46).

2.1 Study Design

It is an observational, cross–sectional and descriptive study.

2.2 Place of Study

The study was conducted in the Department of Pathology, Heritage Institute of Medical Sciences, Varanasi, India

2.3 Sampling Methods

Convenient sampling.

2.4 Study Population

It was done routinely in all women between age group 21-65 years attending gynecological OPD in HIMS/ or women presenting with any clinical features.

2.5 Study Duration

December 2020 to November 2022.

2.6 Case selection

It is a routine screening procedure done in all women of the age group 21-65 years, and the case selection was based on the clinical features.

2.7 Inclusion criteria

Apart from routine screening, it included all women with the following complaints: bleeding between periods, bleeding after sexual intercourse, discomfort during sexual intercourse, bleeding in post-menopausal women, and vaginal discharge.

2.8 Exclusion criteria

Women with menses, pregnancy, hysterectomy, and diagnosed or under treatment cases of cervical cancer were excluded from the study. The two samples from the transformation zone were taken with the help of Ayer's spatula. Smears were made on glass slides and fixed in absolute alcohol immediately by the Dept of OBG using the convention method. Samples were sent to the Dept of Pathology, Heritage Institute of Medical Sciences. The conventional method of Pap smear collection and processing was performed, and smears were stained by Pap staining method[7], and lesions were classified using Bethesda System of Classification, 2014.

3. RESULTS AND DISCUSSION

A total of 505 pap smears were studied during the study period between the ages 20-65 years, with a mean age of 37.6 years. Most Utero-cervical lesions screened were in the 4th decade (43.56%), and the predominant parity was three (32.87%). The most common presenting clinical symptom was leucorrhoea (45.9%), followed by blood-stained discharge (24.3%), which was commonly associated with NILM (negative for intraepithelial lesion or malignancy) smears. In contrast, post-menopausal bleeding was the common complaint among SIL (squamous intraepithelial lesions) and malignancies.

Table 1: Distribution of pap smear reports and classifying the lesions as per The Bethesda System of Classification 2014 (n=505)

Diagnosis	No. of Cases	Percentage
Inadequate	32	6.33%
Unsatisfactory	24	4.75%
NILM (negative for intraepithelial lesion or malignancy)	383	75.84%
ASCUS(atypical squamous cells of undetermined significance)	18	3.56%
ASC-H(atypical squamous cells cannot rule out high-grade squamous intraepithelial lesions)	4	0.79%
LSIL(low-grade squamous intraepithelial lesion)	12	2.30%
HSIL(high-grade squamous intraepithelial lesion)	23	4.55%
AGC(atypical glandular cells)	5	0.99%
SCC(squamous cell carcinoma)	4	0.79%
TOTAL	505	100%

As seen in Table no. 1, out of 88.92 % adequate smears, the frequency of non-neoplastic lesions-NILM was (75.84 %), indeterminate lesions like ASCUS (Atypical squamous cells of undetermined significance), ASCH (Atypical squamous cells cannot rule out high grade squamous intraepithelial lesion) and AGC (Atypical glandular cells) together were (5.34 %) while SIL and neoplastic lesions were in 7.64 cases. Bacterial vaginosis (Fig. 1) was the most common infection (59.036%) among microbial infections. HSIL was the most common epithelial cell lesion in 4.55% of cases.

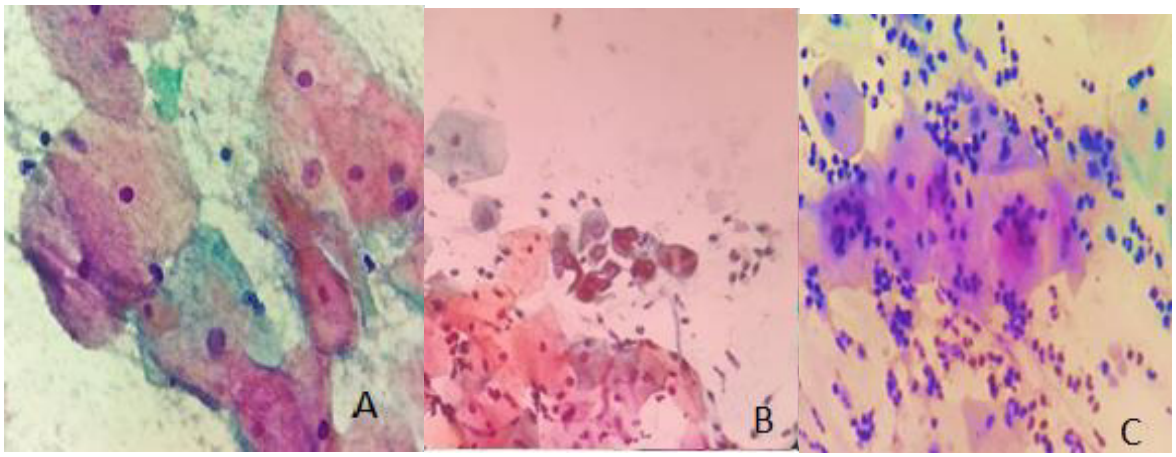

Fig 1: Organisms in PAP smear A) Bacterial Vaginosis: showing a shift in flora (100x, pap stain) B) Herpes simplex C) Candida

In the present study, NILM was most commonly seen with parity 2. Indeterminant lesions (ASCUS, ASCH, AGC) (fig 2) and HSIL were common with parity 3 and 4, while LSIL (low-grade intraepithelial lesion) (Fig 3) was more common among parity 2. Malignancy was associated with increasing age (5th and 6th decade) and parity (parity 4 and above).

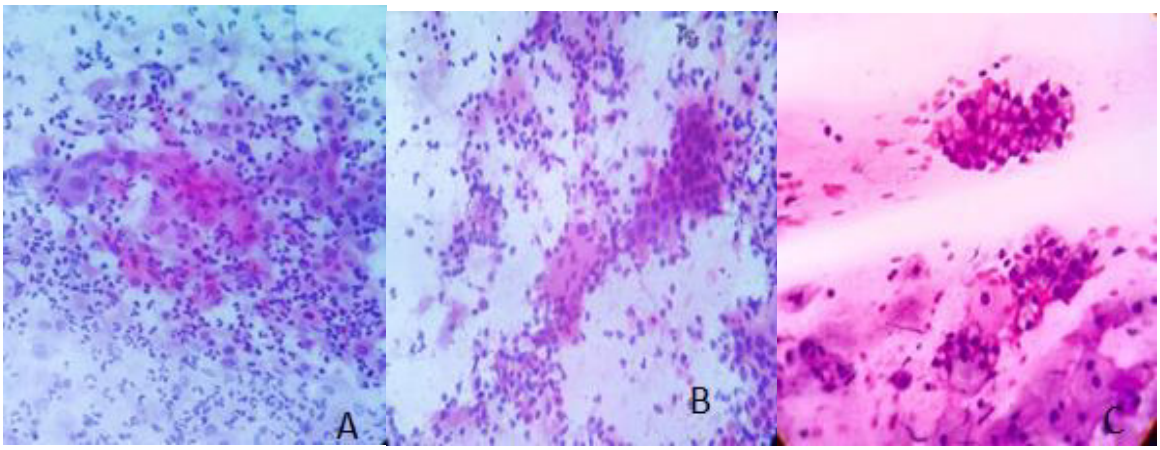

Fig 2: Epithelial cells abnormalities (ECA) A) ASCUS (Atypical squamous cell of undetermined significance), B) ASCH (Atypical squamous cells cannot rule out high-grade dysplasia, C) AGC (Atypical glandular cells)

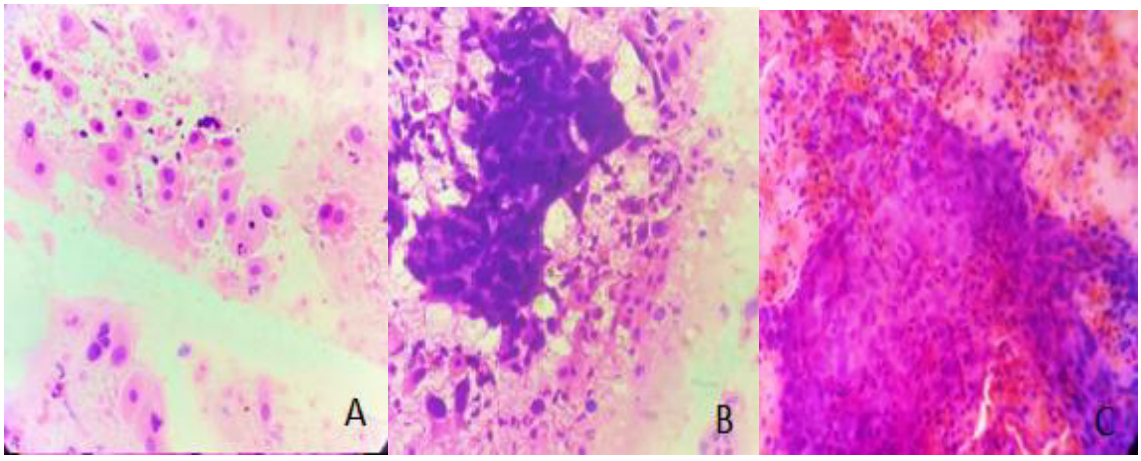

Fig 3: Epithelial cell abnormalities A) LSIL (Low-Grade Intraepithelial lesion) B) HSIL (High-Grade Intraepithelial Lesion) C) SCC (Squamous Cell Carcinoma)

Table 2: Age-wise distribution of lesions in Pap smear

Age (years)	Inadequate	Unsatisfactory	NILM	Ascus	ASC-H	LSIL	HSIL	AGC	SCC	Total
20-30	5	8	92	-	-	1	-	-	-	106
30-40	14	12	178	8	-	4	4	-		220
40-50	8	2	69	7	3	5	10	1	-	105
50-60	4	2	38	3	1	2	9	3	2	64
>60	1	-	6	-	-	-	-	1	2	10
Total	32	24	383	18	4	12	23	5	4	505

In age-wise distribution of lesions, overall, the mean age of presentation was 37.6 years. NILM was the most common lesion in all age groups, and most cases were seen in the 4th decade, as seen in Table 2. 23 HSIL cases were found; the maximum number of cases were seen in the fifth decade. The frequency of distribution of intra-epithelial lesions or malignancy was more commonly seen in the fifth and sixth decades, which signifies that as age increases, risk stratification of malignancy increases.

Table 3: Correlation of Clinical features/symptoms and Cytological Findings

LESIONS	Leucorrhoea	Blood stained discharge	PMB	M.Disorder	Pelvic pain	Prolapse	Asymptomatic	Total
Inadequate	09	02	04	03	07	02	5	32
Unsatisfactory	05	02	00	04	08	01	4	24
NILM	207	94	04	48	12	08	10	383
ASCUS	05	09	04	00	00	00	00	18
ASC-H	01	02	01	00	00	00	00	04
AGC	00	02	03	00	00	00	00	05
LSIL	03	04	05	00	00	00	00	12
HSIL	02	09	10	02	00	00	00	23
SCC	00	01	03	00	00	00	00	4
Total no. of cases	232	123	31	57	28	11	19	505
Percentage	45.9%	24.3%	6.1%	11.28%	5.5%	2.17%	3.76%	100%

Note (PMB- post-menopausal bleeding, M disorder - menstrual disorder)

As seen in Table 3, leucorrhoea was the most common clinical symptom in 232 cases (45.9%), followed by blood-stained discharge in 123 cases (24.3%). The most common presenting feature of NILM was leucorrhoea in 207 cases (54.04%).
In LSIL, HSIL, and SCC, the most common presenting symptom was post-menopausal bleeding in 05 (41.6%), 10 (43.47%), and 3 cases(75%), respectively.

Table 4: Cyto-Histological Correlation of Cervical Lesions

Histo diagnosis / Cyto diagnosis	Nonneoplastic (inflammatory)	Benign neoplasm	Premalignant Lesion	Malignant lesion
NILM	31	03	00	01
ASCUS	14	00	03	00
ASCH	02	00	02	00

AGC	03	02	00	00
LSIL	01	00	10	00
HSIL	00	00	19	02
SCC	00	00	00	04

In 97 cases, cytology pap smear and histopathology were done, and the findings were correlated, as shown in Table 4 above. A total of 35 cervical biopsies, which were reported as NILM on a pap smear, were received and correlated, in which 31 cases were non-neoplastic on histopathology, including chronic non-specific cervicitis with papillary endo-cervicitis and squamous metaplasia and chronic granulomatous cervicitis, three cases were of benign neoplasm including endocervical polyp, angiomyxoma, and one case was of endometrial cancer invading cervix. There was a total of 18 ASCUS cases reported in pap smear cytology, out of which, biopsy for 17 cases were received for HPE, which showed 14 nonneoplastic lesions, including chronic non-specific cervicitis with papillary endo-cervicitis with squamous metaplasia and 3 premalignant lesions including focal low-grade dysplasia and CIN I. Similarly, out of 4 ASCH cases, 2 were nonneoplastic, and 2 were premalignant, including high-grade dysplasia on histopathological examination. In AGC cases, 3 were nonneoplastic, and 2 were benign neoplasms comprising benign endocervical polyps. Out of 12 LSIL cases reported in PAP smears, 11 cervical biopsies were received, in which 1 case showed chronic cervicitis with squamous metaplasia, whereas 10 cases were premalignant lesions on HPE, including low-grade dysplasia and high-grade dysplasia. Similarly, out of 23 HSIL cases in PAP smears, 21 cases received cervical biopsies, in which 19 cases showed premalignant lesions, including high-grade dysplasia, and 2 cases with focal in situ carcinoma on histopathology. Squamous cell carcinoma (4 cases) showed a 100 % correlation in cytology and histopathological findings.

Table 5: Correlation of Sensitivity, specificity, and Diagnostic accuracy of Pap smear about Histopathology. (test and disease correlation)

True Positive (TP) (A) 35	False Positive (FP) (B) 1
False Negative (FN) (C) 7	True Negative (TN) (D) 33

Sensitivity is the ability of a test to correctly identify patients with the disease (true positives); specificity is the ability of the test to correctly identify people without the disease (true negatives) Positive Predictive Value (PPV) is the ratio of patients truely diagnosed as positive to all those with positive test results. Negative Predictive Value (NPV) is the ratio of patients truely diagnosed as negative to those with negative test results.

Sensitivity = (true positives / total diseased cases) A/(A+C) = 0.833 (83.33%) Specificity = (true negatives / total disease-free cases) D/(D+B) = 0.97 (97.05%) PPV = A/(A+B) = 0.97 (97.22%)
NPV = D/(C+D) = 0.82 (82.50%) Diagnostic Accuracy of the test = (TP + TN) / TP + FP + FN +TN) = 89.47 % The diagnostic accuracy of the pap test is 89.47%.

Pap smear is an integral part of comprehensive health care for women.[8] Besides being a tool for cancer diagnosis, it is used to identify infections such as trichomonas, herpes, and HPV and classify the hormonal pattern. Smears with inflammatory changes were seen mainly in women in the reproductive age group.[9] Cervical cancers is a preventable disease. However, it is the most common cause of cancer morbidity and mortality in developing countries.[10] The present study was about the spectrum of cervical lesions using a conventional pap smear test in a tertiary care center. The study group comprised of women between 20 and 65 years of age. This age group was taken because sexually transmitted infections are more common in the younger age group[11], and 20% of cervical cancers are detected in the perimenopausal groups.[12]

3.1 Comparison of age-wise distribution of cases in the present study and various studies:

In the present study, the most common age group screened for pap smear was the 4th decade, which was similar to most of the studies[9,12-15], while in the study of Sharma P et al. [16], the subjects screened were most commonly from the 3rd decade.

3.2 Relationship of age with Non-neoplastic findings in the present study and other studies:

In the present study, non-neoplastic findings, especially inflammatory smears, were common in 4th decade followed by 3rd decade, which was comparable with a study by Devi J *et al.*,[13] and Sharma *et al* .[16]

3.3 Relationship of age with lesions of Epithelial Cell Abnormality (ECA) and carcinoma in the present study and other studies

In our study, ASCUS was most commonly seen in the fourth decade. LSIL, HSIL, and ASCH were common in the 5th decade, whereas AGC and SCC were commonly seen in the 6th and 7th decade, respectively, similar to the study of Das debasmita[14] *et al.* and others.[14] On the contrary, LSIL was more commonly seen in the 4th decade in a study by Sharma et al., Devi J *et al.*, etc.[13,16] The frequency of distribution of SIL increases with the increasing age. Few previous studies showed the most common age to develop carcinoma cervix is the 5th decade, and the precursor lesions occur 5-10 years before the development of invasive carcinoma.[13,17]

3.4 Relationship of parity with inflammatory lesions, SIL, and carcinoma in the present study and other studies:

Multiparity (parity>3) and decreasing spacing between deliveries are risk factors for carcinoma cervix.[16] In the current study, most cases belong to parity 3 (32.87 %), similar to other studies.[16,18] NILM was most commonly seen with parity 2, similar to other studies.[16,18] LSIL was common among parity 2, while HSIL was more common among parity 3 in the present study. Contrary to this, in other studies, SIL was more common among parity 3 or more. SCC was seen more commonly with parities 4 and 5, similar to other studies.[16,18] From the above discussion, the frequency of premalignant and malignant lesions increases with increasing parity. Multiparity and decreasing spacing between deliveries are risk factors for carcinoma cervix.[16]

Table 6: Comparison of clinical parameters and lesions in the present study and various studies

S. No.	Studies	m/c symptom	2nd m/c symptom
I	Present study	Leucorrhoea (45.9 %)	Blood-stained discharge (24.3%)
2	Devi J et al	Leucorrhoea (47.02%)	Blood-stained discharge (25.66%)
3	Ghimire P et al	Leucorrhoea (29.3%)	Lower abdominal pain (26.3%)
5	Sachan et al	Leucorrhoea (36.96%)	Pain in abdomen (25.63%)
6	Das D et al[74]	Leucorrhoea (63%)	Lower abdominal pain (25.02%)
7	Umarani MK et al.[69]	Irregular bleeding per vagina (19.61%)	Leucorrhoea (19.18%)
8	Bal M S[75]	Leucorrhoea (59%)	Pain lower abdomen (19.3 %)

The most common clinical presentation was leucorrhoea in the present study, which was comparable with other studies.[10,13,14,15,16,18] In contrast to the above, in the study of Umarani MK et al., the most common presenting symptom was irregular bleeding per vaginum followed by leucorrhea.[9]

Table 7: Comparison of infections in NILM smear in different studies

Studies/infections	BV	Candida	Trichomonas	HSV	CMV	Actinomycosis	Total infection cases
Present study	98 (56.97%)	64 (37.20%)	05 (2.90%)	4 (2.4%)	00	01(0.5%)	172
Ghimire P et al[10]	26 (26.26%)	38 (38.38%)	30 (30.30%)	4 (4.04%)	00	1 (1.11%)	99
Barouti E et al[19]	91 (61.07%)	56 (37.5%)	2 (1.3%)	00	00	00	149
Ahmed I et al [20]	(48.4%)	34.5%	17.1%	00	00	00	108

As seen in Table No. 6, Bacterial vaginosis was the most common microbial infection found in the present study and other studies, followed by candida.[19,20] In contrast, candida was the most common infection in a study by Ghimire P et al., followed by trichomonas.[10]

Table 8: Comparison and Categorization of cyto-diagnosis in various studies

Cytological. Diag. Studies	NILM / Inflammatory.	ASCUS	ASCH	AGC	LSIL	HSIL	SCC	Adenocarcinoma
Present study	383 (75.8%)	18 (3.56%)	04 (0.79%)	05 (0.99%)	12 (2.3%)	23 (4.55%)	04 (0.79%)	00
Devi J et al [13]	428 (87.88%)	22 (4.51%)	05 (1%)	00	12 (2.4%)	18 (3.69%)	02 (0.4%)	00
Ghimire P et al [10]	688 (85.95%)	19 (2.03%)	06 (0.64%)	07 (0.75%)	40 (4.2%)	34 (3.6%)	08 (0.85%)	00
Sharma P et al [16]	61 (61%)	01 (1%)	00	07 (7%)	20 (20%)	04 (4%)	07 (7%)	00
Sachan et al.[18]	1510 (91.51%)	48 (2.90%)	00	00	84 (5.09%)	08 (0.48%)	00	00
Das D et al [14]	4571 (90.97%)	05 (0.09%)	07 (0.13)	00	26 (0.5%)	18 (0.35%)	64 (1.2%)	02 (0.03%)
Umarani MK et al [15]	273 (91%)	01 (0.33%)	00	00	08 (2.66%)	02 (0.66%)	03 (1.0%)	01 (0.33%)

As stated in Table 7 above, the most common finding in all studies was NILM, ranging from 61 % to 91 %.[15,16] Among SIL, in the current study, HSIL was more common (4.5%) than LSIL (2.3%), similar to the study of Devi J et al. with 3.69 % HSIL cases and 2.4% LSIL cases. In contrast, in other studies, LSIL was more common than HSIL [10,15,16,18.] The percentage of malignant lesions was less than SIL in the current study and other studies[10,13,15,16,18]contrast to which SCC was more common than SIL in a study by Das D et al.[14] Variations were observed while comparing the findings of SIL and malignancy in the present study and other studies which may be due to unawareness about risk factors and disease progression. The disease may have already progressed by the time the findings are acknowledged. It may also be due to negligence of female health in the family, low personal hygiene, poor

socioeconomic status, and illiteracy. In summary, the frequency of non-neoplastic lesions, i. e., NILM (75.84 %), was the commonest cytological finding on a pap smear. Amongst infections, bacterial vaginosis was the most common microbial infection (59.036%), indeterminate lesions were 5.34 %, while SIL and neoplastic lesions were 7.64 % cases. It was found that, cervical lesions were most common in the 4th decade (43.56%) and parity 3, where malignancy was seen as being associated with increasing age (5th and 6th decade) and increasing parity (parity 4 and above). The premalignant lesions were found a decade earlier than malignant lesions. In cytological-histopathological correlation, the PAP smears showed 83.33 % sensitivity, 97.05% specificity, 97.22 % PPV and 82.50 % NPV. The diagnostic accuracy of the pap test is 89.47 %.

4. CONCLUSION

The study concluded that non-neoplastic lesions were the most common findings in pap smears, with bacterial vaginosis as the most prevalent infection. Indeterminate lesions were also observed, while squamous intraepithelial lesions (SIL) and neoplastic lesions were less common. The study found that cervical lesions tended to be more frequent among women in their 40s with moderate parity, while malignancies were typically seen in older women with higher parity. Premalignant lesions were often identified a decade before malignant lesions. The cytological-histopathological correlation demonstrated that pap smears are generally reliable, with high sensitivity and specificity, suggesting their value in the early detection and diagnosis of cervical abnormalities. For future research, there is a need to explore the underlying risk factors contributing to cervical lesions and the progression to malignancy. Studies could focus on the effectiveness of different screening strategies and the potential for personalized screening protocols based on patient age and parity. Moreover, research into advanced diagnostic techniques could further improve the accuracy of Pap smears and reduce false-positive and false-negative results. It could contribute to better early detection and improved patient outcomes.

5. AUTHORS CONTRIBUTION STATEMENT

Dr. Pooja Awasthi Mahajan gathered the data and prepared the original draft. Dr. Vaishali Kotasthane and Dr. Dhananjay Kotasthane conceptualized and designed the study and provided the necessary inputs. All the authors read and approved the final version of the manuscript.

6. ACKNOWLEDGEMENTS

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7. CONFLICT OF INTEREST

Conflict of interest declared none.

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