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Proportion of cervical intraepithelial neoplasia in patients with persistent inflammatory Paps smear

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Abstract: ***Background:*** Among the chronic diseases, cervical cancer is still a public health problem. An inflammatory Pap smear may miss cervical precancerous changes due to low sensitivity and high false negativity of Pap smear. ***Methods*****:** This was a cross-sectional type of descriptive study on 384 married non-pregnant patients aged ≥ 18 years presented with persistent inflammatory changes on Pap smear attending in the OPD of Obstetrics and Gynecology, Rajshahi medical college Hospital, Rajshahi over a period of 1 year from June 2020 to July 2021. Pre-designed, validated, semi-structured questionnaire and purposive sampling technique were used to gather information from the patients. ***Results:*** According to colposcopic grading, 46.60% of the women harbor CIN-1, 10.70% CIN-2, 2.60% CIN-3 and remaining 40.10% chronic cervicitis among the women with persistent inflammatory changes on Pap smear. Again, according to histological grading, 26.60% of the women had CIN-1, 4.70% CIN-2 and remaining 68.80% chronic cervicitis. ***Conclusions:*** Colposcopy is an excellent tool for evaluation of cervical carcinoma if operator is properly trained. Concomitant histology also increases the sensitivity and specificity of the test.

Keywords: Cervical intraepithelial neoplasia, Colposcopy, Pap smear.

Original Research Article

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Article at a glance:

Study Purpose: *The purpose of this study was to evaluate whether persistent inflammatory changes on Pap smear could be the first indication of premalignant changes in the cervix and whether further evaluation by colposcopy would help to triage these women.*
Key findings: *As a diagnostic test the sensitivity and specificity of colposcopy were 87.50% and 52.70%, respectively for CIN.*
Newer findings: *Positive and negative predictive value were 45.65% & 90.25%, respectively for colposcopy in diagnosis of CIN.*
Abbreviations: *ASCUS: Atypical squamous cells of undetermined significance, CIN: Cervical intraepithelial neoplasia and LSIL: Low grade squamous intraepithelial lesion.*

INTRODUCTION

Cervical cancer is a major cause of death in women around the world, killing 270,000 women each year. It indicates that somewhere in the world a woman dies in every two minutes from this disease. In Bangladesh, every year 17686 women are diagnosed with cervical cancer and 10364 die of the disease.[1] Everyday 28 women die which ranks the most frequent cancer death in women in Bangladesh. Cervical cancer has been the subject of several epidemiological studies since last 150 years. World over, Pap smear has been the standard test for screening of cervical cancer and its precursors. Although widespread institution of Pap smear screening over the last 4 decades has led to marked reduction of its incidence and mortality, it is still a public health menace. Inflammatory Pap smear is the most common report received by the gynaecologists.[2]

However, due to the low sensitivity and high false negative rate of Pap smear, there is a possibility that an inflammatory Pap smear may miss cervical premalignant changes. The cervical screening algorithm for benign cellular changes on the Pap smear recommends treatment of infection if indicated and a repeat Pap smear in 4 to 6 months' time.[3] To overcome this problem many algorithms have been devised to manage ASCUS or LSIL on pap-smear. These involve HPV DNA testing, colposcopy or both. However, no such algorithms are available for further management of an inflammatory Pap smear. If the inflammatory changes still persist, the patient is subjected to colposcopic evaluation.[4] However, in practice, this is not followed, especially in developing countries like ours where proper screening protocols are not available. Hence, a good number of patients in the premalignant stage are being missed.

Since the incidence of inflammation on Pap smear is very high (14%-19%),[5,6] it may not be possible to subject all patients with inflammation to colposcopy or HPV DNA testing. This study was designed to evaluate whether persistent inflammatory changes on Pap smear could be the first indication of premalignant changes in the cervix and whether further evaluation by colposcopy would help to triage these women. The data obtained from the proposed study might be helpful to define a diagnostic and management protocol for patients with persistent inflammatory cellular changes with ultimate aim of reducing morbidity and mortality from the disease.

METHODS

This cross-sectional type of descriptive study was conducted in the Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi on 384 patients with persistent inflammatory changes on Pap smear attending at the Out-patient Department over a period of one year from June 2020 to July 2021 to identify the premalignant stage by colposcopy and histopathology in patients with persistent inflammatory Paps smears without atypia. Prior to the commencement of the study, approval of the Ethical Review Committee (ERC) was obtained and a purposive sampling technique was used to get data collection by administering a semi-structured questionnaire by face-to-face interview.

Prior to data collection, women were briefed about the purpose of the study and their informed written consent was taken. After taking informed written consent, complete history taking and physical examination were done and recorded in preformed data sheet. Patients first enrolled for Pap's smear test. If Pap's smear test exhibited inflammatory cellular changes without atypia, the patient had received treatment of infection. If the inflammatory changes were persisted, the patient had subjected to colposcopy. If colposcopic evaluation revealed any abnormalities, then biopsy had taken. If the diagnosis was CIN, histopathological grading also had done. The data were analyzed via SPSS (version 24.0) Statistical significance was evaluated as appropriate probability level $p < 0.05$ for all tests.

RESULTS

Age category of the women revealed that majority (81.00%) of the women belonged to the age group of 30-40 years with mean age 36.76±6.84 years (Table 1).

Table 1: Distribution of the women by their age (n = 384)

Age (Years)	Frequency	Percentage (%)
30-40	311	81.00
41-50	64	16.70
51-60	03	0.80
61-68	06	1.60
Total	384	100.00

Majority (80.20 %) of the women married at their age between 13-17 years old and more than 1/5th (19.80%) of them were start married life in between 18-30 years of their age. The women mean (±SD) age of marriage was 15.78 (±2.64) years (Table 2).

Table 2: Distribution of the women according to their age of first sexual activity (n = 384)

Age of first sexual activity Years	Frequency	Percentage (%)
13-17	308	80.20
18-30	76	19.80
Total	384	100.00

Parity of the women revealed that majority (73.95%) of the women were multiparous, one quarter (25.52%) of them were primipara and only a few (0.52%) of the women were nulliparous (Figure 1).

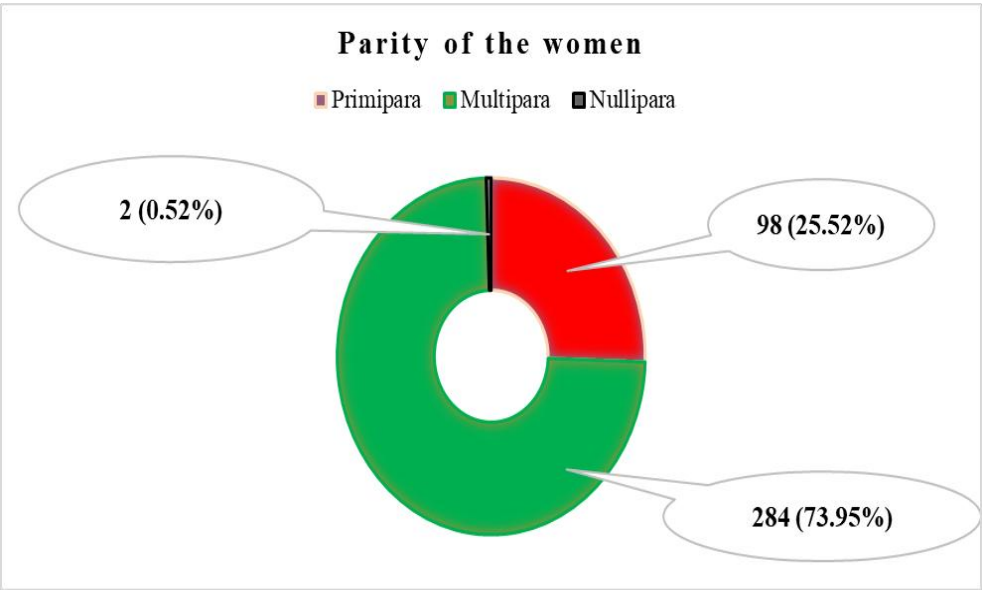

Figure 1: Distribution of the women according to their parity (n = 384)

Clinical symptoms of the women revealed that most (84.10%) of them had vaginal discharge and same proportion (84.10%) had persistent leucorrhoea not responding to antibiotics. About 2/5th (40.10%) of the women had post coital bleeding and 1/5th (21.90%) of them had inter menstrual bleeding (Table 3).

Table 3: Distribution of the women according to their presenting clinical symptoms (n = 384)

Clinical symptoms of the women		Frequency	Percentage (%)
Vaginal discharge	No	61	15.90
	Yes	323	84.10
Post coital bleeding	No	230	59.90
	Yes	154	40.10
Intermenstrual bleeding	No	300	78.10
	Yes	84	21.90
Persistent leucorrhoea not responding to antibiotics	No	61	15.90
	Yes	323	84.10

Per-speculum examination findings showed that all (100%) of the women had normal cervix and only more than one quarter (35.40 %) of them had cervical erosion (Table 4)

Table 4: Distribution of the women according to their per-speculum examination findings (n = 384)

Per-speculum examination findings		Frequency	Percentage (%)
Cervix	Normal	384	100.00
Cervical	No	248	64.60
erosion	Yes	136	35.40

According to P/V findings of the women it found that almost all (98.20%) of the women had normal size of the uterus except few (1.80%) of them had bulky uterus. Again, Fornix of the uterus of all (100.00%) women were free and none had thickened fornix (Table 5).

Table 5: Distribution of the women according to P/V findings (n = 384)

P/V findings		Frequency	Percentage (%)
Size of uterus	Bulky	7	1.80
	Normal	377	98.20
Fornix	Free	384	100.00

Pap smear findings of the women showed that only few of the women had bacterial vaginosis, candidiasis and Trichomonas vaginalis (0.5%, 1% & 0.5%, respectively) (Table 6).

Table 6: Distribution of the women according to Paps smear findings (n = 384)

Pap smear findings		Frequency	Percentage (%)
Bacterial	No	382	99.50
vaginosis	Yes	2	0.50
Candida	No	380	99.00
albicans	Yes	4	1.00
Trichomonas	No	382	99.50
vaginalis	Yes	2	0.50

Colposcopic grading of the women showed that more than 2/5th (46.60%) of them had CIN-1, 2/5th (40.10%) of them had chronic cervicitis, some (10.70%) of them had CIN-2 and only few (2.60%) had CIN-3 (Table 7).

Table 7: Distribution of the women according to colposcopic grading (n = 384)

Colposcopic grading	Frequency	Percentage (%)
CIN-1	179	46.60
CIN-2	41	10.70
CIN-3	10	2.60
Chronic cervicitis	154	40.10
Total	384	100.00

Histological grading of the women showed that one quarter (26.60%) of the women had CIN-1 and some (4.70%) of them had CIN-2 and remaining more than 3/5th (68.80%) of them had chronic cervicitis (Table 8).

Table 8: Distribution of the women according to histological grading (n = 384)

Histological grading	Frequency	Percentage (%)
CIN-1	102	26.60
CIN-2	18	4.70
Chronic cervicitis	264	68.80
Total	384	100.00

The relationship between colposcopic grading and histology grading in patients with persistent inflammatory Paps smear was found statistically significant ($\chi 2$ =165.92, df= 2, p < 0.001) (Table 9).

Table 9: Relationship between colposcopic grading and histology grading in patients with persistent inflammatory Paps smear (n = 384)

Colposcopy grading	Histology Grading			χ^2 (df)	p
	CIN-1	CIN-2	Chronic cervicitis		
CIN-1 (n=179)	61 (34.10%)	0 (0.00%)	118 (65.9%)		
CIN-2 (n=41)	16 (39.00%)	18 (43.90%)	7 (17.1%)		
CIN-3 (n=10)	10 (100.00%)	0 (0.00%)	0 (0.0%)	165.9	<
Chronic cervicitis (n=154)	15 (9.70%)	0 (0.00%)	139 (90.3%)	2 (2)	0.001
Total (n=384)	102 (26.60%)	18 (4.70%)	264 (68.8%)		

Colposcopic impression as a diagnostic test regarding proportional occurrence of CIN in respect of histological comments regarding diagnosis of CIN had 87.50% sensitivity and 52.70% specificity. Positive predictive value and negative predictive value were 45.65% & 90.26%, respectively. The relationship between positive and negative comments about colposcopic impression of occurrence of CIN of the women related to histology comments regarding the occurrence of CIN was found statistically significant ($\chi 2$ = 55.37, df= 1, p < 0.001) (Table 10).

Table 10: The sensitivity and specificity of comments on colposcopic impression in respect of histology comments (n=384)

Closposcopic comments	Histology comments		$\chi 2$ (df)	p
	Positive (CIN present)	Negative (No CIN)		
Positive (n= 230)	105 (TP= 45.65%)	125 (FP= 54.35 %)	53.37	<
Negative(n=154)	15 (FN=9.74 %)	139 (TN = 90.26 %)	(1)	0.001
Total	120 (31.25 %)	264 (100.0%)		

χ^2 = 55.37, df = 1 p < 0.001

Sensitivity = $\frac{TP}{TP+FN} \times 100 = \frac{105}{105+15} \times 100 = 87.5\%$

Specificity = $\frac{TN}{TN+FP} \times 100 = \frac{139}{139+125} \times 100 = 52.7\%$

Positive predictive value = $\frac{TP}{TP+FP} \times 100 = \frac{105}{105+125} \times 100 = 45.65\ \%$

Negative predictive value = $\frac{TN}{TN+FN} \times 100 = \frac{139}{139+15} \times 100 = 90.26\ \%$

DISCUSSION AND CONCLUSIONS

Carcinoma of cervix is almost curable when diagnosed in early stage. Colposcopy is an excellent tool for evaluation of cervical carcinoma if operator is properly trained in concomitant histology which increases the sensitivity and specificity of the test. In this study, 81.00% of the women belongs to 30-40 years age and mean age of the women was 36.76±6.84 years. Similar findings were found in a study done by Moss et al.[7] where mean age was 37.5 years. Age group was between 20-30 year in a study done by Nahar et al.[8] which was the highest frequency among all women and another study showed that mean age of the women with persistent inflammatory Pap smear was 30.43± 6.10 years[3] and these findings were not similar to

present study. In a study which was conducted in Rajshahi by Jesmin et al.[9] among 600 women with unhealthy cervix found 30-39 years women were in highest proportion (42.00%) which was similar to present study. The mean age was slightly higher in other studies as reported by Saha et al.[10], Thapa et al.[11] and slightly lower in a study conducted by Tuon et al.[12] All these studies indicate that carcinoma cervix is common in elderly age group.[13] In the present study, 73.95% of the women were multiparous and 25.52% were primipara which was not similar to a study where the multipara was highest (93%) percentage.[8] In the current study, almost all (98.20%) of the women had normal size of the uterus except few (1.80%) had bulky uterus which was not similar with a study where 59% of the women had the size of uterus.[8]

In this study, 59.90% of the women had colposcopically positive comments regarding presence of CIN and according to colposcopic grading 46.60% of the women had CIN-1, some (10.70%) had CIN-2, only few (2.60%) had CIN-3 and remaining 40.10% had chronic cervicitis. A study conducted by Parvin et al.[14] where 51 women were evaluated for cervical neoplasia. Among them 36 patients showed inflammatory smears, colposcopy revealed inflammation in 14 (37.83%), CIN I in 13 (35.13%) and CIN II in 1 (2.70%) patient which findings were similar to present study regarding chronic cervicitis and CIN-2 but proportionately less than CIN-1. Another study showed that colposcopic positivity was in 54.29% women and among them CIN-1 was in maximum (63.16%) as well as 43.48% had CIN-2 and 10.53% had CIN-3.[8] This study findings were near similar proportion to the colposcopically positive of the present study but higher proportion of occurrence of CIN-1, CIN-2 and CIN-3 than the study. In the present study, relationship between colposcopic grading and histology grading in patients with persistent inflammatory Paps smear was found statistically significant ($\chi 2$ =165.92, df= 2, $p < 0.001$). Higher proportion from the present study was found in a study done by Jesmin et al.8 among 600 women with unhealthy cervix. This discrepancy might be due to difference in the selection criteria of the study subjects where some studies were done on unhealthy cervices and some were on abnormal pap's smear group.

In this study the sensitivity and specificity of colposcopic impression as a diagnostic test for CIN were 87.50% and 52.70%, respectively. Positive predictive value and negative predictive value were 45.65% and 90.25%, respectively which were statistically significant ($\chi 2 = 55.37$, df= 1, $p < 0.001$). Jesmin et al.8 conducted a study on 600 women with unhealthy cervix and found a good correlation between colposcopy findings and biopsy report represented with sensitivity was 91.6% and specificity was 94.3% which were similar regarding sensitivity but much disproportionate to septicity. There were some limitations of the study such as it was a single center-based study on small sample and sampling technique was purposive. Detection of HPV infection was not included in this study which is crucial in the development of CIN and cervical cancer and all the questions were not included in the study that might reflect a broad range of topics in the research for evaluation of the total factors related to cervical cancer.

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Authors' contributions

RA and IS: Concept and design, data acquisition, interpretation, drafting and final approval. IS, SAS and NNP: Analysis plan, data analysis and interpretation, writing manuscript and drafting the article and finally all authors revised the manuscript and approved it for publication.

Declarations

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Conflict of interest

Authors declared no conflict of interest.

Ethical approval

Ethical approval of the study was obtained from the Ethical Review Committee, Rajshahi Medical College, Rajshahi and informed consent was taken from all participants. Methodology of the

study was carried out following the relevant ethical guidelines and regulations.

Consent for publication

Taken

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