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Colposcopic Evaluation of Cervix with Persistent Inflammatory Pap Smear

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ABSTRACT

Background and Objectives: The cervical screening algorithm for benign cellular changes on the Pap smear recommends treatment of infection if indicated and a repeat Pap smear should be done in 4-6 months time. If repeat smear suggests continuation of inflammatory changes, the patient is subjected to colposcopic evaluation. During this lag time, a good number of patients in their premalignant stage may be missed or undergo malignant transformation. Recent studies advocate a repeat Pap smear if treatment of infection for 2-4 weeks does not respond and if repeat Pap smear suggests persistence of inflammatory changes, the patient should be evaluated colposcopically to determine the rate of undetected cervical intraepithelial neoplasia/dysplasia in patients with persistent inflammatory Pap smear. The present study was undertaken to that end.

Patients & Methods: This cross-sectional study was carried out in the Department of Obstetrics and Gynaecology, Institute of Child & Mother Health (ICMH), Dhaka, over a period of 12 months from July 2013 to June 2014. Patients with two consecutive reports of inflammatory cellular changes without atypia on Pap smears despite anti-inflammatory therapy were the study population. A total of 1456 women underwent Paps test at the above mentioned place during the study period for gynaecological problems. Of them 312(21.4%) were reported as 'inflammatory cellular changes'. After giving anti-inflammatory treatment most of them were cured leaving 128(8.8%) cases with repeat report of inflammatory cellular changes on Pap smear and hence were included in the study.

Results: The mean age of the enrolled women was 32.6 ± 7.2 years. Mean age of the patients at marriage and mean age at first child birth were 14.9 years (range: 12-23 years) and 16.5 years (range: 13-26 years) respectively. Majority (94.5%) of the patients were multipara. Of the 128 women, 66(51.6%) were colposcopically positive for CIN. Of them over two-thirds (68.2%) were graded as CIN-1, 25.8% as CIN-2, and 6% as CIN-3. Histological evaluation of biopsy material taken from these 66 cases revealed 25(37.9%) with abnormal cytology (3-CIN-1, 18-CIN-2 and 4 with invasive carcinoma) which accounts for 19.5% of the persistent Paps smear cases. Comparing age at marriage, age at first childbirth and parity between patients with CIN (including invasive disease) and without CIN revealed that the former group married and experienced child birth relatively earlier than the latter group ($p = 0.001$ and $p < 0.001$ respectively). The average parity was also significantly higher in the CIN group.

Conclusions: A high proportion of patients with persistent inflammatory Pap smear can harbour CIN and sometimes even early stage of invasive carcinoma. So patients with persistent inflammatory cellular changes on Pap smear if does not respond to treatment, they should be subjected to a repeat smear within 2-4 weeks and if inflammatory changes continue, they should be immediately evaluated by colposcopy.

Key words: Cervix, persistent inflammatory Pap smear, colposcopy and cervical intraepithelial neoplasia.

INTRODUCTION

Cervical cancer has been the subject of several epidemiological studies since last 150 years. It is the second most common cancer in women after breast cancer.[1-3] Chronic inflammation of cervix, either specific or non-specific, is thought to be one of the factors responsible for carcinogenesis. Inflammatory Pap smear is the most common

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report the gynecologist receives even when the cervix appears normal. The recommended treatment for benign cellular changes on Pap smear screening is treatment of infection followed by a repeat Pap smear in 4 to 6 months time. If the inflammatory changes continue, the patient is to be subjected to colposcopy.[4,5] However, this is hardly followed, especially in resource poor countries, where proper cervical screening protocol has not been established yet. Hence, a good number of patients in the premalignant stage (which may undergo malignant transformation during the lag-time) are missed. So the patients with persistent inflammatory Pap smears should be prospectively evaluated using colposcopy.

There are very few studies in the literature where the incidence of premalignant and malignant lesions was looked into in cases of inflammatory Pap smear. Inflammation can obscure few malignant cells and may result in high false negative rates which may be reduced by employing liquid based cytology.[6] However, it was reported that liquid based cytology was not cost-effective for developing countries and the recent studies found no statistically significant difference of accuracy between conventional Pap test and liquid based cytology.[7] The main reason for false-negative reports of cytology were found to be sampling errors, with sampling errors as high as 42.5% being suboptimal and 17.5% being inadequate for interpretation.[8] McLachlan et al.[9] studied the colposcopic features and biopsy results of 102 women with persistent inflammatory Pap smears and found 19% cases of CIN 2 or worse. Seckin et al.[10] recommends colposcopic evaluation of patients with persistent inflammatory Pap smear despite therapy in any population in any part of the World. Frisch et al.[11] is of the opinion that colposcopy of women with cytologic diagnosis of inflammatory epithelial changes may be a useful way to detect otherwise unrecognized cases of CIN.

In Bangladesh, every year 17,686 women are diagnosed with cervical cancer; of them 10,364 die of the disease. Although services required for carcinoma of cervix screening are available in Bangladesh, it is not practically feasible to subject all women with inflammatory Pap smear to colposcopy in our country. Therefore, this study was carried out with the aim to explore whether women with persistent inflammation on Pap smear need further evaluation with colposcopy. 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.

Patients & Methods

This cross-sectional study was carried out in the Department of Obstetrics and Gynaecology, Institute of Child & Mother Health (ICMH), Dhaka, over a period of 12 months from July 2013 to June 2014. Patients with two consecutive reports of inflammatory cellular changes without atypia on Pap smears despite anti-inflammatory therapy were the study population. A total of 1456 married non-pregnant women (aged 18 years or more) complaining of different gynaecological problems (vaginal discharge, postcoital bleeding, intermenstrual bleeding and persistent leucorrhoea) underwent Paps test at the above mentioned place during the study period for gynaecological problems. Of them 312(21.4%) were reported as having 'inflammatory cellular changes'. After giving anti-inflammatory treatment most of them were cured leaving 128(8.8%) cases with repeat report of inflammatory cellular changes on Pap smear and hence were included in the study. Colposcopic findings included in the study were acetowhite areas at squamo-columnar junction (SCJ), punctuation and mosaicism, colposcopic diagnosis and grading. Colposcoic findings were finally judged against histopathologic evaluation, the 'Gold standard' for evaluation of cervical biopsy specimen.

Study procedure

On arrival of patients at Gynae Out-patient Department (OPD) of ICMH at the age of ^{3}18 yrs with the complaints of excessive vaginal discharge, post coital bleeding etc, they were

advised for Pap's smear. If Pap's smear test exhibited inflammatory cellular changes without atypia, the patient received treatment of infection with Doxcycline daily for 14 days or metronidazole or ornidazole or third generation cepholosporines and povidone iodine-containing suppositories for 7 days or both and a repeat Pap's smear was performed after 14 days. If the inflammatory changes persist, the patient was subjected to colposcopy. If colposcopic evaluation revealed any abnormalities then biopsy was taken (the detail of the colposcopic procedure is given in the box below). The specimen was fixed with formalin and was sent to histopathology for confirmation of diagnosis.

Colposcopic procedure: To perform colposcopic examination, the cervix was first cleaned by 0.9% saline solution and visualized at low magnification and pathologies of vasculature were investigated under green filter. Then 5% acetic acid was applied and after waiting 60 seconds cervix was visualized under low and high magnification. Aceto-white areas and atypical vasculature were determined. Visual inspection with acetic acid (VIA) positivity was considered if there were acetowhite areas in the transformation zone close to squamo-columnar junction or the os. Iodine negative areas were determined at cervix by applying lugol solution. A biopsy was performed from aceto-white, mosaic, iodine-negative areas and from punctuations, atypical vasculatures, and erosions. When these pathological findings were not determined a blind punch biopsy was performed from four quadrants of cervix and biopsy specimens were sent to pathology laboratory inside formal for histopathpologic examination.

Statistical analysis

Data were processed and analysed using computer software SPSS (Statistical Package for Social Sciences). The test statistics used for analysis of data were Chi-square Test (for comparison of categorical data between groups), Student's t-Test (for comparison of continuous data between groups). For any analytical test the level of significance was set at 0.05 and p-value < 0.05 was considered significant.

RESULT

Nearly half (48.5%) of the study subjects were between 20 - 30 years with mean age of the patients being 32.6 (range: 18 - 48) years. Mean age of the patients at marriage was 14.9 years (range: 12-23) and the mean age at first child birth was 16.5 years (range: 13-26). In terms of parity majority (94.5%) of the patients was multipara (Table I). Contraceptive behavior shows that over two-thirds (68%) used oral contraceptives. In about 15% cases their husbands used condom and only 2.3% adopted other protection measures (Fig. 2). Almost all patients complained of persistent leucorrhoea

TABLE I. Distribution of respondents by their age (n = 128)

Age (years)*	Frequency	Percentage
<20	4	3.1
20 - 30	62	48.4
30 - 40	50	39.1
³40	12	9.4

***Mean age** = (32.6 ± 7.2) years; **range** = (18 - 48) years*

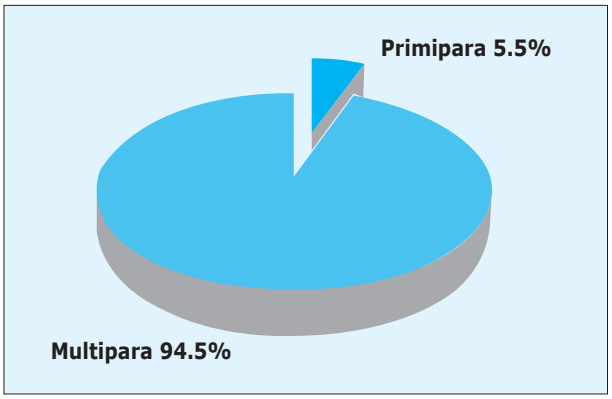

***FIGURE 1:** Distribution of respondents by their Parity (n=128)*

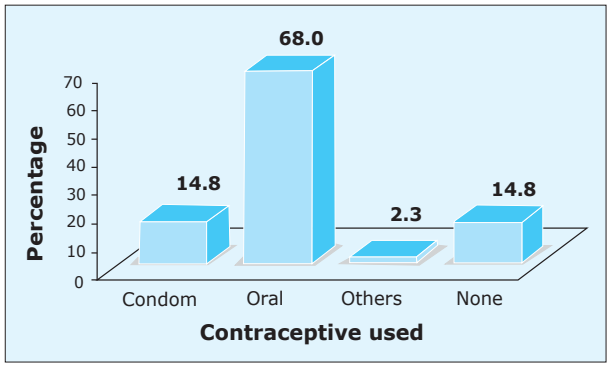

FIGURE 2: Distribution of respondents by use of contraceptive (n = 128)

TABLE II. Distribution of respondents by their reproductive life-events (n=128)

Reproductive life-events	Mean ± SD	Range
Age at marriage (yrs)	14.9 ± 1.7	12-23
Age at first child birth (yrs)	16.5 ± 1.9	13-26

not responding to antibiotics (99.2%). Vaginal discharge (97.7%) was the predominant complain followed by postcoital bleeding (16.4%) and intermenstrual bleeding (3.1%). Most of the cervices were broad (78.1%) and cervical erosion was found in 13.3% cases. Nearly 60% of uterus was of normal size and 41.4% bulky. Almost all of the uteri exhibited free fornix (Table III). PAP-smear test revealed bacterial vaginosis and Trichomonasvaginalis infection in 2.3% and 6.3% cases respectively (Table IV). Colposcopic examination showed squamocolumnar junction (SCJ) clearly in all cases. Visual inspection with acetic acid (VIA) exhibited about 25% SCJ as light acetowhite,72.7% as dense acetowhite and 3.1% as mosaic appearance. Of the 128 women, 66(51.6%) were colposcopically positive for CIN. Of them over two-thirds (68.2%) were graded as CIN-1, 25.8% as CIN-2, and 6% as CIN-3. Histological evaluation of biopsy-material taken from these 66 cases revealed 25(37.9%) with abnormal cytology (3-CIN-1, 18-CIN-2 and 4 with invasive carcinoma) which accounts for 19.5% of the persistent Paps smear cases (Table V). Of the 25 histopathologically confirmed cases, 72.2% had CIN-2, 12% had CIN-1 and the rest 16% had invasive carcinoma (Table VI). As potential risk factors were compared between patients with and without positive histopathological findings, it was found that early age at marriage and early child-birth and high parity were significantly associated with development of cervical intraepithelial neoplasia or dysplasia ($p = 0.001$, $p < 0.001$ and $p = 0.006$ respectively) (Table VII).

TABLE III. Distribution of subjects by their clinical characteristics (n=128)

Clinical characteristics	Frequency	Percentage
History		
Persistent leucorrhoea not responding to a antibiotics	127	99.2
Vaginal discharge	125	97.7
Post-coital bleeding	21	16.4
Intermenstrual bleeding	4	3.1
Perspeculum examination		
Cervix		
Broad	100	78.1
Hypertrophy	16	12.5
Normal	12	9.4
Cervical erosion	17	13.3
P/V findings		
Size of uterus		
Bulky	53	41.4
Normal	75	58.6
Fornix		
Free	127	99.2
Thickened	1	0.8

TABLE IV: Distribution of subjects by their Pap smear findings (n=128)

Pap smear findings	Frequency	Percentage
Bacterial vaginosis	3	2.3
Trichomonasvaginalis	8	6.3

TABLE V: Distribution of subjects by their colposcopic evaluation (n = 128)

Colposcopic evaluation	Frequency	Percentage
Squamo-columnar junction (SCJ) seen clearly VIA with 5% acetic acid	128	100.0
Acetowhite Light	31	24.2
Acetowhite Dense	93	72.7
Mosaicism	4	3.1
Colposcopic comment (n = 128)		
Positive	66	51.6
Negative	62	48.4
Colposcopic Grading (n = 66)		
CIN-1	45	68.2
CIN-2	17	25.8
CIN-3	4	6.0

TABLE VI. Patients stratified by histopathological comment and grading (n = 66)

Histopathological comment and grading	Frequency	Percentage
Comment(n=66)		
Positive	25	37.9
Negative	41	62.1
Grading (n=25)		
CIN-1	3	12.0
CIN-2	18	72.0
Invasive carcinoma	4	16.0

TABLE VII. Association between CIN and putative risk factors

Suspected risk factors	Histopathology comment		p-value
	Positive (n=25)	Negative (n=41)	
Age* (yrs)	33.1 ± 7.3	30.8 ± 7.5	0.170
Age at marriage* (yrs)	13.6 ± 1.2	14.6 ± 1.1	0.001
Age at first child birth* (yrs)	14.9 ± 1.2	16.3 ± 1.1	< 0.001
Parity*	3.0 ± 0.9	2.4 ± 0.8	0.006
Contraceptive used#			
Condom	2(28.6)	5(71.4)	
Oral contraceptive	21(38.9)	33(61.1)	
Other	1(100.0)	0(0.0)	0.531
None	25(37.9)	41(62.1)	

Figures in the parentheses denote corresponding percentage
**Data were analysed using Unpaired t-Test and were presented as mean ± SD.* #Data were analysed using Chi-square (?2) Test.

Discussion

Pap smear test is a major screening test for early diagnosis and treatment of cervix cancer. Inflammation on Pap smear is considered a relatively benign finding. However, due to the low sensitivity and high false negative rate (as high as 20%) of Pap smear, there is a possibility that an inflammatory Pap smear may miss cervical premalignant changes and in rare cases malignant changes as well. Since the incidence of inflammation on Pap smear is very high (14%-19%),[9,10,12,13] it may not be possible to subject all patients with inflammation to colposcopy or HPV DNA testing. Keeping this view in mind, 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.

In the present study a total of 1456 women underwent Pap test during the study period for gynaecological problems like vaginal discharge, postcoital bleeding, intermenstrual bleeding and leucorrhoea. Of them 312(21.4%) were reported as having 'inflammatory cellular changes'. Anti-inflammatory treatment given to these patients cured most of them leaving 128(8.8%) cases with a repeat report of inflammation on Pap smear which also compares well with the study of Bhutia et al.[14] Similar results were reported by Seckin et al.[10] But the prevalence was lower than that reported by Sandmire et al[15] (35.1%). The prevalence of inflammatory Pap smear in various Indian studies is reported to vary between 70% and 80.5%.[12,16] However, in a recent study the reported prevalence was lower (24.3%) is quite consistent with the findings of the present study.

Among the persistent inflammatory Pap smear cases, 66(51.6%) were colposcopically positive for CIN and biopsymaterial histologically, exhibited abnormal cytology in 25(37.9%) cases (CIN-1 12%, CIN-2 72% and invasive carcinoma 16%) which accounts for 19.5% of the 128 women

with persistent Paps smear included in the study. In another study, out of the 30 women with persistent inflammatory Pap smear 16(53.3%) women had abnormal colposcopic findings and CIN was found in 5 of these women meaning 16.3% women with persistent inflammatory Pap smear were harboring CIN. Various studies have found the possibility of CIN with a report of persistent inflammatory smear to range from 18 to 35%.[9,10]

The mean age of the women with persistent inflammatory Pap smear was 32.6 ± 7.2 years which is fairly comparable with the findings of Bhutial et al[14] (30.43 ± 6.1 years). Comparison of age at marriage, age at first childbirth and parity between patients with CIN (including invasive disease) and without CIN revealed that the former group married and experienced child birth significantly earlier than the latter group ($p = 0.001$ and $p < 0.001$ respectively). The average parity was also significantly higher in the CIN group than that in women without CIN. Bhutiaet al.[14] reported that mean age at marriage was 18.9 ± 2.6 years among women with persistent inflammatory smear while that with the women with CIN was 16.8 ± 2 years ($p= 0.05$). The mean parity was also higher in the former group ($p> 0.05$) thus favouring the findings of the present study.

According to various studies, ASCUS (atypical squamous or glandular cells of undetermined significance) on Pap smear has a 10-20% chance of harboring CIN.[17,18] This is the reason why we triage women with ASCUS on Pap smear with either repeat cytology, HPV DNA testing, or colposcopy.[19] Our study has shown a sizable proportion of women (about 20%) with persistent inflammation on Pap smear could be harboring CIN. Moreover, the incidence of CIN and invasive carcinoma in women with persistent inflammatory Pap smears over just 2 weeks was found to increase to 20.6% and 0.7%, respectively, in a study by Dasari et al.[5] Hence, by waiting for a longer period of time before repeating the Pap smear may lead to a delay in diagnosis of CIN in a high percentage of cases.

The mechanism involved in the transformation of chronic inflammatory cells to carcinogenic cells is not clear. However, persistent inflammation is thought to increase cellular turnover, especially in the epithelium, and provides a selection pressure that results in the emergence of cells that are at a high risk for malignant transformation.[20] Hence, all women with persistent inflammation on Pap smear should be subjected to further evaluation. One must not see a report of inflammation on Pap smear in isolation and ignore it as being absolutely insignificant. Following treatment with antibiotics, a repeat Pap smear is needed in 2-4 weeks apart and if it persists in any patient, she must be evaluated further by colposcopy.

Conclusion

On the basis of the findings of the study, it can be concluded that patients with persistent inflammatory Pap smear can harbor a high proportion CIN and sometimes even early stage of invasive carcinoma. Pap smear report of persistent inflammatory cellular changes should not be considered as a variant of normal, specially when it does not respond to adequate recommended therapy. Such patients must be referred to further evaluation by colposcopy. A large-scale study should be conducted to validate the findings of the present study.

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