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## Original Research Article

# A study on cervical cytopathology in HIV positive pregnant women in Southern part of Assam, India

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## ABSTRACT

**Background:** The association between abnormal cervical cytology and HIV infection status in pregnant women was evaluated to correlate with CD4 cell count, viral load and ART compliance in HIV positive pregnant patients with the presence of ASC-US, LSIL and HSIL.

**Methods:** Cervical samples were collected at the Antenatal Clinic of Silchar Medical College and Hospital. An Ayre's spatula was used to collect samples from the ectocervix and a cytology brush to collect samples from the endocervix.

**Results:** Of a total of 75 antenatal attendees, 43 were HIV positive and 32 were HIV negative. Abnormal cytology (N=26, 60.46%) was more common in HIV positive group compared to the HIV negative group (N=7, 21.87%) with a p value of <0.05. Cytological abnormalities were found to be associated with immunosuppression, defined as CD4 count <200 cells/mm<sup>3</sup> and was also associated with high viral load (>10,000/mm<sup>3</sup>) and poor treatment follow up with ART.

**Conclusions:** HIV positive pregnant women are more likely to have cervical lesions as compared to the HIV negative. This higher frequency of abnormal findings in PAP cytology in HIV positive pregnant women with higher viral loads suggest association between preinvasive cervical lesions and human immune deficiency.

**Keywords:** Cervical dysplasia, HIV infection, Pregnant woman, Assam

## INTRODUCTION

Assam is categorised as a low HIV prevalence state with an estimated adult HIV prevalence of 0.07%, which is lower than national prevalence of 0.27%. According to the Assam state AIDS control society data 2015, the geographical distribution of HIV epidemic in Assam shows specific focus of the epidemic in Barak Valley region of South Assam with prevalence >1%.

ANC attendees are considered as proxy for general population, which showed a rising trend in HIV prevalence in southern province.<sup>1</sup> A study by Bhattacharjya et al also showed that the two southern districts- Cachar et al have the highest percentage of cases around 25% in comparison with other districts.<sup>2</sup> In India, the prevalence of HIV infection in pregnant women ranges from 0.7% to 1.2%.<sup>3</sup>

Cervical intraepithelial neoplasia occurs as a continuum of atypical metaplasia caused as a result of persistent HPV infection due to immune suppression. The role of frequent HPV infection in HIV infected woman is clearly established. HIV mediated immune suppression predisposes to increased HPV mediated cervical cytological abnormalities. In this study, we have evaluated the association between abnormal cervical cytology findings and HIV infection status in pregnant women and to relate the CD4 cell count and viral load of these HIV positive pregnant women with the presence of ASC-US, LSIL and HSIL.

## METHODS

The present study was conducted in Silchar Medical College and Hospital, Assam, a tertiary care centre. The

study was in accordance with the recommendations of the Declaration of Helsinki and was approved by the ethical committee members.<sup>4</sup> All the patients included in the study signed an informed consent form. A total of 75 pregnant women were recruited to the study between February 2020 and April 2021, 43 of whom were confirmed HIV positive and 32 were HIV negative. The clinical and demographic data of these patients were collected using a specific questionnaire applied during antenatal examination. The study inclusion criteria consisted of all pregnant women attending the antenatal clinic between 21 and 28 weeks of pregnancy with similar age, parity and marital status. The patients were given information about the HIV infection and the objectives, constraints and the benefit of the study. Eligible pregnant women who gave consent to participate in the study were offered HIV antibody screening using two enzyme linked immunosorbent assays (ELISA). Discordant samples by ELISA were confirmed by a western blot technique. Two weeks after the HIV screening test, all HIV positive women were enrolled with an almost equivalent number of frequency matched HIV negative women similar in age and parity. The laboratory workers and the nurses were blinded to the HIV serostatus. A Pap smear, CD4 absolute lymphocyte count and HIV viral load detection by PCR was done. Cervical samples were obtained from the ectocervix by using Ayre's spatula and from the endocervix using cyto-brush. Samples were distributed evenly on glass slides, duly identified and fixed using a mixture of polyethylene glycol and 70% ethanol to prevent drying. The smears were then submitted to PAP staining. Data collected in the study were stored and analysed using SPSS software version 24. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

Of the 75 pregnant women studied, 43 were HIV positive and 32 HIV negative. With respect to cytology, 26 (60.46%) of the HIV positive women and 7 (21.87%) of the HIV negative women tested positive for abnormal cytology. A greater frequency of intraepithelial lesions were found in HIV positive compared to HIV negative women,  $p < 0.001$  (Table 1). 17 cases of ASC-US were found, 12 in the HIV positive and 5 in the HIV negative (70.6% vs 29.4% respectively),  $p < 0.0179$  ( $< 0.05$ ), statistically significant. 13 cases of LSIL were found, 11 in the HIV positive and 2 in the HIV negative (84.6% vs 15.4% respectively) with  $p < 0.0005$  ( $< 0.05$ ), statistically significant. Only 3 cases of HSIL were found in all the smears analysed, all those patients were HIV positive (100%), with  $p < 0.0253$  ( $< 0.05$ ), that is statistically significant. Thus, abnormal cytology was related to HIV status, more found in HIV

positive than in HIV negative. When the presence of cytological abnormalities were correlated with CD4 cell count in the HIV positive patients, these abnormalities were found to be more common in women who were immune-deficient, CD4 cell count  $< 200/\text{mm}^3$  with  $p < 0.0249$  ( $< 0.05$ ). Thus, abnormal cervical cytology was related to immunosuppression, more in immunodeficiency than in immunosufficiency. With respect to the viral load, the highest frequency of abnormal cytology was found in patient with a viral load  $> 10,000$  copies/ml. This association was not however statistically significant,  $p < 0.0912$  ( $> 0.05$ ). On evaluation of the patients in relation to their intake of ART, patients who had been well compliant to ART therapy had lesser percentage of abnormal cytology, and the correlation was statistically significant,  $p < 0.0238$  ( $< 0.05$ ).

## DISCUSSION

The highest frequency of abnormal cervical cytology was found in the group of HIV positive pregnant women and was statistically significant. Similar results were found in the studies conducted by Auge et al and Moodley et al where significant difference with respect to human immunodeficiency virus was established when smears with only the cytopathic effects of HPV were considered.<sup>5,6</sup>

In the present study, the presence of lesions was associated with immunosuppression. Bearing with the fact that majority of the patients with cervical dysplasia in the HIV positive group had CD4 cell counts  $< 200/\text{mm}^3$ . This finding was in accordance with the findings of Adam et al who reported that cytological abnormalities were 8 times more frequent in HIV positive patients, were also twice as common in women with a CD4 cell count  $< 200/\text{mm}^3$ .<sup>7</sup> In contrast, Coelho et al evaluated 115 HIV positive women and reported higher CD4 counts associated with LSIL and HSIL, however these results were not statistically significant.<sup>8</sup> Nevertheless, Zimmermann et al reported no difference in CD4+ T cell count in the presence or absence of LSIL or HSIL.<sup>9</sup> The finding of higher viral counts ( $> 10,000$  copies/ $\text{mm}^3$ ) when lesions were present, was conforming with the results reported by Masad et al and emphasises the close association between HIV/HPV and a consequent cytological abnormality.<sup>10</sup> According to the present study, HIV patients on ART had lesser percentage of cervical abnormalities as compared to those without ART, the difference being statistically significant. Firnhaber et al stated that, as HPV infection is an immunomodulated disease, there is some hope that HIV ART would improve regression rates and prevent the progression of cervical dysplasia.<sup>11</sup>

**Table 1: Association between HIV status and cytology findings.**

HIV status	Abnormal smear N (%)	ASC-US N (%)	ASC-H N (%)	LSIL N (%)	HSIL N (%)
<b>Positive</b>	26 (78.787)	12 (70.6)	0 (0)	11 (84.6)	3 (100)
<b>Negative</b>	7 (21.21)	5 (29.4)	0 (0)	2 (15.4)	0 (0)
<b>Total</b>	33 (100)	17 (100)	0 (0)	13 (100)	3 (100)

**Table 2: Frequency of abnormal smear correlated with immunological status in HIV positive woman.**

Abnormal cytology	Immunodeficiency		Immuno sufficiency		Total		P value
	CD4 cell count (<200 cells/mm <sup>3</sup> )		CD4 cell count (>200 cells/mm <sup>3</sup> )		N	%	
	N	%	N	%			
ASC-US	10	83.33	2	16.67	12	100.00	0.0249
LSIL	4	36.36	7	63.64	11	100.00	
HSIL	3	100.00	0	0.00	3	100.00	
<b>Total</b>	19	73.08	7	26.92	26	100.00	

**Table 3: Frequency of abnormal cytology correlated with viral load in HIV positive pregnant women.**

Pre-invasive lesion of cervix	Below detection limit		<1,000 copies/mm <sup>3</sup>		>10,000 copies/mm <sup>3</sup>		Total		P value
	N	%	N	%	N	%	N	%	
ASC-US	5	41.67	1	8.33	6	50.00	12	100.00	0.0912
LSIL	0	0.00	2	18.18	9	81.82	11	100.00	
HSIL	0	0.00	0	0.00	3	100.00	3	100.00	
<b>Total</b>	5	19.23	3	11.54	18	69.23	26	100.00	

**Table 4: Frequency of abnormal cytology in HIV positive pregnant women depending on ART intake.**

Abnormal cytology	HIV positive			P value
	On anti-retroviral therapy	Without anti-retroviral therapy	Total	
ASC-US	1 (8.3)	11 (91.7)	12 (100)	0.0238
LSIL	6 (54.5)	5 (45.5)	11 (100)	
HSIL	0 (0)	3 (100)	3 (100)	

### Limitations

Although the inclusion of HIV negative pregnant women allowed us to confirm that cervical dysplasias were HIV related, this study could not establish a causal association between HIV infection and cervical abnormalities. The other factors such as age, age at first intercourse, parity, STDs and number of sexual partners may be confounding factors in the analysis of this association. We were not able to collect information about the HPV infection, limiting our ability to study their association with cervical abnormalities in HIV infected pregnant women.

### CONCLUSION

According to the ICMR data, Cachar district in south Assam has the highest prevalence of Ca cervix (15.4%), as compared to the other region in Assam. With an increased association of cervical dysplasia or squamous intraepithelial lesions observed among HIV infected pregnant women in the southern part of Assam and considering the fact that cervical dysplasia may evolve into invasive cervical cancer with inadequate follow up, this could become an increasing problem in these populations. However, with adequate screening cytology (Pap smear), ART intake and conventional follow up guidelines, it would be possible to curb the incidence of cervical cytological abnormalities in HIV positive pregnant women to a considerable extent.

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