

# Predictors of Unsatisfactory Conventional Pap Smears

Reetika Sharma, Marie Moses Ambroise, Anita Ramdas, Kandasamy Ravichandran<sup>1</sup>

Departments of Pathology and <sup>1</sup>Biostatistics, Pondicherry Institute of Medical Sciences, Puducherry, India

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ABSTRACT

**Objective:** The objective of this study is to determine the clinical predictors of unsatisfactory Pap smears. **Methodology:** This was a case-control study done in a tertiary care institute. All unsatisfactory conventional pap (CP) smears between January 2015 and June 2017 were retrieved, and the slides were viewed. Clinical details were recorded from request forms and case files. Simple and multiple logistic regression analyses were used to identify the predictors of unsatisfactory CP smears. **Results:** In this study, we have included 314 unsatisfactory Pap smears and 541 controls with satisfactory Pap smears. Clinical parameters such as older age and cervical erosion proved to be important predictors of unsatisfactory pap smears. The most common reason for unsatisfactory pap smears was due to a paucity of epithelial elements (66.6%), followed by obscuration of smear details by blood/inflammatory cells/mucus (9.9%) and air drying artifacts (4.4%). There were multiple reasons in 19.1% of cases with unsatisfactory pap smears. **Conclusion:** Our study shows that older age groups and cervical erosion are predictors of unsatisfactory pap smears. Incidence of unsatisfactory pap smears can be reduced by education and retraining of health-care workers and doctors.

**KEYWORDS:** Case-control studies, mass screening/methods, papanicolaou test, uterine cervical neoplasms/prevention and control

## INTRODUCTION

Cervical cancer is the fourth most common cancer after breast, colorectal, and lung cancer and also the fourth leading cause of cancer deaths among women.<sup>[1]</sup> Worldwide 0.6 million cases and 0.3 million deaths/year are due to cervical cancer. China and India together contribute 35% of global burden. In high-resource countries, the cumulative rates of cervical cancer incidence and mortality are two to four times lower than low-resource countries.<sup>[1]</sup> Cervical cancer mortality has been reduced due to screening program utilizing Pap test.<sup>[2]</sup> The procedure for making Pap smear is viewed by most of the women as unpleasant, and further an unsatisfactory result is quite annoying for them.<sup>[3]</sup>

Cervical cytology smears that are unsatisfactory for interpretation accounts for a number of screening failures and wastage of resources.<sup>[4]</sup> The unsatisfactory Pap smear by definition indicates unreliability for the detection of cervical epithelial abnormalities. Considering unsatisfactory, Pap smears as negative is incorrect since negative means absence of disease

(squamous intraepithelial lesion or malignancy), and there may not be adequate follow-up measures.<sup>[5]</sup> This study has been undertaken to provide an insight into the clinical parameters associated with unsatisfactory conventional pap (CP) smears. If any of these determinants are present, optimal collecting devices or better sampling techniques can be considered to decrease the incidence of unsatisfactory Pap smears.

## METHODOLOGY

This was a case-control study done in Tertiary Care Institute in Puducherry. All unsatisfactory CP smears between January 2015 and June 2017 were retrieved, and the slides were reviewed. The smears were collected by the gynaecologists with the help of Ayer's Spatula. One smear was taken from ecocervix and one from

**Address for correspondence:** Dr. Marie Moses Ambroise, Department of Pathology, Pondicherry Institute of Medical Sciences, Puducherry, India.  
E-mail: drmosesambroise1978@gmail.com

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endocervix. The slides were immediately fixed in 90% of alcohol. A consensus opinion was taken before labeling a smear as unsatisfactory. The criteria for determining adequacy were according to the 2014 Bethesda system. The reasons for unsatisfactory smears were noted. Clinical details were recorded from request forms and case files. Details such as patient age, postmenopausal status, cervical erosion/ulcer, vaginal bleeding/spotting, abnormal vaginal discharge (suggestive of infection or foreign body reaction), endocervical polyps, oral contraceptive usage, and other significant findings were noted. History of pelvic malignancy, pelvic irradiation, chemotherapy, and hysterectomy were also recorded. Exclusion criteria were pelvic irradiation, pelvic malignancy, chemotherapy, and hysterectomy. Cases in which the complete clinical details could not be obtained were also excluded from the study.

Subjects with satisfactory Pap smears were considered as controls. Controls were selected randomly. The same clinical details were also collected for controls. All the smears included in this study were CP smears.

Pearson's Chi-square test/Fisher's exact test was used to determine the statistical significance of the observed difference in clinical parameters between satisfactory and unsatisfactory smears. Simple and multiple logistic regression analyses were used to identify the predictors. Variables which are significant at  $\leq 0.1$  in simple regression were considered for multiple logistic regression analysis. All reported  $P$  values were two-sided, and a  $P < 0.05$  was considered significant for statistical tests. Data were entered into a Microsoft Excel file. Analyses were performed using the Statistical Package for the Social Science (version 20.0; SPSS, Chicago, IL, USA).

The study was approved by the institutional ethics committee (mention IEC Number), and waiver of informed consent was granted.

## RESULTS

In this study, we have included 314 unsatisfactory Pap smears and 541 controls with satisfactory Pap smears. The comparison of different age groups of women with unsatisfactory smears is shown in Table 1. The

frequency of all the clinical parameters in satisfactory and unsatisfactory smears is shown in Table 2. Among the parameters in Table 2, the postmenopausal status, cervical erosion, cervical ulcer, benign lesions of uterus and adnexa, white discharge, and lower abdominal pain were significantly associated with unsatisfactory Pap smears.

The results of logistic regression in predicting parameters responsible for the unsatisfactory Pap smears are tabulated in Table 3. Increased age, cervical erosion, white discharge, and lower abdominal pain were significantly associated with unsatisfactory Pap smears in univariate and multivariate analysis [Table 3].

Postmenopausal status, cervical ulcer, and benign lesions of uterus and adnexa were found to be significantly associated with unsatisfactory Pap smears in univariate analysis but not in multivariate analysis.

The most common reason for unsatisfactory Pap smears in our study was due to a paucity of epithelial elements (66.6%). Obscuration of smear details by blood/inflammatory cells/mucus accounted for 9.9% and air drying artifacts for 4.4% of unsatisfactory Pap smears. There were multiple reasons in 19.1% of cases with unsatisfactory pap smears.

## DISCUSSION

According to the Bethesda system, smears may be unsatisfactory for a variety of reasons, including paucicellularity, poor preservation of cells, and obscuring blood or inflammation.<sup>[6]</sup> The unsatisfactory smears are associated with benign as well as preneoplastic/neoplastic conditions and these patients should be evaluated carefully.<sup>[5]</sup>

Paulin *et al.*<sup>[3]</sup> performed a case-control study in which older age was found to be a significant predictor of an unsatisfactory cervical cytology smear. Earlier date in the menstrual cycle, postmenopausal status, and usage of oral contraceptives were not significantly associated with unsatisfactory smears.<sup>[3]</sup> Lu *et al.* also did not find postmenopausal status to be significantly associated with unsatisfactory Pap smears.<sup>[7]</sup> In our study also, the postmenopausal status was significant in univariate analysis but not in multivariate analysis. However, an

**Table 1: Satisfactory and unsatisfactory pap smears in different age groups**

Age group (years)	Satisfactory (n=541), n (%)	Unsatisfactory (n=314), n (%)
<30	143 (26.4)	45 (14.3)
30-39	199 (36.8)	106 (33.8)
40-49	141 (26.1)	85 (27.1)
50-59	35 (6.5)	45 (14.3)
$\geq 60$	23 (4.3)	33 (10.5)

The variation with respect to age was statistically significant ( $P < 0.001$ )

**Table 2: Comparison of clinical features in women with unsatisfactory and satisfactory pap smears**

Parameters	Satisfactory (n=541), n (%)	Unsatisfactory (n=314), n (%)	Significance
History of white discharge	184 (34.0)	81 (25.8)	0.012
History of blood stained discharge	17 (3.1)	15 (4.8)	0.225
History of contact bleeding	18 (3.3)	10 (3.2)	0.910
Lower abdominal pain	140 (25.9)	57 (18.2)	0.010
Oral contraceptive	3 (0.6)	0 (0.0)	0.253
Postmenopausal	75 (13.9)	91 (29.0)	<0.001
Cervical erosion	53 (9.8)	54 (17.2)	0.002
Cervical ulcer	3 (0.6)	9 (2.9)	0.012
Cervix bleed on touch	33 (6.1)	21 (6.7)	0.733
Benign lesions in uterus and adnexa*	13 (2.4)	18 (5.7)	0.012

\*Includes benign pathologies like uterine leiomyoma, prolapse uterus, pelvic inflammatory disease, cervical polyp, etc.

**Table 3: Results of logistic regression in predicting parameters responsible for the unsatisfactory pap smears**

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age						
<30	1.00	-		1.00	-	
30-39	1.69	1.12-2.55	0.012	1.66	1.09-2.52	0.017
40-49	1.92	1.25-2.94	0.003	1.78	1.14-2.80	0.012
50-59	4.09	2.35-7.11	<0.001	2.66	1.00-7.08	0.050
≥60	4.56	2.43-8.55	<0.001	2.94	1.06-8.18	0.039
History of white discharge						
No	1.00	-		1.00	-	
Yes	0.67	0.50-0.92	0.013	0.71	0.51-0.99	0.046
History of blood stained discharge						
No	1.00	-	0.228	-	-	-
Yes	1.55	0.76-3.14				
History of contact bleeding						
No	1.00	-		-	-	-
Yes	0.96	0.44-2.10	0.910			
Lower abdominal pain						
No	1.00	-		1.00	-	
Yes	0.64	0.45-0.90	0.010	0.67	0.46-0.97	0.033
Cervical erosion						
No	1.00	-		1.00	-	
Yes	1.91	1.27-2.88	0.002	2.14	1.37-3.33	0.001
Cervical ulcer						
No	1.00	-		1.00	-	
Yes	5.29	1.42-19.69	0.013	2.89	0.72-11.59	0.134
Bleed on touch						
No	1.00	-		-	-	-
Yes	1.10	0.63-1.94	0.733			
Benign lesions in uterus and adnexa						
Absent	1.00	-		1.00	-	
Present	2.47	1.19-5.11	0.015	1.94	0.89-4.23	0.097
Menopausal status						
Premenopausal	1.00	-		1.00	-	
Postmenopausal	2.54	1.80-3.58	<0.001	1.33	0.60-2.95	0.476

CI: Confidence interval, OR: Odds ratio

increase in age is found to be an important predictor for the unsatisfactory Pap smear in our study similar to other studies.<sup>[3,8,9]</sup>

In the study done by Gupta *et al.*,<sup>[9]</sup> age ≥45 and history of hysterectomy, radiotherapy, or chemotherapy were found to be significant for unsatisfactory

outcomes ( $P < 0.001$ ), with the highest odds ratio for radiotherapy (2.81). Inadequate cellularity was the major reason for unsatisfactory cytology in both the treatment and nontreatment groups. However, we excluded the cases with a history of radiotherapy and chemotherapy as the 2014 version of the Bethesda System emphasizes that general criterion for minimum squamous cellularity is not applicable to women who had received radiotherapy, chemotherapy, or hysterectomy for invasive cervical cancer. Lu *et al.* showed that lower cellularity could be used as a satisfactory threshold for patients undergoing radiotherapy or chemotherapy.<sup>[8]</sup>

Cervical erosion was also found to be significant in our study. The reason for this could be obscuration of more than 75% of the cells by mucus, inflammatory cells, or by blood. Low squamous cellularity was the most common cause of unsatisfactory smears in all age groups in the study by Garza *et al.*<sup>[10]</sup> Another contributing factor was the obscuration of lesional cells by excessive blood or inflammation. The most common reason for unsatisfactory specimens was scant cellularity, which was related to the technique of sampling, and therefore, they emphasized that sample collection by well-trained persons will reduce the overall rate of unsatisfactory specimens.

History of white discharge and lower abdominal pain were also found to be significant in our multivariate logistic regression analysis. By these findings we can notice that white discharge and lower abdomen pain is also associated with unsatisfactory pap smears. The health care workers/ gynaecologists have to take extra care for sampling to avoid unsatisfactory results. Other studies have not commented on these rather common clinical findings.

The most common reason for unsatisfactory Pap smears in our study was a paucity of epithelial elements (66.5%). The most common cause was scant cellularity in other studies also.<sup>[3,7-9]</sup> This probably occurs due to the technique of the sampling,<sup>[6]</sup> or due to the scarring effect of radiotherapy/chemotherapy.<sup>[9]</sup> scant cellularity occurs due to increasing age but is not directly related to menopause.<sup>[3]</sup> This may be related to differences in the smear technique or accessibility of the transformation zone to sampling. This justifies our results also.

There has been a significant decrease in unsatisfactory rates for liquid-based cytology (LBC) as compared with CP.<sup>[11]</sup> However, in resource-limited settings such as ours, where the CP tests are being used, this problem persists. Thus, it is very important to identify the clinical parameters associated with unsatisfactory Pap smear

so that extra care can be taken by clinicians before obtaining a Pap smear to decrease the incidence of unsatisfactory smears.

The preferred management for unsatisfactory Pap tests is to repeat the smear within 2–4 months,<sup>[12]</sup> but this is rarely done.<sup>[13]</sup> The biggest drawback of this study was that we could not find out the follow-up for unsatisfactory smears. Most of the patients with unsatisfactory smears lacked a repeat smear. The clinicians should put efforts to convince the patients with unsatisfactory pap smears for repeat smear examination as there are high chances of abnormal results in future. However, the sample size is the strength of this study.

We have made persistent efforts to reduce the number of unsatisfactory Pap smears in our institute over the years. The percentage of unsatisfactory Pap smears is a quality indicator in gynecologic cytology. Currently, two pathologists review the Pap smear before labeling it as unsatisfactory. Root cause analysis is done for all unsatisfactory Pap smears. Regular feedback about the causes of unsatisfactory Pap smears is given to the doctors involved in the Pap smear collection. Education and retraining are provided periodically for junior doctors. LCB reports fewer number of unsatisfactory smear and has found to be superior to conventional pap smear.<sup>[14]</sup> LBC has also been introduced in our institute.

## CONCLUSION

Our study shows that older age groups and cervical erosion are associated with unsatisfactory pap smears. The doctor/health-care workers collecting the Pap smear should be well trained for sample collection and patients can be told about the chances of unsatisfactory smears. By this, there may be an improvement of the follow-up and detection of any abnormality at the earliest. Liquid-based cytology and better sampling techniques should be considered to decrease the incidence of unsatisfactory smears when clinical parameters associated with unsatisfactory Pap smear are present.

## Key points

- Unsatisfactory Pap smears do not rule out intraepithelial lesion/malignancy
- Older age and cervical erosion are significantly associated with unsatisfactory Pap smear
- Paucity of epithelial elements is the most common reason for unsatisfactory pap smears in our study
- Root cause analysis and follow-up repeat smears should be done for all the unsatisfactory Pap smears.

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## Conflicts of interest

There are no conflicts of interest.

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