

Original Research Article

Clinico-Histopathological Evaluation and Correlation in Women with Gynecology Problems

Author

Dr B.Rajsekhar

Associate Professor, Dept. of Pathology
P.K. Das Medical College, Ottapalayam, Kerala

ABSTRACT

Patients who were symptomatic attended the gynecology OPD of RMMCH with complaints of white discharge; irregular menstrual bleeding, postmenopausal bleeding and post coital bleeding between Dec 2003 to June 2005 were included in this study. All these patients were subjected to routine tests and also PAP smears were taken and also colposcopy biopsy was done where ever required. Later the clinico-histopathological correlation was done and compared with other studies.

Aims and Objectives: *The present study was undertaken to evaluate the clinico-histopathological pattern in symptomatic women aged 21yrs and above attending the gynecology OPD of RMMCH with complaints of white discharge, irregular menstrual bleeding, postmenopausal bleeding and post coital bleeding between Dec 2003 to June 2005 were included in this study. Clinical features and histopathological examination were studied.*

Introduction

Cytology of Normal Female Genital Tract- Anatomy and Histology¹

The vagina and portiovaginalis or ectocervix are normally covered by a smooth, white non keratinized stratified squamous epithelium. This mucosa terminates toward the anatomic external os of the cervix where it is replaced by the pink endocervical simple columnar type of epithelium. Squamocolumnar junction is seen in 60% of adult patients, microscopically ill defined with the presence of an irregular intermediate (transitional or transformation) zone.

Endocervical Glands

Endocervical glands are seen mainly in the portio supravaginalis of the cervical canal. Formed by branching folds of tall columnar cells with oval, eccentric nuclei, 2 to 3 mm thick, mono layered **Histology Of Stratified Squamous Epithelium**² Section of the nonkeratinized vaginocervical stratified squamous epithelium has 4 distinct zones:

1. Basal layer or stratum cylindricum
2. Parabasal layer or stratum spinosum
3. Intermediate layer
4. Superficial layer or cornified layer.

Richart (1966) used Cervical Intraepithelial Neoplasia (CIN) as a single descriptive term to

bring all grades of dysplasia and carcinoma-in-situ under a single morphological unit³. Lucus et al (1967) studied cervical cytology of patients attending venereal disease clinic⁴. Rotkin et al (1968) conducted an epidemiological study, which revealed that there is an increased incidence of carcinoma cervix among women who had early onset of sexual activity and multiple sex partners^{5,6}.

Buckley et al and Ferenczy (1982) graded Cervical Intraepithelial Neoplasia(CIN)⁷.

CIN 1=Corresponding to mild dysplasia.

CIN2 =Corresponding to moderate dysplasia.

CIN3 =Corresponding to both severe dysplasia and carcinoma-in-situ.

Workshop was held at National Cancer Institute in Bethesda, Maryland (1988) where reporting system by Papanicolaou (1940) was replaced by The Bethesda system for reporting cervical/vaginal cytologic diagnoses.⁸

The Bethesda System 1991⁹

Adequacy of the Specimen

Satisfactory for evaluation

Satisfactory for evaluation but limited by.....
(specify reason)

Unsatisfactory for evaluationspecify reason)

General Categorization (Optional)

Within normal limits

Benign cellular changes

Epithelial cell abnormality

Descriptive Diagnoses

Benign cellular changes

Infection

Trichomonas vaginalis

Fungal organisms morphologically consistent with Candida species.

Predominance of coccobacilli consistent with shift in vaginal flora Bacteria morphologically consistent with Actinomyces species

Cellular changes associated with Herpes Simplex Virus

Others.

Reactive Changes

Reactive cellular changes

Associated with Inflammation (includes typical repair).

Atrophy with inflammation (atrophic vaginitis).

Radiation

IUD

Others

Epithelial Cell Abnormalities

Squamous Cell

Atypical Squamous Cells of Undetermined Significance

Low grade SIL encompassing HPV, mild dysplasia / CIN 1

HSIL encompassing moderate and severe dysplasia, CIS/CIN 2 and CIN 3

Squamous cell carcinoma

Glandular Cell

Endometrial cell, cytologically benign, in postmenopausal women

Atypical Glandular Cells of Undetermined Significance (AGUS).

Endocervical adenocarcinoma

Endometrioid adenocarcinoma

Extra uterine adenocarcinoma

Adenocarcinoma- Not Otherwise Specified.

Other Malignant Neoplasms

Hormonal evaluation (applies to vaginal smears only).

Hormonal pattern compatible with age and history

Hormonal pattern incompatible with age and history.

Hormonal pattern not possible.

Epithelial Cell Abnormality, Squamous

Atypical Squamous Cells

In The Bethesda System 2001¹⁰ classification system, ASC-US is the more numerically prominent qualifier and should account for 90 to 95% of all ASC results. The use of the qualifier “undetermined significance” emphasizes that a specific diagnosis cannot be made and that further

triage may be appropriate. ASC-US will include most cytology results previously categorized as “ASCUS, not otherwise specified” (ASCUS-NOS) or “ASCUS, favor SIL”. ASC-US excludes cytology suggestive of HSIL. ASC-H is interpreted as cytologic changes that are suggestive of HSIL but lack criteria for definitive interpretation. ASC-H is the less common qualifier, accounting for 5 to 10% of all ASC cases, but the risk of an underlying high-grade lesion is higher in this category than in ASC-US¹¹. The positive predictive value for HSIL (Cervical Intraepithelial Neoplasia [CIN] 2, 3) in ASC-H is higher than the category ASC-US but not as high as in the category HSIL.¹²

Low-Grade Squamous Intraepithelial Lesion

The category of LSIL is unchanged in TBS 2001¹⁰ and continues to include the following categories: Human Papillomavirus (HPV), mild dysplasia, and CIN1. The debate at TBS 2001¹⁰ concerning CIN2 being included either in LSIL or HSIL resolved with the decision that the dividing line between LSIL and HSIL would remain between CIN1 and CIN2. It has been shown that there is less reproducibility for LSIL than for HSIL,¹³ and that the rate of LSIL is more variable than the rate of HSIL.¹⁴ The accuracy rate of interpretation of LSIL is approximately 80%.¹⁵

High-Grade Squamous Intraepithelial Lesion

The category of HSIL is unchanged in TBS 2001¹⁰ and includes moderate dysplasia, severe dysplasia, and carcinoma in situ, or CIN2,3.

Epithelial Cell Abnormality, Glandular

The Bethesda System 1988¹⁶ used the term “Atypical Glandular Cells of Undetermined Significance” (AGUS) to describe “cells showing either endometrial or endocervical differentiation displaying nuclear atypia that exceeds obvious reactive or reparative changes but lack unequivocal features of invasive adenocarcinoma”.

Other

The Bethesda System 2001¹⁰ designates an “other” category for reporting normal or abnormal endometrial cells in women who are 40 years or older.¹⁰ The presence of even benign-appearing endometrial cells on cervical cytology in women who are at least 45 of age is more often associated with endometrial adenocarcinoma and endometrial hyperplasia than with benign endometrium.¹⁷

PAPANICOLAOU SYSTEM	WHO SYSTEM (1973)	BETHESDA SYSTEM (1988)
Class I	Normal	Within normal limits
Class II	Atypical	Reactive or reparative changes
Class III	Dysplasia	Atypical or abnormal squamous cells
	Mild	Low grade includes HPV- SIL
	Moderate	Low grade SIL
	Severe	High grade SIL
Class IV	Ca in situ	Squamous cell carcinoma
Class V	Adenocarcinoma	Adeno-carcinoma and glandular cell abnormalities

Soost HJ et al (1979) reported a peak incidence of carcinoma-in-situ and severe dysplasia between 25th and 29th year of life, with a second lower peak at around the 65th year. The high frequency of cervical carcinoma was noted in old age.¹⁸

Bang et al (1989) in their study observed high prevalence of gynaecological diseases in rural Indian women. Of 650 women who were studied- 55% had gynaecological complaints and 45% were free from symptoms. 92% of all women were found to have one or more gynaecological or sexual diseases. Only 8% of the women had undergone gynaecological examination and treatment in the past.¹⁹

Krane J.F et al (2001) observed that sensitivity of a single Papanicolaou (PAP) smear for cervical adenocarcinoma was between 45% and 76% depending on the classification of negative slides that were not available for review, comparable to previously reported sensitivity for adenocarcinoma in situ.²⁰

JS Misra et al (2003)-In their study revealed a higher incidence of LSIL and of frank cancer in menopausal women than in women in the

reproductive age group (9.1% and 3.3% as against 2.1% and 0.9% respectively)²¹

Chhabra et al (2003) conducted cytomorphological study of cervical PAP smears for precancerous and cancerous lesions in 1812 patients (from June 1999 to May 2001) who presented with complaints of white discharge, irregular bleeding, postmenopausal bleeding and postcoital bleeding. Cytohistological correlation was done in 384 cases.²²

Misra JS et al (2004) in their study of 19,449 women (from 1991 to Aug 2002) revealed inflammatory smears in 8354(42.9%), LSIL-mild dysplasia-403/8354(4.8%), HPV-108/8354(1.2%) and HSIL-moderate dysplasia-14/8354(0.1%). Erosion cervix was commonly associated with inflammatory changes (46.6%) Associated with gynaecological symptoms White discharge-1152 (13.7%) Menorrhagia-4.2%. Contact bleeding 46 (0.5%) Postmenopausal bleeding-21 (0.2%)²³.

Materials and Methods

Women aged 21yrs and above attending the gynecology OPD of RMMCH with complaints of white discharge, irregular menstrual bleeding, postmenopausal bleeding and post coital bleeding between Dec 2003 to June 2005 were included in this study. Clinical features and histopathological examination were studied..

Preparation of Pap Stain

1.Preparation of Harris Haematoxylin

Haematoxylin powder	2.0gm
Ethylene glycol	250ml
Aluminium sulphate	17.6gm
Distilled water	750ml
Sodium iodate	0.2gm
Glacial acetic acid	20.0ml

The ingredients were added in order as written above in a dry clean bottle and the mixture was vigorously shaken for 1 hour at room temperature. The staining solution could be stored over one year.

2.Preparation of Orange G Stain

Orange G stock solution

Orange G stain	9.05gm
Distilled water	100ml

Orange G working solution

Orange G stock solution	20ml
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Phosphotungstic acid	0.15gm
95% ethyl alcohol	980ml

Orange G working solution was changed every fortnight. The stain was filtered before use and stored in a dark bottle.

3.Preparation of E.A Stain (Modified)

Light green stock solution

Light green SF yellowish	3.17gm
Distilled water	100ml

Eosin Y Stock Solution

Eosin Y	20.8gm
Distilled water	100ml

E.A Working Solution

95%ethyl alcohol	700ml
Stock eosin y	20ml
Stock light green	10ml
Absolute methanol	250ml
Phosphotungstic acid	2gm
Glacial acetic acid	20ml

This working solution was changed every week.

Staining of Pap Smear

The fixed slides are transferred directly from the fixative into the following solutions.

1. 80% ethyl alcohol	10dips
2. 70%ethyl alcohol	10dips
3. 50%ethyl alcohol	10dips
4. Distilled water	10dips
5. Harris haematoxylin	3min
6. Running tapwater	1min
7. 0.5%HCL	5dips
8. Running tapwater	1min
9. Dilute solution of lithium carbonate	1min
10. Running tapwater	1min
11. 50%ethyl alcohol	10dips
12. 70%ethyl alcohol	10dips
13.80%ethyl alcohol	10dips
14. 95%ethyl alcohol	1min
15. Orange G-6	1min
16. 95% ethyl alcohol	10dips
17. 95%ethyl alcohol	10dips
18. EA-36	4min
19. 95%ethyl alcohol	10dips
20. 95%ethyl alcohol	10dips
21. Absolute alcohol	4min
22. Xylene	5min

Slides are then mounted in DPX.

Results

Nuclei-Blue

Superficial cell cytoplasm-Pink

Intermediate and Parabasal cell cytoplasm-Blue-green

Red Blood cells-Orange

Observations

Age Incidence

In the present study, a high incidence of 308 cases (38.5%) was observed in the 3rd decade followed by 241 cases (30.8%) in the 2nd decade and a low of 9 cases (1.12%) was observed in the 6th decade and above. (Table 1., Fig.1)

Table No. 1

Age (years)	Total number of cases	Percentage (%)
21 - 30	247	30.87%
31 - 40	308	38.5%
41 - 50	191	23.87%
51 - 60	45	5.62%
60 >	9	1.12%
Total	800	100%

Clinical Presentation

In the present study, high incidence of 397 cases (49.62%) presented with complaint of white discharge followed by 284 cases (35.50%) with irregular bleeding and low incidence of 13 cases (1.62%) with complaint of post coital bleeding.

Table No. 2

Age (years)	White discharge	Irregular bleeding	Postcoital bleeding	Postmenopausal bleeding
21 - 30	149(31.5%)	90 (31.57%)	08 (61.53%)	Nil
31 - 40	156 (39.29%)	136 (47.71%)	02 (15.38%)	14 (13.2%)
41 - 50	80 (20.15%)	38 (13.33%)	03 (23.07%)	70 (66.03%)
51 - 60	11 (2.77%)	20 (7.04%)	Nil	14 (13.2%)
60 >	01 (0.25%)	Nil	Nil	08 (7.54%)
Total	397 (49.62%)	284 (35.5%)	13 (1.62%)	106 (13.25%)

HPE Vs AGE

In the present study of 800 cases in 146 cases both cytology and histopathology profile of the patients were available

Table No. 3

Age (years)	Normal	Chronic cervicitis	CIN I	CIN II	CIN III	Invasive Squamous cell carcinoma
21 - 30	07 (43.75%)	32 (35.5%)	05 (17.85%)	01 (16.66%)	01 (33.33%)	-
31 - 40	06 (31.5%)	36 (21.42%)	06 (21.42%)	-	-	01 (33.33%)
41 - 50	02 (12.5%)	22 (24.44%)	12 (42.85%)	04 (66.66%)	01 (33.33%)	02 (66.66%)
51 - 60	-	-	03 (10.71%)	01 (16.66%)	01 (33.33%)	-
60 >	1(6.25%)	-	02 (7.14%)	-	-	-
Total	16 (2%)	90 (11.25%)	28 (3.5%)	06 (0.75%)	03 (0.375%)	03 (0.375%)

Discussion

The Bethesda System (TBS) 2001¹⁰ is currently used so as to ensure uniformity in reporting and

allow comparison of results from different centers. Majority of these studies included women in reproductive age group as well as postmenopausal age to find out the prevalence of cervical lesions like chronic inflammation, LSIL, HSIL, carcinoma-in-situ and Carcinoma.

Clinical Presentation

Misra et al (1997) conducted study on 1675 women with vaginal discharge.²⁴

Chhabra et al (2003) conducted cytomorphological study of cervical PAP smears for precancerous and cancerous lesions in 1812 patients who presented with complaints of white discharge 1032 cases (56.95%), irregular bleeding, postmenopausal bleeding and postcoital bleeding.²²

Misra JS et al (2004) conducted study on 19,449 women, of which 1574 presented with white discharge 1152(13.7%), menorrhagia 355(4.2%), contact bleeding 46(0.5%) and postmenopausal bleeding 21(0.2%).²³

In the present study (2006), out of 800 women, 397(49.62%) presented with white discharge, 284(35.5%) with irregular bleeding, 13 (1.62%) with postcoital bleeding and 106 (13.25%) postmenopausal bleeding.

Age Incidence

Misra JS et al (1997) reported in their study, a high incidence of cervical dysplasia in women between 31-40 years of age (4.1%) followed by women between 21-30 years of age (1.9%).²⁴

Misra JS et al (2004) reported in their study, a high incidence (64.7%) of inflammatory smears in women between 31-40 years of age followed by women between 21-30 years of age (28.9%). 201cases (8.3%) of LSIL and 7cases (0.2%) of HSIL were observed in the 2nd decade.²³

In the present study (2006), high incidence of inflammatory smears was observed in women between 31-40 years of age [81 cases (44.02%)] followed by women between 21-30 years of age [78 cases (42.39%)]. A high incidence of LSIL –

12 cases (42.85%) and HSIL-7 cases (58.33%) was observed in the 4th decade.

Reagan (1956) reported that the mean age at which the mild dysplastic lesions equivalent to LSIL were detected was 34.2 years and that of severe dysplasia was 41.4 years.²⁵

Di Bonito et al., in the study of 1000 cases found that average age of the patient was 34.6 years; ranged from (14-80) years.²⁶

Cytohistopathological Correlation

Di Bonito L et al (1993) reported a cytohistopathological concordance of 63.5% for CIN1, 43.6% for CIN2, 92.3% for CIN 3 and 100% for SCC.²⁶

Srisupundit and Bullangpot (1979) reported a 45% concordance.²⁷

Jones (1987) reported sensitivity of cytology as 17% and specificity 98%.²⁸

August (1991) observed sensitivity of cytology as 26% and specificity 97%.²⁹ Rasbridge and Nayagam (1995) reported a diagnostic concordance rate of 35% before review and 52% after review in cases of CIN2.⁵⁰ 52% accuracy was reported by Maturra et al(1996) in their series which included only severe dysplasia to frank invasive carcinoma cases.³⁰

Mostafa et al (2000) in their study of abnormal cervical smears reported 48% accuracy on cytology compared to histology.²⁷

Chhabra et al (2003) reported 80% accuracy of cytology in comparison to histology.²²

In the present series (2006) the cytohistopathological correlation was available in 146 cases out of 800 cases. In cases of LSIL and HSIL 100% cytohistopathological concordance was observed, while in cases of inflammatory smears it was 84.9%. 16 cases (15.1%) reported as inflammatory smears on cytology are reported normal on biopsy.

Table No 4 Cytohistopathological Concordance

Author	Inflammation	CIN I	CIN II	CIN III	Carcinoma
DiBonito et al (1993)	-	63.5 %	43.6 %	92.3 %	100%
Rusbridge and Nayagam (1995)	-	-	52%	-	-
Mostafa et al (2000)	-	62%	40%	57 %	SCC - 55% Ad - 66%
Chabra et al (2003)	86.6%	0	66.6 %	-	92.3%
Present series (2006)	84.9%	100%	100%	-	-

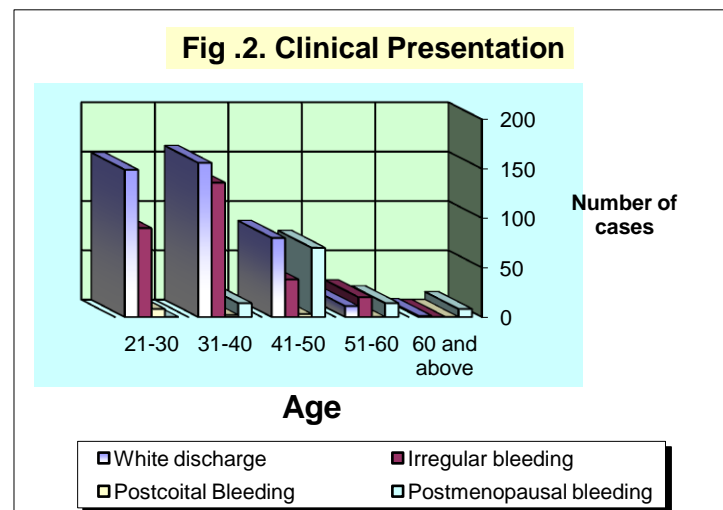
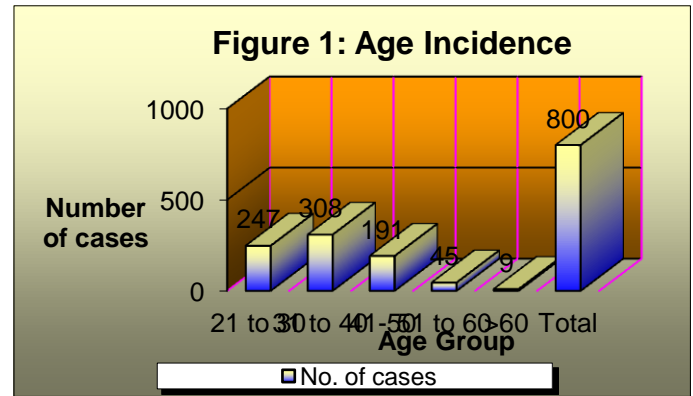
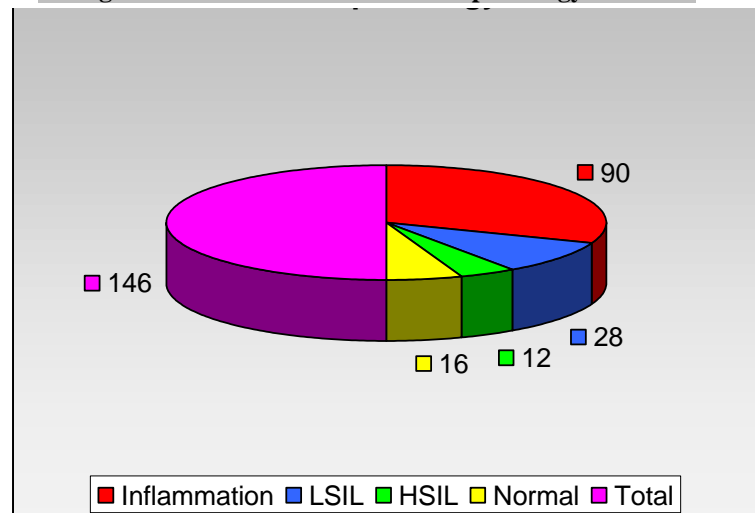
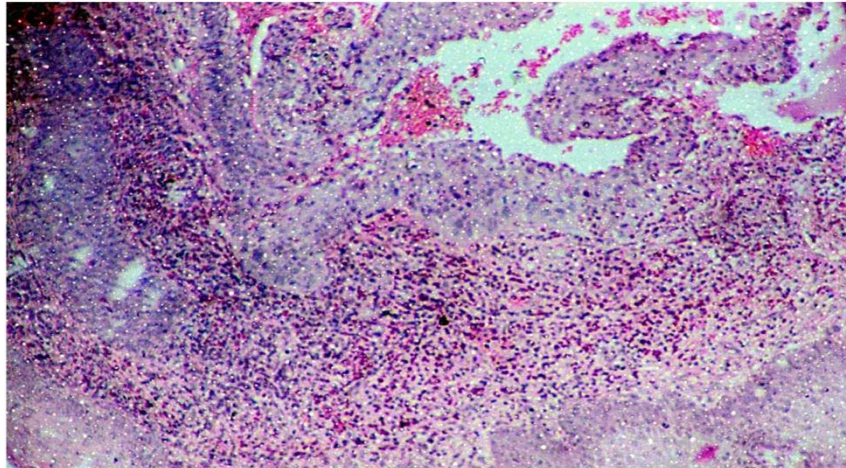
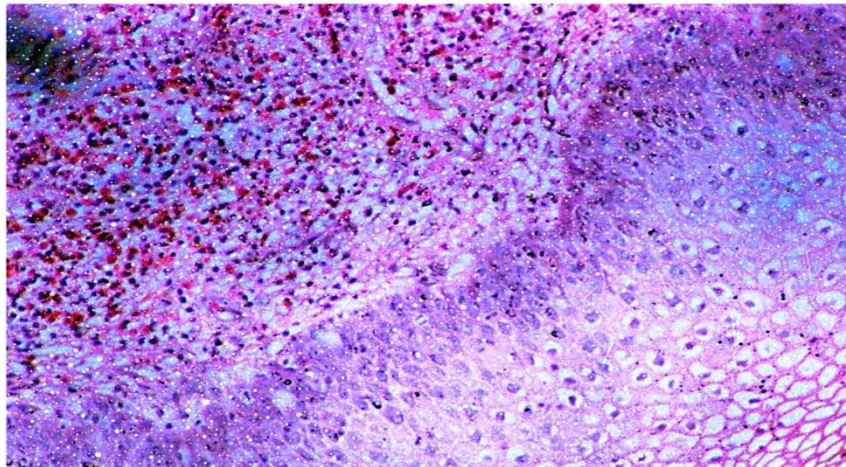


Fig:3 Distribution of Lesions-Histopathology

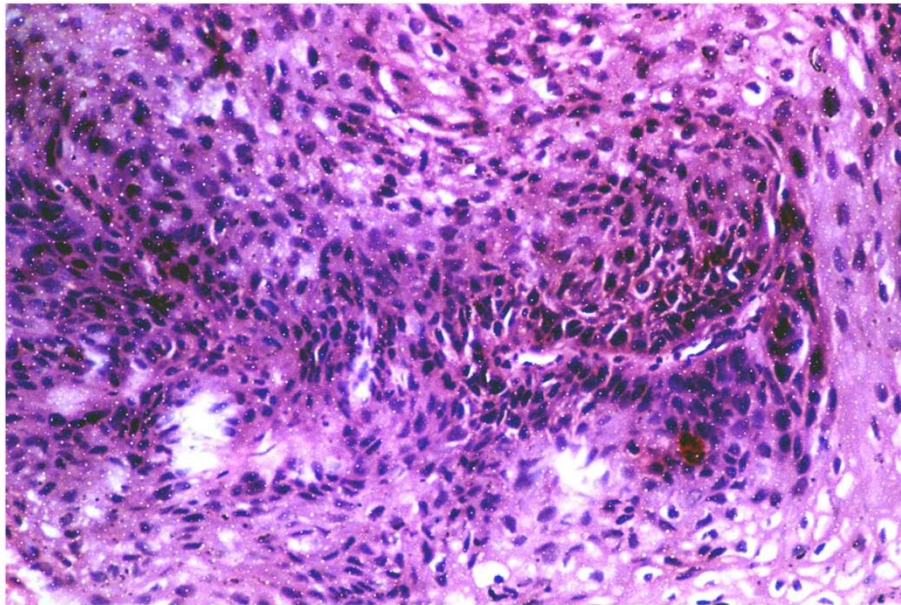




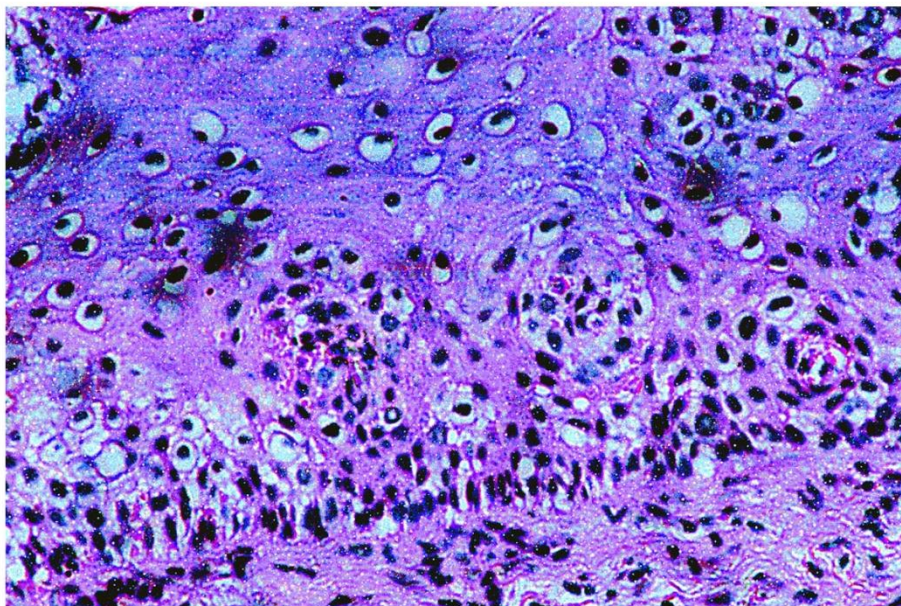
Chronic non-specific cervicitis x 20 H&E



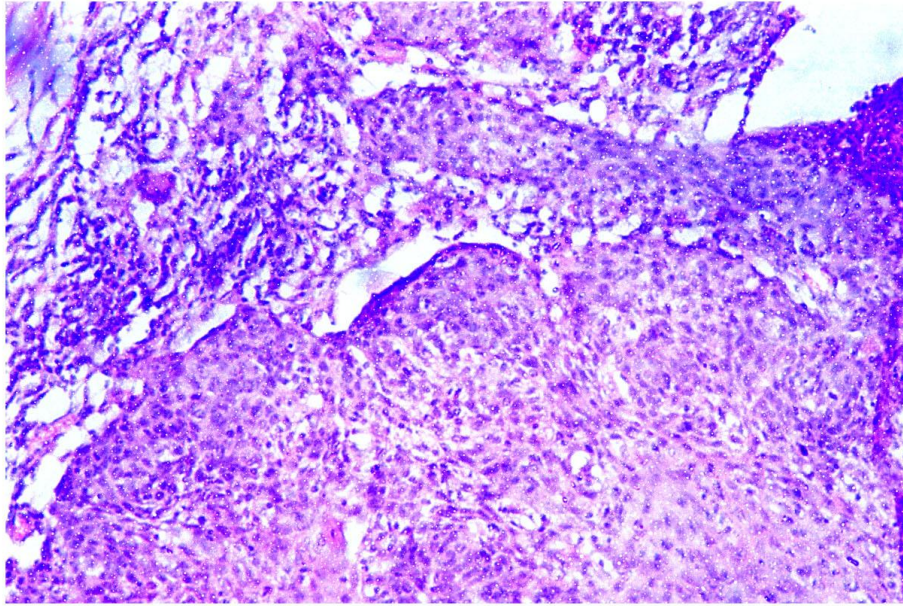
Chronic non-specific cervicitis X 40 H&E



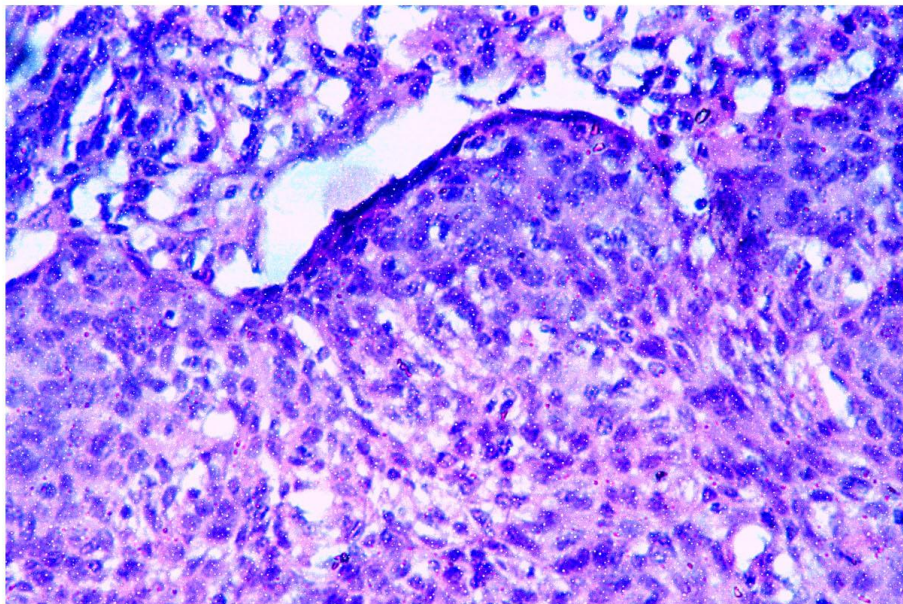
Cervical Intraepithelial Neoplasia (CIN) I X20 H&E



Cervical Intraepithelial Neoplasia (CIN) II –III X 40 H&E



Invasive Squamous cell Carcinoma X 20 H&E



Invasive Squamous cell carcinoma X 40 H&E

Summary

Patients above 20 years of age were included in the study. The youngest patient was 21 years of age and the oldest patient 80 years. The mean age of the patients was found to be 41.8 years.

The most common presenting symptom was white discharge 397 (49.62%) followed by irregular bleeding 284 (35.5%), postmenopausal bleeding 106 (13.25%) and postcoital bleeding 13 cases (1.62%).

Of these 760 cases (95%) were inflammatory, 28 cases (3.5%) were LSIL and remaining 12 cases (1.5%) were HSIL.

Out of 800 patients in the present series cervical biopsy was available in 146 cases. Chronic non-specific cervicitis accounted for 90 (61.6%), CIN I 28 (19.17%), CINII 6 (4.1%), CIN III 3 (2.05%) and invasive carcinoma 3 (2.05%). Among the cases, of invasive carcinoma - 2 were squamous cell carcinoma and one adenocarcinoma.

An overall accuracy 130/146 (89.04%) is found in the present series.

Interest of conflict: None

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