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IMPORTANCE OF CLINICAL HISTORY AND ENDOMETRIAL HISTOMORPHOLOGY IN TREATMENT DYSFUNCTIONAL UTERINE BLEEDING

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ABSTRACT

Introduction: Dysfunctional Uterine Bleeding (DUB) seen in 10-15% of women attending gynaecological clinic has variations in endometrial patterns. Modern treatment depends upon physiology and morphological pattern.

Aims: This study was undertaken to analyse types, frequencies and histomorphology of DUB in a part of India where this was the first study of its kind, to analyse hormonal effects and to evaluate percentage of hyperplasia and pre-neoplastic features as per WHO 2008 and Endometrial Intraepithelial Neoplasia (EIN) criteria.

Method: 237 curettage and 126 hysterectomy samples of DUB patients were assessed between July 2012 - July 2013 in a tertiary care teaching hospital.

Results: DUB was common between 31-50 years. Adolescents were not seen to have DUB. Early menopause at 40 years was seen in 14.3% cases. Ovulatory cases comprised 34.7% and anovulatory 50.5%. Hyperplasia comprised 5.5% and 1.7% had malignancy. One case of simple hyperplasia had EIN. Tuberculous endometritis is not common in our district though pulmonary tuberculosis is rampant.

Conclusion: Regional differences in age of presentation and socioeconomic differences in organic pathologies are noted in different parts of India. Different treatment options make it essential to differentiate DUB into ovulatory/anovulatory, disordered proliferative endometrium or hyperplasia.

Key Words: Dysfunctional uterine bleeding, Exogenous hormones induced endometrial changes, Endometrial intraepithelial neoplasia, Endometrial hyperplasia, Disordered proliferative endometrium

INTRODUCTION

Endometrium being a hormonally sensitive tissue continuously undergoes rhythmic changes during reproductive life. Normal menstruation occurs as bleeding from a secretory endometrium and does not exceed 5 days (ovulatory cycle). Any bleeding outside this criteria is known as Abnormal Uterine Bleeding (AUB). AUB in absence of any organic pathology is called Dysfunctional Uterine Bleeding (DUB). DUB is one of the common complaint seen in 10-15% of women attending a gynaecological clinic.**[1]** Since it is associated most commonly with anovulatory menstrual cycles perimenopausal and to a lesser extent adolescent women are particularly vulnerable. DUB also occurs in ovulatory cycles. Post menopausal bleeding is also included in DUB.**[1]** DUB has great variation in the endometrial patterns and treatment depends upon ovulation physiology and morphological pattern. Freely prescribed hormonal treatment by gynaecologists as well as by general practitioners and easily available oral contraceptive pills cause various abnormalities in histology of endometrium. However, the history of such hormone intake is not available to the pathologist in most cases. It adds to the dilemma of the reporting pathologists. The present study was undertaken to analyse types, frequencies and histomorphology of DUB in a part of India where this was the first study of its kind, to analyse hormonal effects and to evaluate percentage of hyperplasia and pre-neoplastic features as per WHO 2008 and Endometrial Intraepithelial Neoplasia (EIN) criteria. **[2,3,4,5]**

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MATERIALS AND METHODS

The study was conducted on patients of Dysfunctional Uterine Bleeding attending Gynecology OPD during the period of July 2012 to July 2013 of a district level tertiary medical care hospital of Bhavnagar, Gujarat state. Clinical colleagues were asked to give precise history for this study undertaken by pathology resident. Institutional review board (IRB) permission was taken. The study included both curettage and hysterectomy specimens of DUB patients. The uterus of a patient already curetted was not considered as a new case.

Inclusion criteria were patients with history of

- Dysfunctional uterine bleeding at any age
- Post menopausal bleeding

Exclusion Criteria were patients known to have

- Acute Pelvic Inflammatory Disease
- In situ intrauterine contraceptive device
- Systemic Bleeding disorders

The bleeding patterns and LMP were recorded from the requisition slips. The morphological histopathology evaluation of slides was done by a single experienced senior consultant. Cases with morphology of hormonal treatment were requestioned before final diagnosis. WHO classification of 2008 of hyperplasia were strictly followed. Cases of hyperplasia were further evaluated for Endometrial Intraepithelial Neoplasia in relation to Endometrial Intraepithelial Neoplasia diagnostic criteria.**[2,5]**

RESULTS

A total of 237 curettage and 126 hysterectomy specimen were studied during this study.

Figure 1 shows age wise distribution of patients having DUB in our study and figure 2 shows age wise histomorphological spectrum.

Menorrhagia and polymenorrhoea were found in 85% and 10% respectively equally in 21-30 and 31-40 years age group. Polymenorrhoea and metrorrhagia respectively occupied around 60% and 70% in 41-50 years age group.

When continuous bleeding (24.2%) and DUB were mentioned as type of bleeding they were clubbed with menorrhagia for facilitation of comparison with other studies.

15% cases in 31-40 year group presented with post menopausal bleeding.

Proliferative pattern was the commonest endometrial pattern in all ages seen in 196 out of 363(54%) cases across all bleeding types. Out of these 196 cases of proliferative pattern, 31.6% were true proliferative phase as per last menstrual period (LMP) and rest 68.4% were proliferative phase of anovulatory cycles and showed morphology of weak proliferation and persistent estrogen effect.**[Fig. 3A]** Atrophic and isthmic endometrium were seen in 3.6% and 0.6% respectively.**[Fig. 3 B,C]** Secretory phase was seen only in the age groups between 31-40 years and 41-50 years where it comprised – 3.03% and 2.20% respectively. Progestin pill effects were seen in 1.9%.**[Fig. 3D]**

In PMB group (35 cases) only 17.1% cases were due to malignancy and 57.1% due to hyperplasia. Rest belonged to non-neoplastic category. Few organic pathologies came up unsuspected in this study of DUB. Figure 4 shows percentage distribution of organic pathologies.

Hyperplasia were seen in only 5.5% cases. Surprisingly menorrhagia was the commonest presenting bleeding pattern of hyperplasia. 70% of the Hyperplasia cases were Simple Typical hyperplasia and most of them were seen in the age between 31-50years. Disordered proliferative endometrium was seen in 3.6% of total cases. **(Fig. 5 A,B,C)**

The 20 cases of Hyperplasia were evaluated for Endometrial Intraepithelial Neoplasia. One case met all the criteria of Endometrial Intraepithelial Neoplasia (EIN). **(Fig. 5 D)**

6 cases of malignancy were detected, all were postmenopausal and above 55 years. 3 cases had Endometrial adenocarcinoma one of which showed secretory variant, 2 had Endometrial adenocarcinoma with benign squamous component (Endometrial Adenoacanthoma) and one had poorly differentiated Endometrial stromal sarcoma.**(Fig. 6 A,B,C,D)**

3 hysterectomy patients had associated ovarian tumors. A 52 year patient had functioning Granulosa cell tumor of ovary. Two other cases were associated with non functional Granulosa cell tumor and non functional Brenner's tumor in 55 and 58 year patient respectively.

10.2% curettage specimens were inconclusive. The predominant reasons were pre analytical (66.7% were due to scanty material, 20.8% due to haemorrhage and 12.5% due to uninterpreteble morphology).

Thus in the entire study ovulatory DUB comprised 34.7%, anovulatory DUB 50.5%, organic pathologies 7.7 and inconclusive 7.1%.

DISCUSSION

The bleeding pattern mentioned in requisition slip did not match with ovulatory or anovulatory bleeding pattern seen on morphology in many cases. It shows that terminologies were not fastidiously used despite the fact this ongoing study

was known to the clinicians. The terminology menorrhagia should be used only for heavy cyclical bleeding and metrorrhagia for intermenstrual bleeding. Continuous bleeding is an ovulatory bleeding and usually seen in hyperplasias. However in our study most common bleeding pattern in hyperplasia appear to be menorrhagia. Oligomenorrhoea seen in perimenopausal anovulatory bleeds was never mentioned in requisition slips. However, the terminology DUB was used frequently. Due to mismatches the final decision of ovulatory or anovulatory bleeds was based on LMP and morphological pattern with an advice to correlate clinically.

Literature states that 10-15% of women of reproductive age suffer from DUB **[1]** of which 20% are adolescent and 50% are in between 40-50 years.**[6]** However, in our study we found no DUB patients in adolescents. This is in concordance with another study from the same state and a very low % in two other studies from Karnataka**[7]** and New Delhi.**[8]** In our study the % of patients in 21-30 years was also only 5% compared to 20-25% in other studies.**[7,8]** The reasons for these regional differences were beyond the scope of this study.

Proliferative pattern was the most common endometrial pattern found in our study group of which 34.7% were ovulatory and 50.5% were anovulatory.

Most studies have not classified patients clearly into ovulatory or anovulatory bleeding which is the basis of determining treatment modality in association with prostaglandin E_2, F_2, I_2 and anti fibrinolytic levels in the patients of DUB.

Incidence of endometrium with progesterone effect in our study is comparable with Jairajpuri et. al.**[8]** but five times less compared to Dadhania et. al.**[10]** This could be due to rampant use of progesterone rich hormonal treatment in the area of the study of the latter.

Atrophic endometrium was diagnosed in our study when glands were lined by flat cuboidal cells and stroma was sparse. It was seen in post menopausal cases. More stromal cellularity and low columnar glands are seen in weak proliferative phase which are features of classical proliferative phase but lesser in intensity. Estrogen excess effect which shows weak proliferative phase or atrophic like endometrium in long standing cases usually gets classified as proliferative phase. Only a strong suspicion and elicitation of detailed history brings to notice such cases as patients may have been inadvertently treated by older generation general practitioners, gynaecologists and orthopedicians(Hormone replacement therapy) with predominant estrogen pills.

Occassionaly curettage has not gone deep enough into uterine cavity and only the lower uterine segment is scrapped showing morphology of isthmic endometrium. This especially happens in teaching hospitals where new residents take over curetting. The diagnosis of isthmic, atrophic or weak proliferative phase can be very confusing. They usually get tagged as proliferative phase to the novice and also due to lack of history and surity of the curettage procedure.

Disordered proliferative endometrium (DPE) is an exaggeration of the normal proliferative phase.**[5]** DPE lies at the lower end of the spectrum extending from hyperplasia to endometrial carcinoma**[8]** and usually gets overdiagnosed (hyperplasia) if strict diagnostic criteria of hyperplasia are not applied. Though other studies have taken into consideration this category, the % of hyperplasias in their studies though are still high.**[7,9,10,11]**

Endometritis is occasionally a direct cause of AUB.**[11]** Chronic endometritis is diagnosed on the basis of presence of plasma cells and can occur as a result of intra uterine contraceptive device (IUCD), pregnancy or incomplete abortion**[8]** in addition to other infectious etiology. Chronic endometritis of tuberculous origin was found in 7.7**%** in Jairajpuri et. al.**[8]** However, in our study there were no cases despite pulmonary and extra pulmonary tuberculosis being common in our population.

Incidence of hyperplasia in our study is comparable with Jairajpuri et. al.**[8]** but in comparison to all other studies**[7,9,10,11]** it is much lower which could be due to strict adherence to the WHO diagnostic criteria for hyperplasia or true regional genetic differences. Most patients presented with lower degrees of Hyperplasia (Simple typical > Simple atypical > Complex typical). Hyperplasias were common in perimenopausal age group in concordance with literature.

One case of hyperplasia met all the criteria of Endometrial Intraepithelial Neoplasia (EIN) but only focally. EIN diagnostic criteria used are described in table 2. Such cases should be followed up with PTEN marker immediately or sonography or curettage every 3 to 6 months as these are at high risk to develop adenocarcinoma. The presence of small focus of EIN in a case of simple typical hyperplasia indicates that all cases of hyperplasia should be evaluated for EIN.

The percentage of endometrial primary malignancy in our study was 1.7% which is similar to other studies. In our study metastatic etiology of DUB was not found.

Over all percentage of ovulatory and anovulatory bleeding in our study were 34.7% and 50.5% respectively. This data is not available in our comparison studies.

History of drugs which affect dopamine levels eg. tri cyclic anti depressants, phenothiazines, risperidone and olanzapine, hypothyroid status, obesity, Von Willebrand factor deficiency, hyperprolactinemic and androgenic states, functional ovarian tumors will be of help to the reporting pathologist. [12]

Ovulatory bleeding can be controlled in 20-40% cases by cyclo oxygenase inhibitors in patients having increased PG E_2 and I_2 levels, 50% cases by tranexamic acid in patients having enhanced endometrial fibrinolysis and 80-90% cases by IUD with levonorgestral. They can also be given trial of non resecting radiofrequency endometrial ablation. Most anovulatory cases respond to cyclical luteal phase progestins and weight reduction in obese patients. Trials of combined contraceptive pills may be effective in both ovulatory and anovulatory cycle.**[12]**

Temporary to lasting effect of leuprolide acetate (GnRH agonist) can be achieved and offered to women who are contemplating hysterectomy but unfit due to low haematocrit. Acute bleeding in chronic DUB may be controlled medically. Hysterectomy is to be considered for DUB only when less invasive treatments fail or if patient refuses to accept these even after medical counselling. Hysterectomy can also be considered in patients with low grade hyperplasia who do not respond to medical treatment, higher grades of hyperplasia and EIN.**[12]**

High percentage of curettage samples (10.2%) had pre analytic errors like scanty material and predominant haemorrhage. Endometrial biopsy is likely to give a better idea of the endometrium rather than crushed and shredded haemorrhagic curettage material.

CONCLUSION

Regional and socioeconomic variations in age of presentation and organic pathologies are noted in different parts of India. End stage estrogen therapy and mixed exogenous hormonal morphologies in endometrium are difficult to diagnose. Hyperplasia comprised only a small percentage in our study. Strict adherence to criteria for Hyperplasia are required to report endometrial material. Differentiating DUB into ovulatory and anovulatory etiology (34.7% and 50.5% respectively in our study) is important in giving appropriate and minimal medical and surgical treatment to the woman rather than subjecting all to hysterectomy as generally practised. For this differentiation fastidious use of bleeding pattern terminologies and precise clinical history is the need of the hour. It is high time for clinicians to use endometrial biopsy rather than curettage material for yielding better morphological diagnosis.

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Table 1: Different Endometrial patterns in patients of DUB (in percentage)

Endometrial Pattern	Pilli et. al. (2002)[9]	Jairajpuri et. al. New Delhi (2005)[7]	Patil et. al. Karnataka (2005-2008)[8]	Dadhania et.al Rajkot (2012) [10]	Anvikar et. al. Maharashtra (2012)[11]	Present study Bhavnagar (2012-2013)
Proliferative P	34	24.92	15.8	25.34	32	57.9
Secretory P	13	28.99	13.9	16.0	14	5.23
Menstrual P	0.0	0.0	0.0	12.0	0.0	12.12
Interval P	0.0	0.0	0.0	0.0	0.0	0.2
Isthmic EM	0.0	0.0	0.0	0.0	0.0	0.6
Atrophic EM	0.0	1.1	0.0	0.0	1.0	3.6
Progestin effect	0.0	1.72	0.0	10.0	0.0	1.93
Disordered EM	0.0	5.7	23.2	2.66	19.0	3.6
Irregular shedding	0.0	2.35	0.0	1.34	0.0	_
Irregular ripening	0.0	0.94	11.7	0.0	0.0	_
Luteal phase defect	0.0	1.88	0.0	0.0	0.0	_
Arias Stella reaction	0.0	0.0	0.4	0.66	0.0	_
Pregnancy	0.0	15.36	0.0	0.0	0.0	_
Hyperplasia	44.0	5.79	34.2	27.34	27.0	5.51
Carcinoma	0.0	0.47	0.8	2.66	1.0	1.40
Sarcoma	0.0	0.0	0.0	0.0	0.0	0.3
Endometritis	0.0	6.24	0.0	2.0	4.0	0.5
Other organic pathology	9.0	1.72	0.0	0.0	2.0	0.0
Inconclusive	0.0	2.82	0.0	0.0	0.0	7.1*

P : Phase
* This includes % of both curettage and hysterectomy cases hence figure is lower.

Table 2: Diagnostic criteria for EIN[2,3,4]

EIN Criteria (all must be met)	Comments
Architecture	Area of Glands>Stroma (Volume percentage stroma <55%)
Cytology	Cytology differs between architecturally crowded focus and background.
Size >1 mm	Maximum linear dimension exceeds 1mm.
Exclude mimics	Benign conditions with overlapping criteria: Basalis, secretory, polyps, repair, etc..
Exclude Cancer	Carcinoma if mazelike glands, solid areas, or significant cribriforming

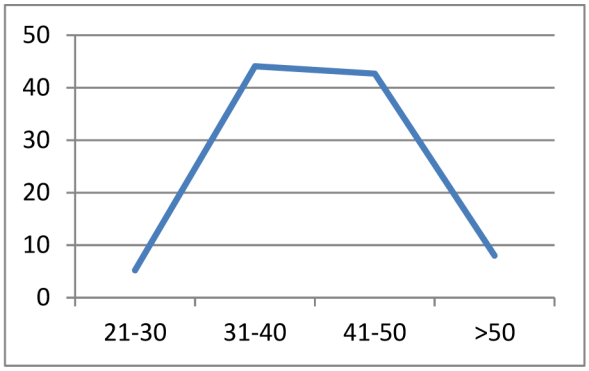


Figure 1: Age wise distribution of cases

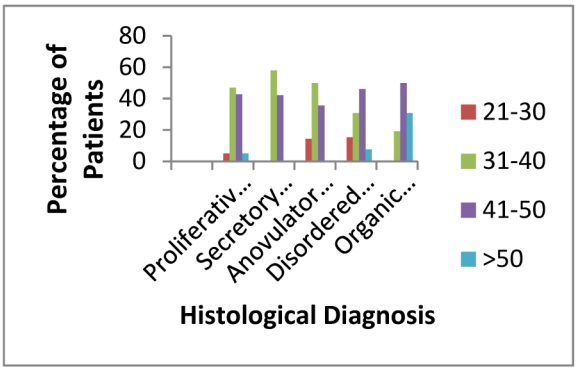


Figure 2: Age wise Histomorphological spectrum

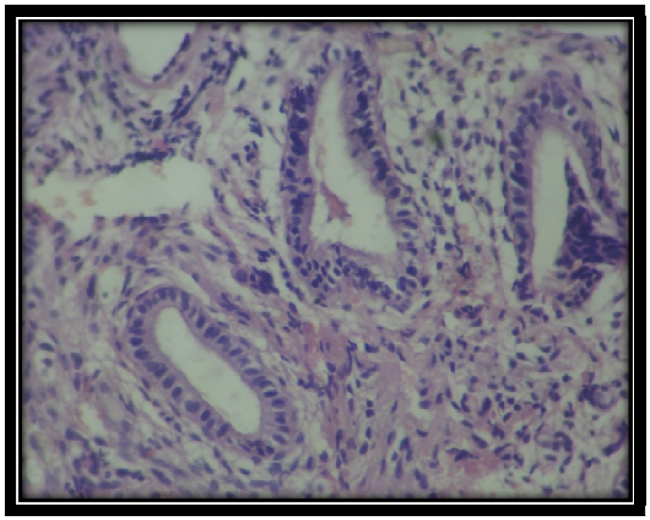


Figure 3A: Weak proliferative phase (estrogen effect) (10x, H&E stain)

Figure 3B: Atrophic endometrium (4x, H&E stain)

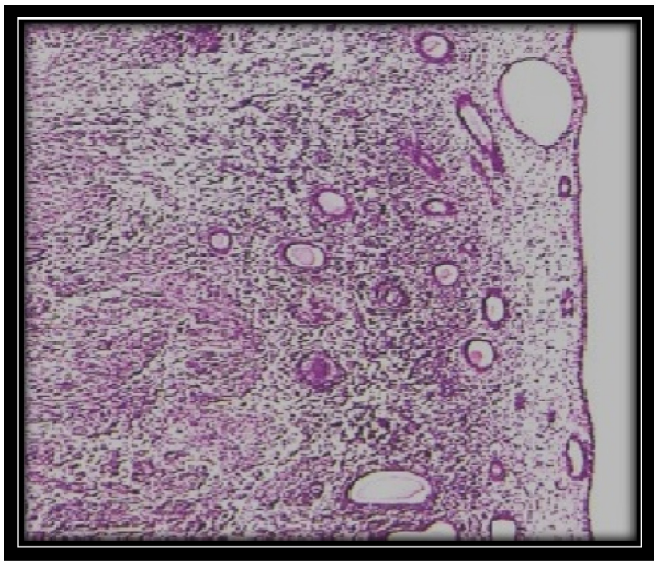
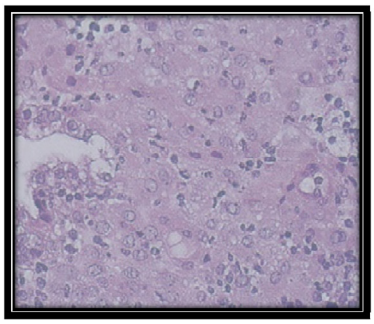


Figure 3C: Isthmic endometrium (4x, H&E stain)



CE : Chronic endometritis
ST HP: Simple typical hyperplasia
SaT HP: Simple atypical hyperplasia
CT HP: Complex typical hyperplasia
AC: Adenoacanthoma
AD: Adenocarcinoma

Figure 3D: Progestin pill effect (10x, H&E stain)

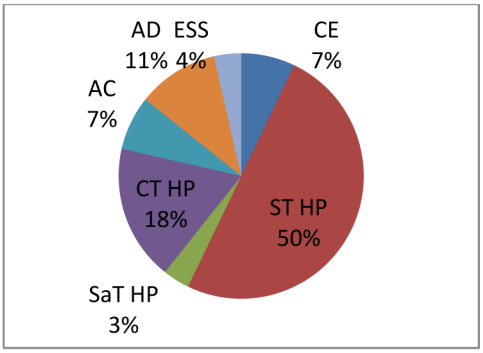


Figure 4: Percentage distribution of organic pathologies

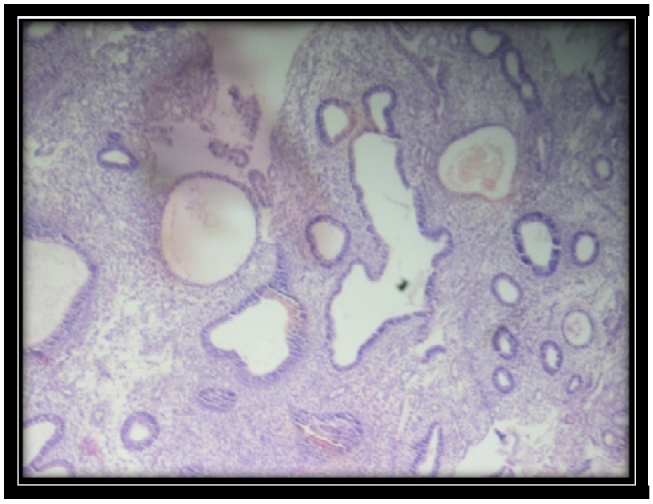


Figure 5A: Disordered endometrium (10x, H&E stain)

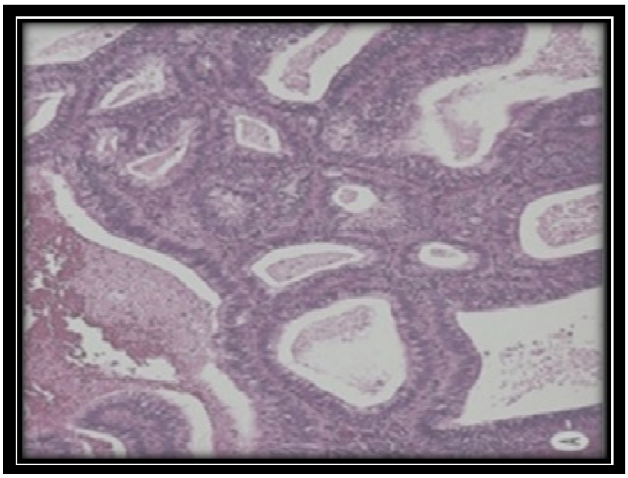


Figure 5B: Simple typical hyperplasia (40x, H&E stain)

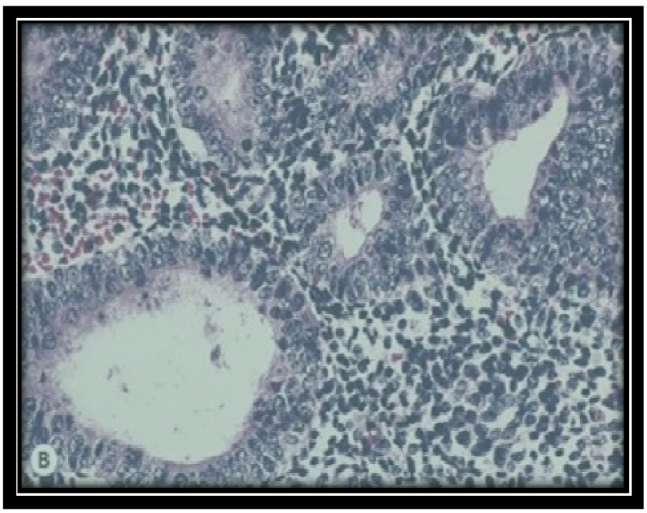


Figure 5C: Complex atypical hyperplasia (40x, H&E stain)

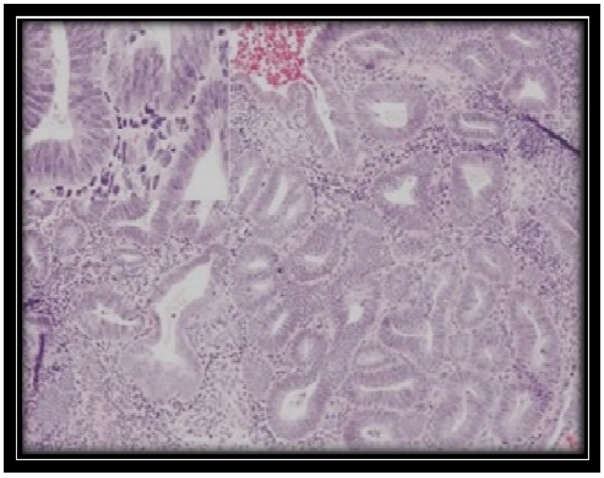


Figure 5D: Endometrial intraepithelial neoplasia (EIN) (10x, H&E stain)

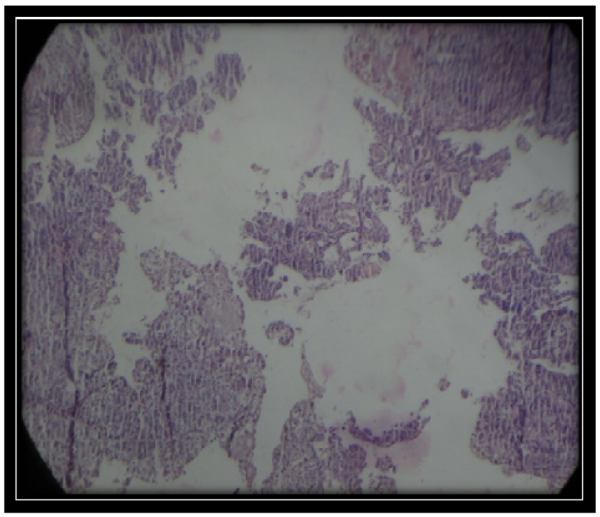


Figure 6A: Endometrium Adenoacanthoma (10x, H&E stain)

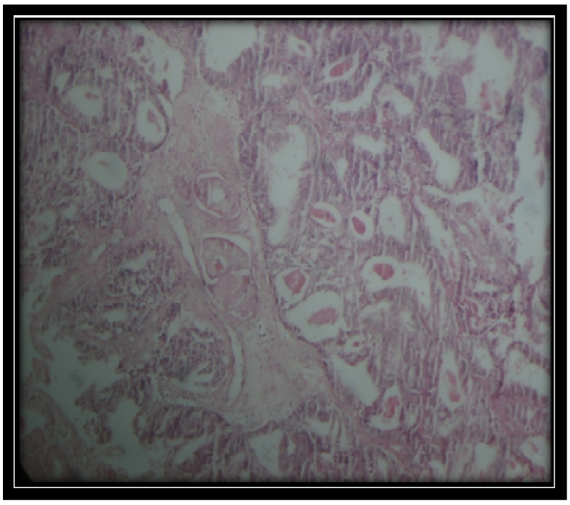


Figure 6B: Endometrial Adenocarcinoma (10x, H&E stain)

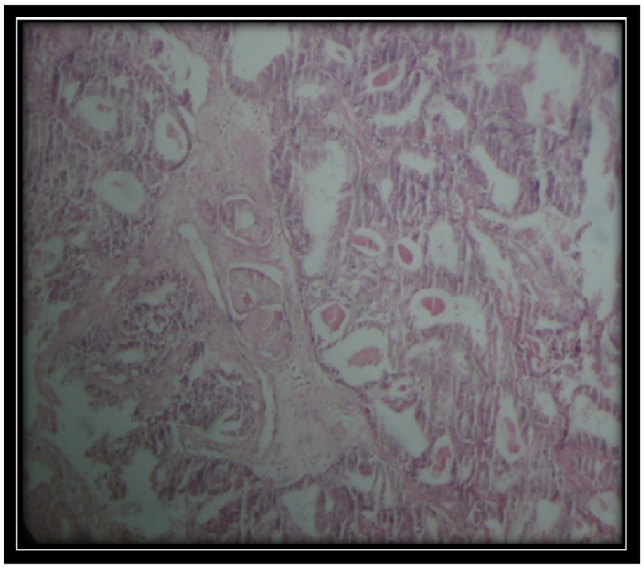


Figure 6C: Endometrial Adenocarcinoma-secretory variant (10x, H&E stain)

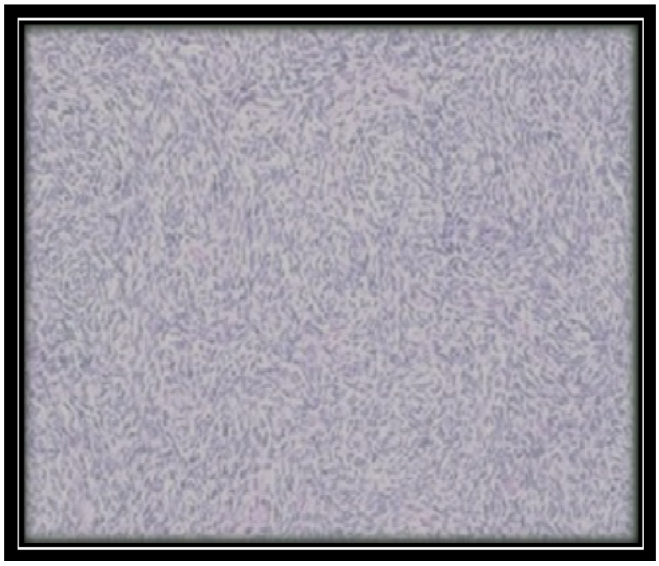


Figure 6D: Endometrial stromal sarcoma (10x, H&E stain)