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The Study of Abnormal Uterine Bleeding, Estrogen and Progesterone Receptor Expression in Cases of Endometrial Hyperplasia and Neoplasia

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Abstract

Background; AUB is the very common condition of patients in gynaecological OPD.The aim of study is to evaluate the histopatholological patterns of endometrium and to correlate it with different age groups and study ER and PR receptor expression in them.

Meterials and Methods: It is a reterograde study from 1 st jan 2021 to 30th june 2022 in the Department of Pathology, T S Misra Medical College and Hospital in collaboration with King George's Medical University. The study includes around 87 patients in the age group 30 to 80 yrs. .All the relevant cinical details and investigations was obtained from patients record.The study includes AUB cases of histopathologicaly diagnosed endometrial pathology .Those cases with inadequate sample or with history of pregnancy was excluded from study.The specimens were routinely processed and Hand E stained slides are studied for endometrial patterns and their frequencies and percentages were classified age group wise.ER and PR positivity percentage was determined in different patterns with immunohistochemistry.
Results: Number of patients falling in different age groups were noted and the result concluded was maximum number of AUB cases were in 40 -50 yrs in perimenopausal and post menopausal age group

less number was in the reproductive age group Number of patients in different histopathological pattern was also noted. Endometrial patterns included non malignant(65/87,) proliferative (%) followed by secretary (%) and endometrial hyperplasia without atypia(%),simple hyperplasia with atypia (%) ,complex hyperplasia with atypia (%) and malignant(22/87)endometrial carcinoma (25.3%). ER and PR positivity rate was 95.4% and 96.6% respectively in whole study. ER and PR expression in each pattern was also studied.

Conclusion; **H**istopathological examination of endometrial pathologies ranges in different patterns from normal cyclical to hyperplasia to carcinoma The study of ER and PR receptor expression in endometrial pathologies helps in determining prognosis for survival and planning for hormone replacement therapy.

Keywords: Estrogen Receptor, Progesterone Receptor

INTRODUCTION

Abnormal uterine bleeding is defined as any uterine bleeding that is more than the normal volume, of longer duration and varying in regularity or frequency. It is the very common condition of patients in gynaecological OPD AUB and its sub group, heavy menstrual bleeding (HMB), are common conditions affecting women of and may have a significant impact on their physical, social, emotional and material quality of life (1,2,3) An endometrial biopsy is done in women over 35 years of age with AUB and in women between the age of 18 and 35 years with AUB who have risk factors for endometrial cancer or if AUB fails to resolve with medical management.(4)

The uterine endometrium thus undergoes repetitive and physiological cycling of tissue injury and repair every month[5] (5)The endometrium is characterized by features of rapid repair without residual scarring or loss of function, similar to a fetus in utero[6,7] (6)The endometrium is dynamic and highly responsive to the varying circulating levels of the sex steroid hormones ovarian 17β-oestradiol (oestradiol) and pregn-4-ene-3,20-dione (progesterone).

Understanding this tightly regulated endocrine environment could help identify new therapeutic strategies for AUB Therefore, both endogenous and exogenous hormone exposure affects endometrial bleeding patterns. Oestradiol and progesterone induce their physiological effects in the endometrium primarily via their cognate receptors, the oestrogen receptor (ER) and the progesterone receptor (PR). Current medical treatments for AUB largely focus on hormonal management strategies, using a combination of oestrogen and progestins or progestins alone

METERIAL AND METHOD

This is a reterospective study from 1st jan 2021to 30 jun 2022 in the Department of Pathology T S Misra Medical college and Hospital in collaboration with KGMU. The study includes around 87 histopathologically diagnosed cases of abnormal uterine bleeding in the age group 30 to 80Yrs. Detailed clinical history and menstrual history, personal history, investigations, were obtained from case records. Ethical clearance was obtained from both the institutions before commensment of study. Inclusion criteria ; patients with isolated endometrial causes of Abnormal uterine bleeding Exclusion criteria ; patients having inadequate sample and those with history of pregnancy and its complications, with IUCD insertion cases were excluded from study.

Immunohistochemistry for ER and PR status was done using strict immunohistochemistry protocol an ER, PR expression was interpreted as brown nuclear staining in the glandular epithelium and stroma of all cases as a positive reaction.

RESULTS

Table 1: Age Profile of Source Women

SN	Age Group	No. of women	Percentage
1.	≤30 Years	6	6.9
2.	31-40 Years	19	21.8
3.	41-50 Years	24	27.6
4.	51-60 Years	22	25.3
5.	61-70 Years	12	13.8
6.	71-80 Years	4	4.6
Mean age±SD (Range) in years		48.67±12.58 (22-78)	

Age of women ranged from 22 to 78 years. Majority of them were aged between 41 and 60 years (n=46; 52.9%) years. There were only 6 (6.9%) women aged ≤30 years and 4 (4.6%) women aged >70 years. Mean age of women was 48.67±12.58 years (Table 1; Fig. 1

Table 2: Distribution of women according to duration of complaints

SN	Duration of complaints	No. of women	Percentage
1.	≤ 6 months	68	78.2
2.	6-12 months	9	10.3
3.	12-24 months	5	5.7
4.	24-60 months	4	4.6
5.	>60 months	1	1.1

More than three-fourth (78.2%) women had duration of complaints ≤6 months followed by 6-12 months (10.3%), 12-24 months (5.7%), 24-60 months (4.6%) and more than 60 months (1.1%) respectively (Table 2; Fig.

Table 3: Distribution of women according to Histopathological Diagnosis

SN	HPE Diagnosis	No. of women	Percentage	Total % in whole sample
1.	Non-malignant	65		
	Proliferative endometrium	10		11.55%
	Secretory endometrium	10		11.5%
	Simple hyperplasia without atypia	36		41.38%

	Simple hyperplasia with atypia	6		6.9%
	Complex hyperplasia with atypia	3		3.45%
2.	Malignant	22	25.3	25.3%
	Endometrial adenocarcinoma	19		21.83%
	Endometrial carcinoma villoglandular	1		1.14%
	Serous endometrial carcinoma	1		1.14%
	Endometroid endometrial carcinoma NOS	1		1.14%

Among non-malignant cases, maximum (n=10; 15.4% each) were secretory and proliferative endometrium respectively. There were 45 (51.7%) cases with endometrial hyperplasia. Among these maximum were simple hyperplasia without atypia (n=36; 55.4%) followed by simple hyperplasia with atypia (n=6; 9.2%) and complex hyperplasia with atypia (n=3; 4.6%) respectively (Table3).
Among 22 malignant cases, maximum (n=19/22; 86.4%) were endometrial adenocarcinoma. There was 1/22 (4.5%) case each diagnosed as endometrial carcinoma villoglandular type, serous endometrial carcinoma and endometrioid endometrial carcinoma NOS respectively

Table 4) Age wise distribution of histomorphological patter ns of endometrium

Serial no	**Histomorphological pattern**	**Reproductive Pd (18-40) yrs**	**Perimenopausal Pd (41-50) yrs**	**Postmenopausal Pd (>50 yrs)**
1	**Proliferative Endometrium**	**8(32%)**	**1(4.17%)**	**1(2.63%)**
2	**Secretary Endometrium**	**8(32%)**	**1(4.17%)**	**1(2.63%)**
3	**End. hyperplas Simple hyperplasia with0ut atypia**	**7(28%)**	**15(62.5%)**	**14(36.84%)**
	Compex hyperplasia with atypia	**1(4%)**	**1(4.17%)**	**1(2.63%)**
	Endometrial Carcinoma	**1(4%)**	**3(12.5%)**	**18(47.36%)**
	Simple hyperplasia with atypia	**0**	**3(12.5%)**	**3(7.9%)**

	Total	**25 (28.73%)**	**24 (27.58%)**	**38(43.67%)**

Most of the cases were in post menopausal age group (38/87,43.67%). Reproductive age group includes (25/87,28.73%) cases, perimenopausal age group contains (24/87,27.58%) cases.In the reproductive period most common pathology is normal endometrium(proliferative or secretary) followed by endometrial hyperplasia without atypia.In the post menopausal age group endometrial carcinoma cases are (18/38,47.36%)followed by endometrial hyperplasia without atypia (14/38,36.84%)

Table 5 : Comparison of ER/PR Status according to Histopathological Diagnosis

SN	Receptor	HPE Diagnosis	Positive		Negative	
			No.	%	No.	%
1.	ER	Proliferative endometrium (n=10)	10	100	0	0
		Secretory endometrium (n=10)	10	100	0	0
		Simple hyperplasia (n=36)	35	97.2	1	2.8
		Simple hyperplasia with atypia (n=6)	6	100	0	0
		Complex hyperplasia with atypia (n=3)	3	100	0	0
		Endometrial carcinoma (n=22)	19	86.4	3	13.6
2.	PR	Proliferative endometrium (n=10)	10	100	0	0
		Secretory endometrium (n=10)	10	100	0	0
		Simple hyperplasia (n=36)	36	100	0	0
		Simple hyperplasia with atypia (n=6)	6	100	0	0
		Complex hyperplasia with atypia (n=3)	3	100	0	0
		Endometrial carcinoma (n=22)	19	86.4	3	13.6

All the normal endometrium (proliferative and secretary) is 100% positive for ER and PR.35/36 cases of endometrial hyperplasia without atypia showed positivity for ER and all cases of endometrial hyperplasia with or without atypia showed PR positivity proportion of those with negative status was higher in endometrial carcinoma as compared to other diagnoses yet this difference was not significant statistically ($p>0.05$) (Table 5)

DISCUSSION

The present study was undertaken to study ER and PR receptor expression in cases of abnormal uterine bleeding. For this purpose, a total of 87 patients were enrolled in a cross-sectional study

that included, a total of 10 cases each of proliferative and secretory endometrium, 45 cases of endometrial hyperplasia and 22 cases of endometrial carcinoma respectively. Age of patients ranged from 22 to 78 years and mean age of the patients was 48.67±12.58 years.

In the present study peak age incidence is present in the age group 40-50 yrs(27.7%) followed by 51-60 yrs(25.3%) comparable to other studies Prathippa R , Divya J peak age incidence is among the age group 41 to 50 yrs (108 cases,42.19%) Sharma K et al (37.26%) ,Singh S et al (34%),Puvitha R D et al (48.70%) ,Samal R et al , Bindro S et al (43.2%) But in Dwedi S S et al peak age incidence is less than 40 yrs with mean age of patients with AUB in their study was 39.6 years.(8—14)

In the present study, more than three-fourth (78.2%) patients had clinical manifestation of only 6 months or less. There was only one (1.1%) case with duration of complaints >60 months. One of the reasons for this could be the fact that endometrial pathologies remain asymptomatic for a long period. It is also highlighted as one of the reasons for late detection of endometrial carcinoma, particularly in advancing age in post-menopausal women. Another reason for high proportion of symptomatic patients in shorter duration could be the fact that abnormal uterine bleeding happens to be the most common manifestation which is a highly discomforting warning sign that prompts the patients to seek clinical help immediately Histopathological examination of the endometrial samples in present study shows the spectrum of non malignant(65/87) and malignant endometrial lesions.(22/87) In non malignant lesions includes normal cyclical proliferative endometrium (10/65,15.4%) ,Secretary endometrium (10/65) 15.4 % , In the present study, we used WHO (1994) criteria for classification of (45 /65)endometrial hyperplasia cases in our study and found that maximum number of cases were simple hyperplasia without atypia (n=36/6555.4%). There were 6/65 (9.2 %) cases of simple hyperplasia with atypia and 3 (4.6 %) cases of complex hyperplasia wit atypia and 22/87(25.3%) cases were of endometrial carcinoma.,(malignant) Corresponding to newer 2014 WHO classification, a total of 36/45 (80%) cases could be categorized as hyperplasia without atypia and remaining 9 / 45as atypical hyperplasia/endometrioid intraepithelial neoplasia. Thus in present study endometrial hyperplasia remains to be one of the most commonly overdiagnosed conditions in diagnostic surgical pathology(45)and hence it is essential that better diagnostic modalities should be evolved that could help in correct identification of endometrial hyperplasis and its different forms and its differentiation from the endometrial cancer.Similarly, Moghal N described similar results citing endometrial hyperplasia as the most common cause of AUB following endometrial polyp (15) In Sajitha et al study the most common endometrial pathology was endometrial hyperplasia(39/156) case s followed by disordered proliferative endometrium (19/156) cases and pill endometrium.(16) where as in another study by Nivedita et al Proliferative endometrium was the most common(17)

. Thus the most common pathology in the reproductive period in present study is normal endometrium (proliferative and secretary 32% each,) followed by endometrial hyperplasia(28%) without atypia.where as in other studiy R Khan et al hormonal imbalance was the most frequent endometrial pathology in reproductive age group followed by endometrial hyperplasia(.18)

In perimenopausal age group in present study endometrial hyperplasia without atypia is more common(15/24,62.5%) followed by endometrial hyperplasia with atypia (3/24 ,12.5%), endometrial carcinoma (3/24, 12.5%).nōrmal cyclical endometrium is least common.In Doraiswami S et al described disordered proliferative pattern as the most common endometrial pathology in perimenopausal age group.(19)

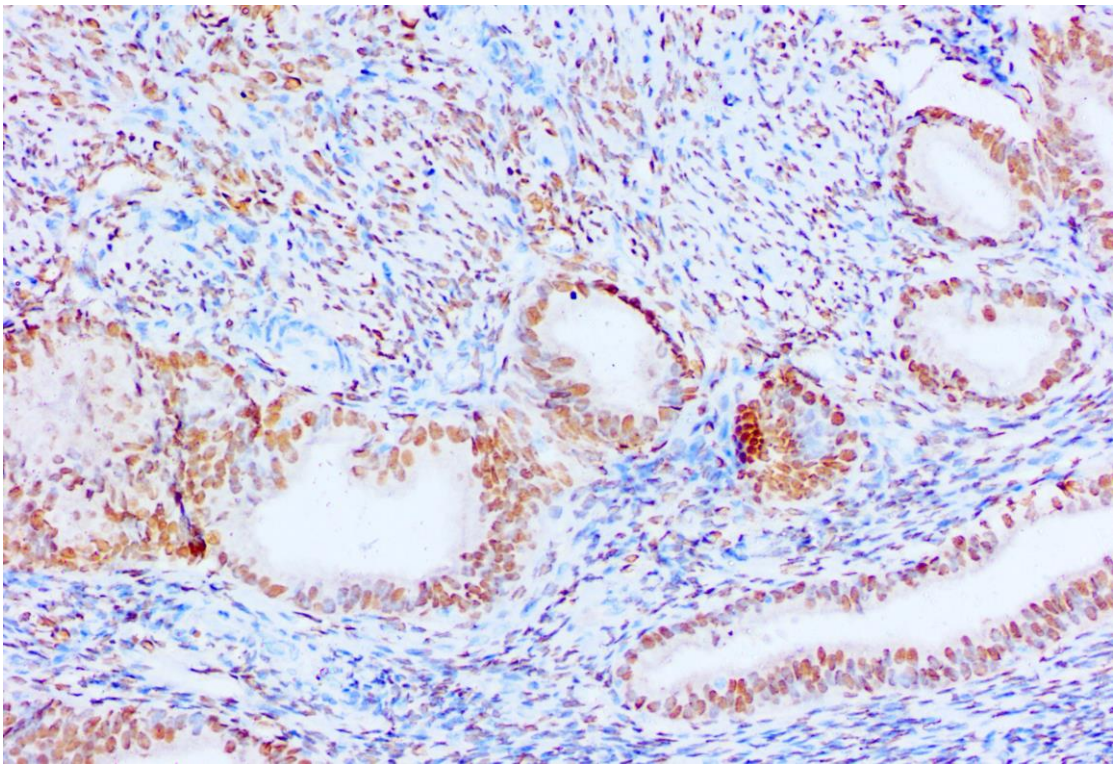
In the present study in post menopausal age group endometrial carcinoma (18/38,47.36%) followed by endometrial hyperplasia without atypia(14/38,36.84%) is the most common finding. Similar to present study Vaidya S et al also found in their study that endometrial hyperplasia and cancer were usually seen in perimenopausal and postmenopausal age groups. (20) whereas In Dwivedi S S in menopausal age group the most common finding was atrophic endometrium (61.11%) followed by hormonal imbalance and pill effect (11.11%),endometrial hyperplasia with atypia (16.67%) and endometrial carcinoma (11.11%)

In the present study, we found ER and PR positivity in 95.4% and 96.6% of study sample irrespective of underlying endometrial pathology.. In the present study no of positive cases was taken into account. We assessed expression of ER and PR in both stroma as well as epithelium and we considered any specimen to be positive even if it was positive in either of these two. Moreover, in the present study, we considered even the low intensity (score 1) as positive. Owing to use of this inclusive criteria,positivity rate was higher in present study.All the (64/65 ,98.46%)of non malignant cases and (19/22,86.4%) of malignant cases showed ER positivity where as all (65/65,100%)and (19/22 ,86.4%) of malignant cases were PR positive.. In Sahar Aly Daoud et al (21) studied the number of positive cases for ER and PR in each group. It found that among 28 cases of nonmalignant endometrium 22 (78.57%) were positive for ER and 19 (67.85%) were 85 positive for PR. Among 20 cases of endometrial carcinoma, 14 (70%) were positive for ER and 12 were positive for PR (60%)

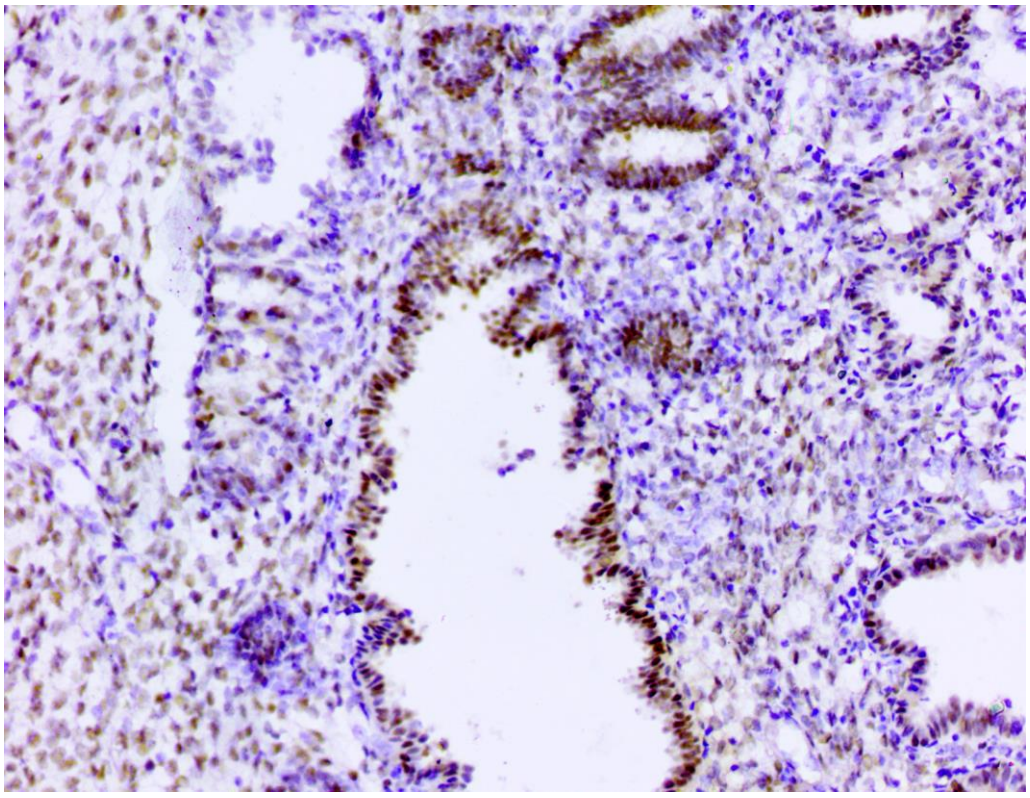
CONCLUSION

Histopathological examination of endometrial pathologies ranges in different patterns from normal cyclical to hyperplasia to carcinoma.It plays a critical role in peri and post menopausal age groups for early diagnosis of premalignant and malignant lesions of endometrium and provide appropriate gynaecological management. Immunohistochemistry reveals that ER and PR expression decreases progressively as we go from the proliferative pattern and hyperplasias to adenocarcinoma. The study of ER and PR receptor expression in endometrial pathologies helps in determining prognosis for survival and planning for hormone replacement therapy.

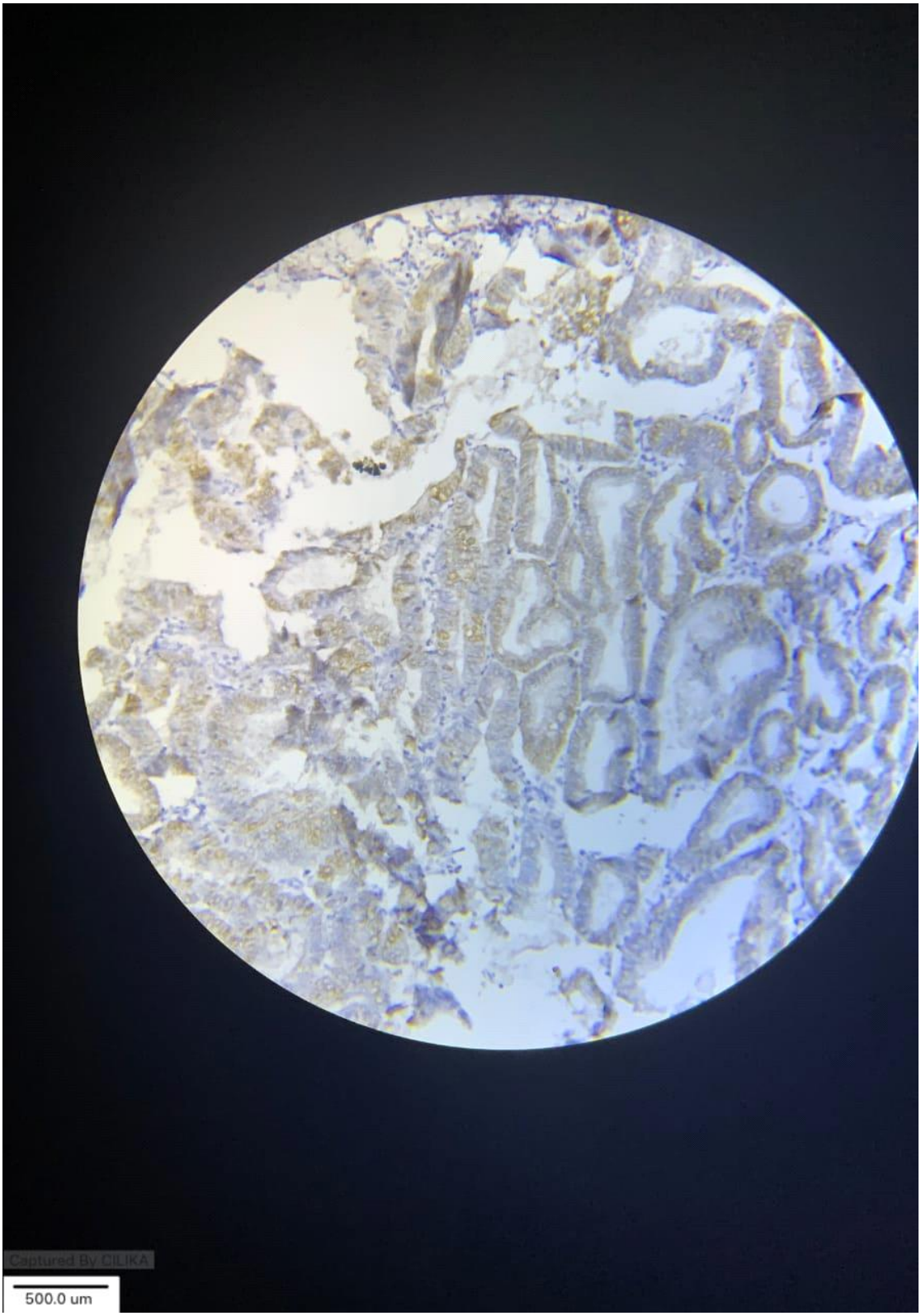
FIGURES ;



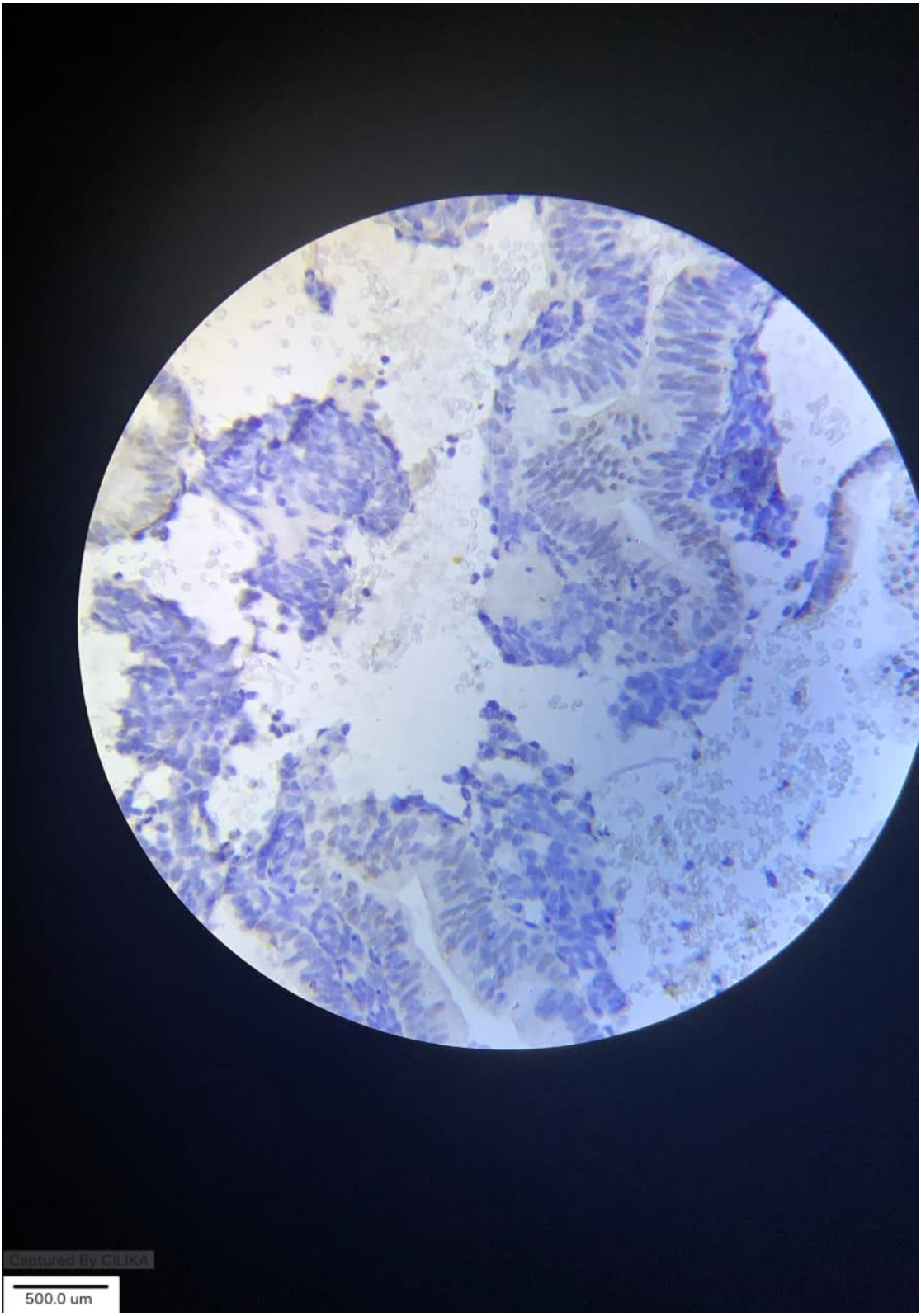
1 PROLIFERATIVE PHASE PR 20X strong gland and stroma positivity



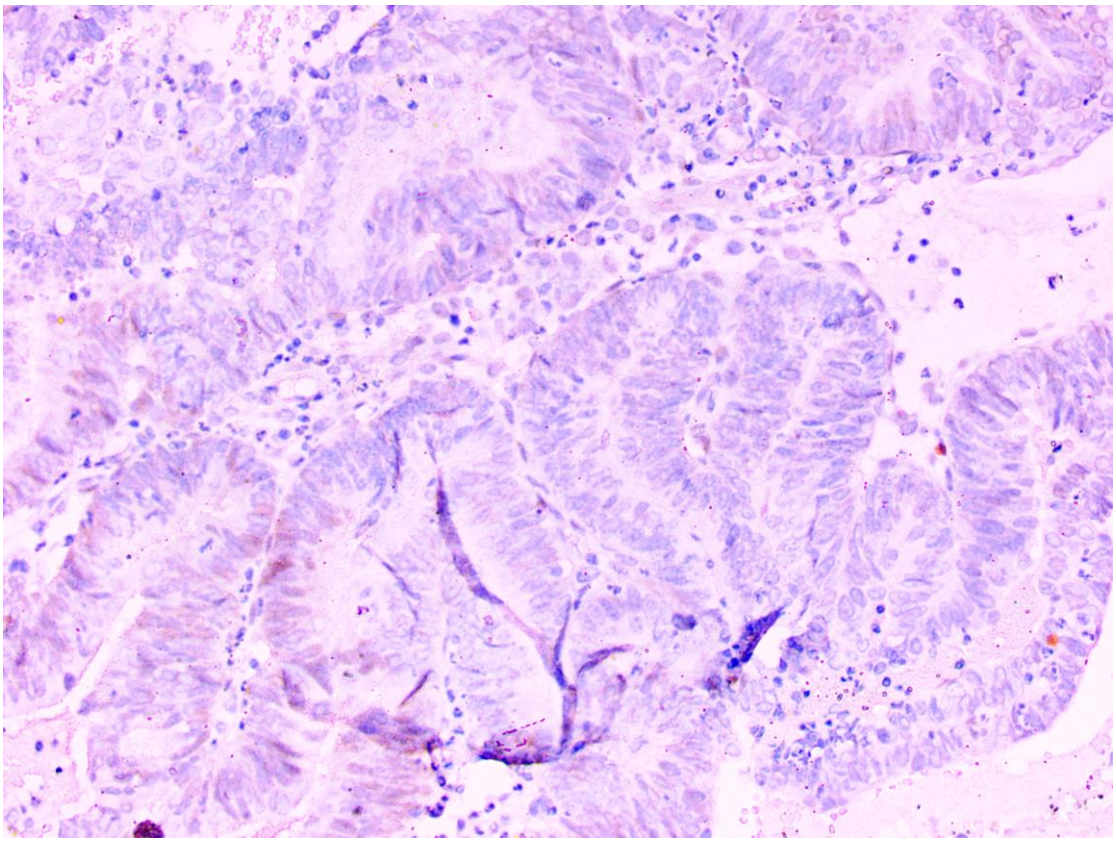
2. secretory phase ER 20x strong gland and stoma positivity



3. ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA 10X STRONG GLAND POSITIVITY



4. ATYPICAL HYPERPLASIA FAINT POSITIVITY PR



5. Endometrial CA E ndometroid variantrpER 20 X faint positivity ER

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