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Original Research Article

An Immunohistochemical Study of Steroid Hormone Receptors (Estrogen and Progesterone) In Endometrial Hyperplasia and Carcinoma

Dr. Soumya Vellanki[1], Dr. R Manasa Reddy[2], Dr. Vijaya Gattu[3], Dr. K.P.A Chandra Sekhar[4]
[1, 3]Assistant Professor, [4]Professor, Department of Pathology, SVS Medical College, Yenugonda, Mahabubnagar, Telangana
[2]Assistant professor , department of pathology , Prathima institute of medical sciences, Karimnagar, Nagunur, Telangana

***Corresponding author**
Dr. Soumya Vellanki
Email: drsoumya_79@yahoo.com

Abstract: The immunohistochemical studies of ER and PR in endometrial hyperplasia and carcinoma and its significance on prognosis and hormonal therapy are few in the literature compared to studies on breast cancer. Our data will be definitely an important addition to the existing literature.
Keywords: immuno histochemical studies, ER and PR

INTRODUCTION:

Endometrial hyperplasia develops in a setting of estrogen excess. Potential precancerous lesions of endometrium such as complex hyperplasia with or without atypia may contain levels of estrogen and progesterone receptors that are distinct from carcinomas [1]. Detection of high levels of steroid receptors denotes a good response to hormonal therapy. In contrast decrease in receptor activity, which is normally found in atypical hyperplasia results in low sensitivity to progesterone therapy. If a higher level is found in some rare incidence of atypical hyperplasia, good response to hormonal therapy can be anticipated and radical surgery can be avoided. Endometrial carcinoma is one of the most common gynecologic malignancies in industrialized and developing countries and is generally accepted to be an endocrine related neoplasm. Endometrial carcinomas also contain estrogen receptors (ER) and progesterone receptors (PR), but several studies have reported that the levels are reduced or absent as compared to normal cyclical endometrium and hyperplastic endometrium. Higher positivity of receptor expression in malignant lesions usually correlates with better differentiation and better survival rates [2, 3].

AIMS & OBJECTIVES

1. To retrieve all the endometrial biopsies and hysterectomy specimens which were diagnosed as hyperplasia and carcinoma?
2. To perform an immunohistochemical study on routinely fixed paraffin embedded endometrial tissue sections of the retrieved cases using monoclonal antibodies for estrogen and progesterone receptors with two step polymer detection method.
3. Semi quantitative scoring system (H SCORES) to analyze the immunohistochemical staining based on percentage of positive cells and staining intensity.
4. Statistical comparision of expression (H SCORES) of steroid hormone receptors (ER and PR) in endometrial hyperplasia, malignancy and normal cyclical endometrium.

METHODOLOGY:

A prospective study was done in the Department of Pathology, SVS Medical College & Hospital, and Mahabubnagar during the period of two years between September 2012 to August 2014. Endometrial tissue was procured from diagnostic curetting and hysterectomy specimens between the age group of 25-70 yrs, with a histological diagnosis of hyperplasia and carcinoma. Normal secretory and proliferative endometrium was also obtained from patients aged
between 30 - 45 yrs served as controls for each batch of immunohistochemical assay.

RESULTS:

A total of 100 cases were evaluated immunohistochemically for Estrogen and Progesterone receptors. These included 39 cases of simple hyperplasia, 5 complex hyperplasias, 5 cases of atypical hyperplasia, and 11 cases of malignancy. The 11 cases of malignancy were subdivided into well-differentiated (5 cases), moderately-differentiated (2 cases) & poorly-differentiated adenocarcinoma (2 cases), 1 case of papillary serous carcinomas and one case of squamous cell carcinoma.

40 cases of normal cyclical endometrium (20 secretory and 20 proliferative) were also studied for the receptor status. Positive staining of both ER and PR was seen as fine granular staining in nuclei of glands and stroma. Staining was scored semi quantitatively taking into consideration both intensity as well as percentage of cells stained in the glands and stroma. A total of 100 cells were counted under oil immersion at hot spot (highest stained area). The positive results were assessed further for intensity of staining, which were graded for scoring and statistical analyses.

H SCORE calculations:

A value was derived for each tissue component consisting of sum of the percentage of positively stained cells multiplied by a weighed intensity of staining for each tissue component. (H SCORE).

Pi is percentage of stained cells at each intensity level and i is intensity (0, 1, 2 and 3). A total tissue H SCORE was calculated as the sum of the component H SCOREs weighed by the fraction of each component observed. H SCORE of 75 or more considered positive. The data obtained was analyzed using SPSS software version 17.0. Appropriate statistical tests were used for comparision. Descriptive results are expressed as mean and SD of various parameters in different groups. Probability value (p value) was used to determine the level of significance p value < 0.05 was considered as significant, p value < 0.01 was considered as highly significant.

Table 1: Comparison of ER staining (H SCORES) between simple hyperplasia (SH) and proliferative endometrium (PE)

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**PE**	**SH**	**PE**
MEAN	284.1	294.5	232.69	315.5
SD	62.5	42.7	72.9	54.3
NO. OF PATIENTS	39	20	39	20
T VALUE	0.752		4.47	
P VALUE	0.152		<0.001	

In our study ER staining was compared between simple hyperplasia & proliferative endometrium and observed that the mean of H- score staining intensity in epithelium of simple hyperplasia was not statistically significant when compared to proliferative endometrium (p>0.05), whereas the mean of H score staining intensity in stroma of proliferative endometrium was significantly more when compared to simple hyperplasia (p<0.05)..001

Table 2: Comparison of ER staining (H SCORES) between simple hyperplasia (SH) and secretory endometrium (SE).

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**PE**	**SH**	**PE**
MEAN	284.1	294.5	232.69	315.5
SD	62.5	42.7	72.9	54.3
NO. OF PATIENTS	39	20	39	20
T VALUE	0.752		4.47	
P VALUE	0.152		<0.001	

In our study ER staining was compared between simple hyperplasia & secretory endometrium. It was observed that the mean of H score staining intensity in epithelium of secretory endometrium was significantly more when compared to simple hyperplasia (p<0.05). The mean of H score staining intensity in stroma of secretory endometrium was

significantly more when compared to simple hyperplasia ($p<0.05$).

Table 3: Comparison of ER staining (H SCORES) between simple hyperplasia (SH) and Adenocarinoma (AC).

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**AC**	**SH**	**AC**
MEAN	284.1	112.2	232.69	81.1
SD	62.5	100.6	72.9	101.9
NO. OF PATIENTS	39	9	39	9
T VALUE	6.19		5.25	
P VALUE	<0.001		<0.001	

In our study ER staining was compared between simple hyperplasia & adenocarcinoma. It was observed that the mean of H score staining intensity in epithelium of adenocarcinoma was significantly less when compared to simple hyperplasia ($p<0.05$). The mean of H score staining intensity in stroma of adenocarcinoma was significantly less when compared to simple hyperplasia ($p<0.05$).

Table 4: Comparison of PR staining (H SCORES) between simple hyperplasia (SH) and Secretory Endometrium (SE)

	EPITHELIUM		**STROMA**	
PR STAINING	**SH**	**PE**	**SH**	**PE**
MEAN	326.9	338.5	276.67	262.6
SD	51.2	39.1	74.3	67.8
NO. OF PATIENTS	39	20	39	20
T VALUE	0.885		0.708	
P VALUE	0.38		0.48	

In the study PR staining was compared between simple hyperplasia & proliferative endometrium. It was observed that the mean of H score staining intensity in epithelium of simple hyperplasia was not statistically significant when compared to proliferative endometrium ($p>0.05$). The mean of H score staining intensity in stroma of proliferative endometrium was not statistically significant when compared to simple hyperplasia ($p>0.05$).

Table 5: Comparison of PR staining (H SCORES) between simple hyperplasia (SH) and Secretory Endometrium (SE)

	EPITHELIUM		**STROMA**	
PR STAINING	**SH**	**SE**	**SH**	**SE**
MEAN	326.9	337	276.67	312.6
SD	51.2	41.8	74.3	59
NO. OF PATIENTS	39	20	39	20
T VALUE	0.758		1.87	
P VALUE	0.45		0.006	

In our study PR staining was compared between simple hyperplasia & secretory endometrium. It was observed that the mean of H score staining intensity in epithelium of simple hyperplasia was not statistically significant when compared to secretory endometrium ($p>0.05$). The mean of H score staining intensity in stroma of secretory endometrium was not statistically significant when compared to simple hyperplasia ($p>0.05$).

Table 6: Comparison of PR staining (H SCORES) between simple hyperplasia (SH) and Adenocarcinoma (AC).

	EPITHELIUM		**STROMA**	
PR STAINING	**SH**	**AC**	**SH**	**AC**
MEAN	326.9	176.6	276.67	135.5
SD	51.2	77.3	74.3	107.25
NO. OF PATIENTS	39	9	39	9
T VALUE	7.17		4.7	
P VALUE	<0.001		<0.001	

In our study PR staining was compared between simple hyperplasia & adeno carcinoma. It was observed that the mean of H score staining intensity in epithelium of simple hyperplasia was significantly more when compared to adenocarcinoma ($p<0.05$). The mean of H score staining intensity in stroma of simple hyperplasia was significantly more when compared to adeno carcinoma ($p<0.05$).

Table 7: Comparison of ER staining (H SCORES) between Simple Hyperplasia and Atypical hyperplasia (AH)

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**AH**	**SH**	**AH**
MEAN	284.1	290	232.69	198
SD	62.5	110.4	72.9	60.1
NO. OF PATIENTS	39	5	39	5
T VALUE	0,181		1.017	
P VALUE	0.857		0.315	

In the present study ER staining was compared between simple hyperplasia & atypical hyperplasia. It was observed that the mean of H score staining intensity in epithelium of atypical hyperplasia was not statistically significant when compared to simple hyperplasia ($p>0.05$).

Table 8: Comparison of ER staining (H SCORES) between simple hyperplasia (SH) and complex hyperplasia (CH)

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**CH**	**SH**	**CH**
MEAN	284.1	286	232.69	197
SD	62.5	83.5	72.9	126
NO. OF PATIENTS	39	5	39	5
T VALUE	0.06		0.94	
P VALUE	0.95		0.35	

In the present study ER staining was compared between simple hyperplasia & complex hyperplasia. It was observed that the mean of H score staining intensity in epithelium of complex hyperplasia was not statistically significant when compared to simple hyperplasia ($p>0.05$). The mean of H score staining intensity in stroma of complex hyperplasia was not statistically significant when compared to simple hyperplasia ($p>0.05$).

Table 9: Comparison of PR staining (H SCORES) between simple hyperplasia (SH) and atypical hyperplasia (AH)

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**AH**	**SH**	**AH**
MEAN	326.9	298	276.67	222
SD	51.2	69.74	74.3	70.85
NO. OF PATIENTS	39	5	39	5
T VALUE	1.14		1.55	
P VALUE	0.259		0.27	

In the present study PR staining was compared between simple hyperplasia & atypical hyperplasia. It was observed that the mean of H score staining intensity in epithelium of simple hyperplasia was not statistically significant when compared to atypical hyperplasia ($p>0.05$). The mean of H score staining intensity in stroma of atypical hyperplasia was not statistically significant when compared to simple hyperplasia ($p>0.05$).

Table 10: Comparison of PR staining (H SCORES) between simple hyperplasia (SH) and complex hyperplasia (CH)

	EPITHELIUM		**STROMA**	
ER STAINING	**SH**	**CH**	**SH**	**CH**
MEAN	284.1	301	276.67	258
SD	62.5	65.03	74.3	74.9
NO. OF PATIENTS	39	5	39	5
T VALUE	1.03		0.528	
P VALUE	0.307		0.6	

In the present study PR staining was compared between simple hyperplasia & complex hyperplasia. It was observed that the mean of H score staining intensity in epithelium of simple hyperplasia was not statistically significant when compared to complex hyperplasia ($p>0.05$). The mean of H score staining intensity in stroma of complex hyperplasia was not statistically significant when compared to simple hyperplasia ($p>0.05$).

DISCUSSION:

Fifty percent of patients undergoing hysterectomy or endometrial biopsy have dysfunctional uterine bleeding. Patients with dysfunctional uterine bleeding have endometrial hyperplasia on histology, which may show altered expression of steroid hormone receptors, suggest that unopposed estrogen effect could have an important role in the pathogenesis of abnormal uterine bleeding. Nuclear localization of steroid hormone receptors such as ER and PR has been observed in the immunohistochemical studies done on normal cyclic human endometrium as well as in hyperplastic and malignancy [4, 5]. Lessey *et al*.; [6] reported that the ER in the proliferative endometrium (PE) was significantly higher than those in the secretory endometrium. Mylonas *et al*.; [5] have suggested that ER and PR declined significantly in glandular epithelium from proliferative to late secretory phase.

The immunohistochemical assay of the ER and PR in our studies shows that their expression levels are similar in both secretory and proliferative endometrium. Steroid hormone receptor pattern observed in normal cyclical endometrium in our studies is similar to results reported on cyclical endometrium in another study done by Bergeron *et al*.; [4]**.** The present study was carried out to understand the steroid hormonal status and evaluate ER alpha and PR contents in hyperplastic endometrium and endometrial adenocarcinoma.

Nyholm *et al*.; [1] and Bergeron *et al*.; [4] reported that ER and PR levels were high in the epithelium of simple and complex hyperplasia (SH and CH) and, low in simple hyperplasia with atypia (SHA) and complex hyperplasia with atypia (CHA) and much lower in adenocarcinoma (AC). Daniela llie *et al*.; [7] stated that ER and PR levels were increased in hyperplastic endometrium both in glands and stroma and low in endometrial carcinoma. In study done by V. Kalyan chakravarthy *et al*.; [8] ER and PR levels were found to be elevated in hyperplasias and carcinoma of endometrium.

Table 11: Summary of comparison of ER staining

Summary of	**Epithelial staining P Value**		**Stromal staining P value**	
comparison	**Student T**		**Student**	
of ER staining	**Test**		**T test**	
SH and PE	**0.152**	**Not significant**	**0.001**	**Significant**
SH and SE	**0.001**	**Significant**	**0.0001**	Highly **Significant**
SH and AC	**0.0001**	**Highly significant**	**0.0001**	**Highly Significant**

Table 12: Summary of comparison of PR staining

Summary of	**Epithelial staining P value**		**Stromal staining P value**	
comparison of	**Student T**		**Student**	
PR staining	**Test**		**T test**	
SH and PE	**0.38**	**Not significant**	**0.48**	**Not Significant**
SH and SE	**0.45**	**Not Significant**	**0.006**	**Significant**
SH and AC	**0.0001**	**Highly Significant**	**0.0001**	**Highly Significant**

In this study, no statistical difference was noted in estrogen and progesterone receptor content in epithelium between Simple hyperplasia versus Proliferative endometrium. Also no statistical difference was seen in the epithelial expression of PR between Simple hyperplasia versus Secretory endometrium but we found significant difference in the expression of ER in the epithelium between these groups. Stromal expression of ER in Simple hyperplasia versus Proliferative endometrium and Simple hyperplasia versus Secretory endometrium was significantly different. In stromal expression of PR no difference was noted in Simple hyperplasia versus Proliferative endometrium but statistical significant difference was noted in Simple hyperplasia versus Secretory endometrium. (Table 7& 8)

In this study, we were able to evaluate only five cases of complex hyperplasias and atypical hyperplasia which have showed low to moderate levels of PR as well as ER in both epithelium and stroma. Statistical comparison was not possible due to limited number of cases in this group. Estrogen receptor alpha and Progesterone receptor were present in Adenocarcinoma and were reported to be at lower levels compared with simple hyperplasia and complex hyperplasia with atypia by Osamu *et al*.; [9]. We also found significantly high levels of ER and PR in Simple hyperplasia in both epithelium and stroma compared to glands and stromal expression in adenocarcinoma. Carcinoma of the endometrium is one neoplasm for which a large array of clinical and pathologic factors have been shown to play significant roles in determining the patient's prognosis. Currently, the steroid hormone receptor status of these neoplasms has been demonstrated to be prognostically important.

The advent of immunohistochemical technique has been widely supported as a useful and a practical method for assessment of protein expression in tissue specimens [10]. Using immunohistochemical techniques, the proportional contribution of each tissue element can be assessed and measured in a semi-quantitative fashion. Semi-quantitative methods of analysis varied in different studies [1, 11-13]. H SCORES system is widely used in breast cancer and in some studies on endometrial carcinoma and hyperplasia. Few studies have compared quantitative levels of ER and PR in cancer component obtained by biochemical assays with levels obtained semi quantitatively using H SCORES of IHA [3, 4]. Since these studies found stronger relationship and better sensitivity with H SCORE system, in the current report we have adopted this method of scoring for the evaluation of ER and PR staining, taking both the intensity and percentage of stained cell at each tissue component into consideration.

Few groups have also analysed the steroid hormone receptor content by immunohistochemical methods in endometrial adenocarcinoma and have demonstrated an inverse correlation between ER / PR status and tumor grade. A study was done on benign and malignant endometrial polyps of post-menopausal women by Armando Antunes *et al*.; results indicated that premalignant and malignant polyps had low ER expression. In our study we analysed ER and PR receptor status in 9 adenocarcinoma cases. In these there were five cases in Grade1, two cases in Grade 2, two cases in Grade 3 subtypes. PR was weakly positive in epithelium of all grade 1 and grade 2 tumors and in one case of grade 3 tumor and in the stroma of all grade 1 tumors and in one case of grade 3 tumor subtypes. PR was negative in stroma of grade 2 subtype.

ER was weakly positive in four of five grade 1 tumors, in both grade 2 tumors and negative grade 3 tumors. Though inverse relation with grade was observed in our study as well, statistical analysis was not possible due to less number of cases in each grade. All the studies which are done to analyse the steroid hormone receptor content, percentage of endometrial adenocarcinoma expressing ER or PR varied in their reports. Percentage of endometrial carcinomas

expressing ER or PR reported by various groups including our study has been shown in Table 13.

Table 13: ER and PR Positivity in endometrial adenocarcinoma reported by different groups

Study	ER	PR
Sopli Kounelis *et al*.; in 2000 [14]	54%	53%
Bozdogan O *et al*.; in 2002 [15]	86%	90%
Michelle R N *et al*.; in 2006[2]	67%	60%
Journal of Medical association Thai 2008	76.9%	72.3%
Brunstein *et al*.; in 1989 [16]	40%	46%
Sivridis E *et al*.; in 2001 [17]	35%	32%
Indu Maniketh *et al*.; in 2014 [18]	73%	84%
Present study	**37.5%**	**88.8%**

Also some studies analysed the steroid receptor content in various histological types of endometrial malignancy [2, 19]. Where they have shown that endometrioid carcinomas express highest level of steroid receptor. According to one study 84% of endometrioid carcinomas of grades 1 and 2 expressed ER compared to 50% of grade 3 of the same, 54% of serous carcinomas, and 9% of clear cell carcinomas expressed ER.

A total of grades 1 and 2 endometrioid carcinomas expressing PR was 83% compared to 42% of grade 3carcinomas, 54% of serous carcinomas. Taking into consideration the intensity of staining, tumors showing the strongest immunoreactivity for ER and PR were endometrioid adenocarcinomas of all FIGO grades. Occasional clear cell carcinomas and serous carcinomas showed strong PR staining. When they showed any expression at all, ER expression was weak or at most moderate in clear cell carcinoma, serous carcinoma [2]. Present study showed mild to moderate immunoreactivity of PR in 9/9 (100%) grade 1 and grade 2 endometrioid carcinomas compared to 1/2 (50%) of grade 3 carcinomas. ER expression in our study were 6/9 (66.6%) and can be explained by limited number of cases and also grade 3 tumors contributed to one fourth of cases and were weakly positive to negative. In other histological types evaluated in our study, papillary serous carcinoma and squamous cell carcinoma showed absolutely no ER and PR expression which is consistent with Gordon M [20] who stated that high grade tumors such as serous, clear cell and squamous carcinoma tend to be negative, with antibodies directed towards ER and PR.

Both ER and PR were found to be related to disease recurrence, reports suggest that ER status, as determined by IHC, can be used as an independent predictor for disease recurrence [6, 9]. However there is still significant disagreement in the literature regarding the prognostic significance of ER and PR status in patients with endometrial adenocarcinoma. The numbers in this study were too small to make a definitive statement on the importance of hormone receptor status in patients with endometrial carcinoma; however, there should be some consideration for using IHC to determine the presence of ER as a prognostic factor in the clinical management of these patients.

Both hyperplasias with or without atypia may regress spontaneously over months or years. However, hyperplasia with atypia is a precancerous condition that may progress to overt malignancy and best treated surgically with hysterectomy. In patients with atypia if conserving the uterus is contemplated, a trial of hormonal treatment may be given. Steroid hormone receptor analysis may play an important role or may be an indication in this group of patients to predict the response to hormonal therapy.

Three cases of hyperplasia with atypia with steroid receptor positivity in our study might have responded well if these patients had opted for hormonal therapy. Immunohistochemical analysis of ER and PR in endometrial hyperplasia and endometrial carcinoma specimens allows a more specific determination of cell receptor content and hence yields a more accurate prediction of response to endocrine therapy. These studies should facilitate the development of rational strategies for prevention and treatment of grave and lethal endometrial disorder. Hyperplasia without atypia is known to regress spontaneously after D & C or progestin treatment. In patients with atypia if conserving the uterus is contemplated, a trial of hormonal treatment may be given. Steroid hormone receptor analysis may play an important role or may be an indication in this group of patients to predict the response to hormonal therapy. Three cases of hyperplasia with atypia with steroid receptor positivity in our study might have responded well if these patients

had opted for hormonal therapy. Immunohistochemical analysis of ER and PR in endometrial hyperplasia and endometrial carcinoma specimens allows a more specific determination of cell receptor content and hence yields a more accurate prediction of response to endocrine therapy. These studies should facilitate the development of rational strategies for prevention and treatment of grave and lethal endometrial disorder.

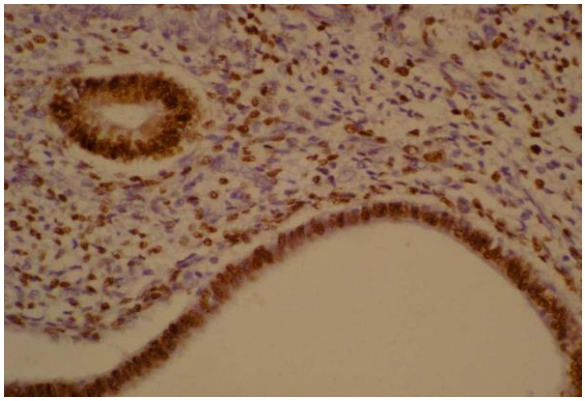

Fig-1: ER staining in simple hyperplasia

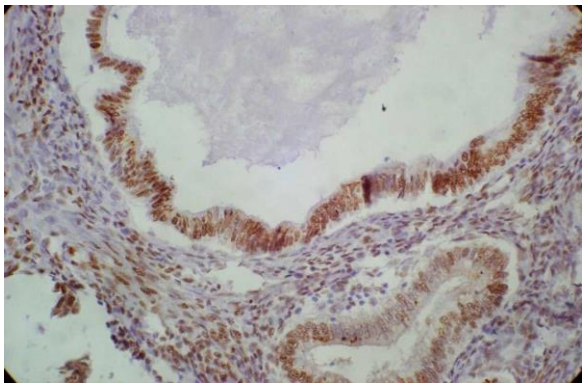

Fig-2:PR staining in simple hyperplasia

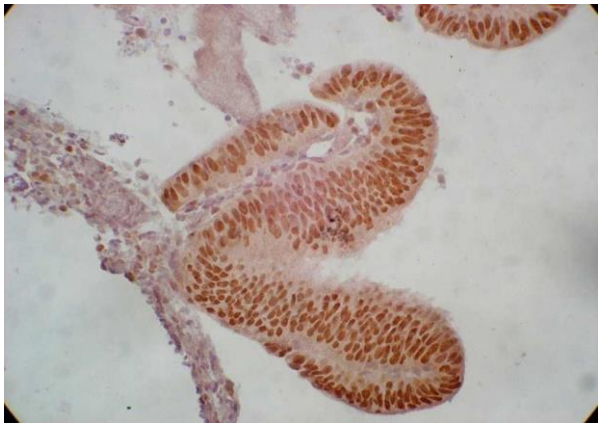

Fig-3:ER staining in complex hyperplasia

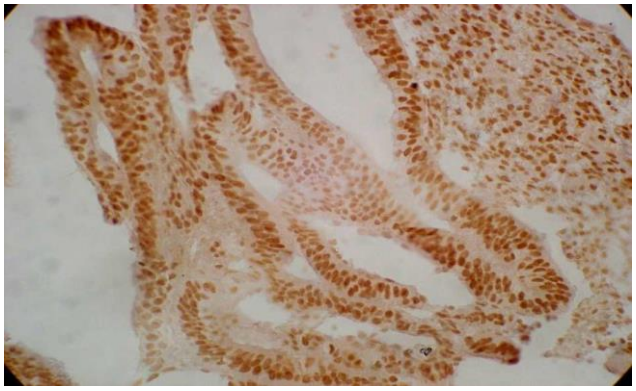

Fig-4: PR staining in complex hyperplasia

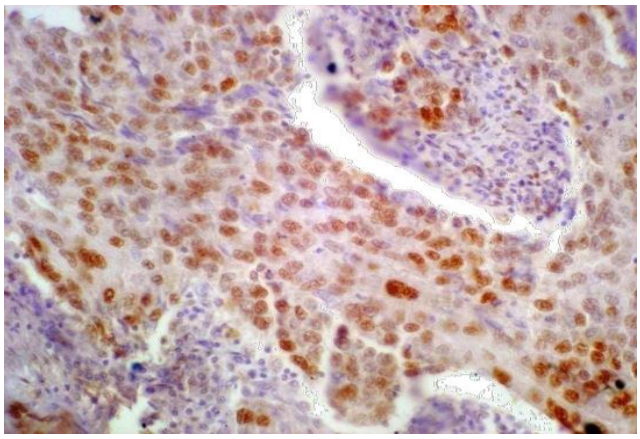

Fig-5: ER staining in adenocarcinoma

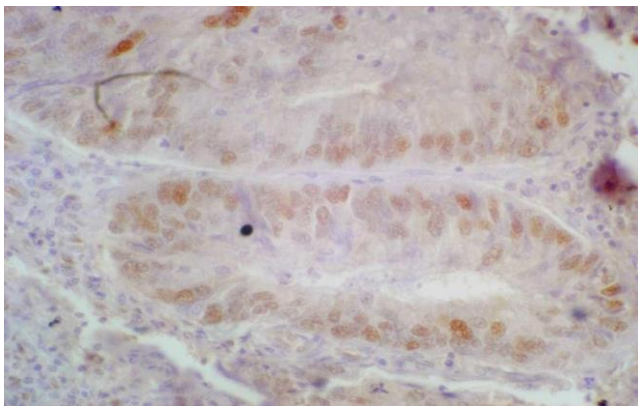

Fig-6:PR staining in adenocarcinoma

CONCLUSION:

Estrogen receptor (ER) and Progesterone receptor (PR) levels are similar in both secretory and proliferative endometrium. There is significant difference in the epithelial and stromal expression of PR between simple hyperplasia and secretory endometrium. High level of ER and PR were found in simple hyperplasia in our study five cases of complex hyperplasias without atypia & atypical hyperplasia (simple & complex) which have showed high levels of progesterone receptor might have responded to hormonal therapy. ER and PR expression was significantly decreased in adenocarcinoma as compared to simple hyperplasia. The immunohistochemical studies of ER and PR in endometrial hyperplasia and/or malignancy and its significance on prognosis and

hormonal therapy are few in the literature compared to studies on breast cancer. Our data will be definitely an important addition to the existing literature.

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