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Original Article

ER and PR Receptor Expression in Cases of Endometrial Hyperplasia and Malignancy

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Abstract

Objectives: The aim of the present study was to evaluate estrogen receptor (ER) and progesterone receptor (PR) expression in the glandular epithelium and stroma of benign and malignant endometrial samples of women in the age group of 30–80 years.

Materials and Methods: A total of 87 females underwent D and C, hysterectomy or endometrial biopsy at the King George's Medical University and T S Misra Medical College and Hospital, Lucknow, were included in the study. Patients with the normal menstrual cycle between 30 and 45 years were included as controls. Patients with pregnancy and those with inadequate sample were excluded from the study. Endometrial lesions were histologically classified as benign lesions (endometrial hyperplasia with or without atypia) and malignant lesions. ER and PR expression was evaluated by immunohistochemistry according to cell staining, intensity of nuclear staining, and final H score was calculated.

Results: Histopathologically lesions were graded as the type of endometrial hyperplasia and the type of carcinoma. The final H score for receptor expression was compared between the non-malignant and malignant lesions. ER and PR expression was higher in non-malignant as compared to the malignant group. ER and PR H scores were calculated separately for the epithelium and stroma and mean H score was calculated for epithelium an stroma. Statistical analysis of H scores was done separately for ER and PR receptor expression in epithelium and stroma of different lesions of non-malignant and malignant group.

Conclusion: ER PR-positive expression and H score is higher in hyperplasia as compared to malignancy.

Key words: Endometrial carcinoma, Endometrial hyperplasia, Estrogen receptor, Progesterone receptor

INTRODUCTION

Endometrium refers to the inner lining of the uterine lumen. It is composed of a number of glands embedded lying in the connective tissue often termed as stroma.[1] In the regular progression of menstrual cycle, the lining of uterus is subject to a pair of steroid hormones, estrogen and progesterone, that exerts an opposing effect on the endometrial glandular epithelium[2-4] are normal and are not considered as any pathological condition and is marked by a normal hormonal profile. However, endometrial hyperplasia, a disordered proliferation of endometrial glands that is considered to be a precursor of endometrial cancer is thought to be resulting from "unopposed estrogenic stimulation of the endometrial tissue with a relative deficiency of the counterbalancing effects of progesterone."[5] Endometrial hyperplasia is characterized by chronic exposure to estrogen coupled with a relative deficiency of progesterone.[6] The progression of endometrial hyperplasia to cytological atypia and finally into endometrial carcinoma is marked by a multitude of clinical, pathological and physiological changes. A number

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of biomarkers viz., "P53, KRAS, PTEN, EGFR, and FGFR, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2, etc." have been shown to have a role in this progression.

In contrast, irregularly in hormone receptor functions can end up in various malignant conditions[7] ER exists in two main isoforms, ER alfa and ER beta. They have a distinct pattern of expression in the tissues[8] which varies during cellular proliferation and differentiation.[9] ER-α binds to estrogens with high affinity and. ER-alfais required for the basic development of estrogen-sensitive tissues. ER-beta inhibits transcription. It is required for the organization and adhesion of epithelial cells and hence for differentiated tissue morphology and its functional maturation.[10] Progesterone (PR) also exists in two isoforms PR alfa and PR-beta modulates the anti-proliferative effects of progesterone in the uterus, i.e., estrogen antagonistic PR beta, induces cell growth and thus plays the role of estrogen agonist.[11] It is well-documented in the literature that "the transcription of PR gene is induced by estrogen and inhibited by progesterone in the majority of estrogen responsive cells, so the expression of ER and PR is considered to be coordinated."[12,13]

Evaluation of estrogen and progesterone receptors plays an important role in the prognosis of endometrial cancer. They are helpful in determining the survival length and function.[14,15] ER/PR positivity helps to determine the need for hormonal treatment for endometrial cancer.[16] Study of ER/PR in pre-cancerous and cancerous conditions also helps to study the tumor biological behavior which determines the subsequent pathways for appropriate treatment strategy formulation[17] Hence, the present study was planned to study the ER and PR receptor expression in cases of endometrial hyperplasia and malignancy using a cross-sectional design.

MATERIALS AND METHODS

It is the prospective cross-sectional study of the 87 cases of the endometrial tissues obtained from diagnostic and curettage and hysterectomy specimens processed for histopathological examination in the laboratory of T S Misra Medical College and Hospital, Lucknow, India, in collaboration with the King George's medical University, Lucknow, from January 1, 2021 to June 30, 2022 (Total duration 1.5 years). The study included 87 histopathologically proven cases of endometrial hyperplasia and malignancy in the age group (30–80 years). However, those cases with normal endometrium (proliferative and secretary) in the age group (30–45 years) were also included in the study as a control for each batch of immunohistochemical assey. Those cases with inadequate sample or with history of pregnancy were excluded from the study. Informed consent was taken from the patients included in the study. All the demographic details, clinical profile, medical, surgical, obstetric, family and personal history were taken from the clinical records and details of investigations and treatment availed was noted. Immunohistochemistry for ER and PR status was done. ER and PR staining reactions was evaluated as brown nuclear staining in the glandular epithelium and stroma of all cases as a positive reactions. Staining was scored semi quantitatively taking into consideration both intensity as well as percentage of cells staining in glands and the stroma and H-score was calculated as Pi(i+1)/100 i=intensity (0,1,2,3) 0-No staining, 1-weak staining, 2-moderate staining, 3-strong staining, Pi=percentage of stained cells (0–100%) of each tissue component (glands and stoma) in each intensity.

RESULTS

Majority of cases (n = 65; 74.7%) were non-malignant. There were 22 (25.3%) malignant cases [Table 1].

Among non-malignant cases, (n = 10; 11.5% 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; 41.4%) followed by simple hyperplasia with atypia (n = 6; 6.9%) and complex hyperplasia without* atypia (n = 3; 3.4%) respectively [Table 1].

Among 22 malignant cases, maximum (n = 19/22; 86.4%) were endometrial adenocarcinoma. There was 1/22 (4.5%) case each diagnosed with endometrial carcinoma villoglandular type, serous endometrial carcinoma, and endometrioid endometrial carcinoma NOS, respectively.

Out of 22 malignant cases, more than three-fourth (77.3%) were low grade/well differentiated, 4 (18.2%) were moderate

Table 1: Distribution of women according to histopathological diagnosis

S. No.	HPE diagnosis	No. of women	Percentage
1	Non-malignant	65	74.7
	Proliferative endometrium	10	15.4
	Secretory endometrium	10	15.4
	Simple hyperplasia without atypia	36	55.4
	Simple hyperplasia with atypia	6	9.2
	Complex hyperplasia with atypia	3	4.6
2	Malignant	22	25.3
	Endometrial adenocarcinoma	19	86.4
	Endometrial carcinoma villoglandular	1	4.5
	Serous endometrial carcinoma	1	4.5
	Endometroid endometrial carcinoma NOS	1	4.5

grade/moderately differentiated, and only 1 (4.5%) was high grade/poorly differentiated carcinoma [Table 2].

Both ER and PR positivity rates were significantly higher in non-malignant as compared to malignant lesions ($P < 0.05$) [Figures 1 and 3 and Table 3].

Overall ER/PR status was both ER/PR positive, ER positive PR negative, and ER negative PR positive in 72.7%, 13.6%, and 13.6% malignant cases, respectively, as compared to 98.5%, 0%, and 1.5% non-malignant cases, respectively. Statistically, there was a significant difference between the two groups with respect to overall ER/PR status ($P < 0.001$) [Figures 1 and 3 and Table 3].

For both epithelium and stroma, mean ER and PR H-scores were significantly higher in non-malignant as compared to malignant lesions ($P < 0.001$) [Figures 2 and 4 and Table 4].

Both ER and PR H-scores in epithelium as well as stroma were maximum in secretory and proliferative endometrium followed by simple hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia. They were minimum in endometrial carcinoma. These trends were significant statistically too ($P < 0.001$) [Table 5].

Table 2: Distribution of cases according to the grade of malignancy (*n*=22)

S. No.	History	No. of women	Percentage
1	Low grade/WD	17	77.3
2	Moderate grade/MD	4	18.2
3	High grade/PD	1	4.5

DISCUSSION

In the past few decades, there has been a high increase in the incidence of endometrial cancer, particularly in developing world, as a result of increasing life-expectancy and changing lifestyle contributing to an increase in obesity which is a recognized risk factor for endometrial cancer.[18,19] In the present study, most of the malignant cases 19/22 (86.5%) were endometroid adenocarcinoma; however, one each (4.5%) was villous, serous, and endometroid carcinoma NOS type. Among malignant cases, 17/22 (77.3%) was low grade, 4/22 (18.2%) moderate grade, and 1/22 (4.5%) high grade. Similar to the present study, Kumari *et al*.[20] also reported a dominance of low grade (66%) but had moderate grade as the least common one (12%). However, in the study by Zidan *et al*.,[21] all the cases were endometrioid carcinoma but representation of all the three grades was much homogenous with Grades 1, 2, and 3 being represented by 38.9%, 27.8%, and 33.3% cases, respectively. Furthermore, it has also been seen in some previous studies that given high value of these markers (ER and PR expression in assessing the treatment response and prognosis, they can also be used successfully for differentiation between endometrial cancer and endometrial hyperplasia (and its different types) successfully and could help to stratify their malignant potential too.[20]

Table 3: ER/PR expression status in malignant and non-malignant specimen

S. No.	Receptor	Status	Malignant (*n*=22)		Non-malignant (*n*=65)		Statistical significance	
			No	%	No	%	χ^2	'P'
1	ER	Positive	19	86.4	64	98.5	5.485	0.019
		Negative	3	13.6	1	1.5		
2	PR	Positive	19	86.4	65	100	9.180	<0.001
		Negative	3	13.6	0	0		
3	Overall ER/PR status							
	ERP PRP		16	72.7	64	98.5	15.28	<0.001
	ERP PRN		3	13.6	0	0		
	ERN PRP		3	13.6	1	1.5		

ER: Estrogen receptor, PR: Progesterone receptor

Table 4: Comparison of ER/PR H-scores in epithelium and stroma between malignant and non-malignant groups

S. No.	Receptor/Source	Malignant (*n*=22)		Non-malignant (*n*=65)		Statistical significance	
		Mean	SD	Mean	SD	't'	'P'
1.	ER						
	Epithelium	1.32	0.50	2.70	0.70	8.506	<0.001
	Stroma	1.23	0.43	2.54	0.70	8.236	<0.001
2.	PR						
	Epithelium	1.35	0.48	2.69	0.68	8.518	<0.001
	Stroma	1.26	0.27	2.65	0.59	10.593	<0.001

ER: Estrogen receptor, PR: Progesterone receptor, SD: Standard deviation

Table 5: Comparison of ER/PR IHC H-scores in epithelium and stroma among different histopathological diagnosis

S. No.	Receptor	HPE diagnosis	Epithelium		Stroma	
			Mean	SD	Mean	SD
1	ER	Proliferative endometrium (*n*=10)	3.14	0.44	3.23	0.29
		Secretory endometrium (*n*=10)	3.01	0.73	2.80	0.74
		Simple hyperplasia (*n*=36)	2.72	0.58	2.51	0.57
		Simple hyperplasia with atypia (*n*=6)	1.87	0.58	1.62	0.26
		Complex hyperplasia with atypia (*n*=3)	1.53	0.06	1.53	0.23
		Endometrial carcinoma (*n*=22)	1.32	0.50	1.23	0.43
		Statistical significance (ANOVA)	F=26.963; *P*<0.001		F=31.471; *P*<0.001	
2	PR	Proliferative endometrium (*n*=10)	2.98	0.29	3.01	0.33
		Secretory endometrium (*n*=10)	2.90	1.04	2.77	0.74
		Simple hyperplasia (*n*=36)	2.69	0.59	2.69	0.51
		Simple hyperplasia with atypia (*n*=6)	2.32	0.54	2.10	0.43
		Complex hyperplasia with atypia (*n*=3)	1.67	0.12	1.63	0.06
		Endometrial carcinoma (*n*=22)	1.35	0.48	1.26	0.27
		Statistical significance (ANOVA)	F=19.281; *P*<0.001		F=35.03; *P*<0.001	

ER: Estrogen receptor, PR: Progesterone receptor, SD: Standard deviation

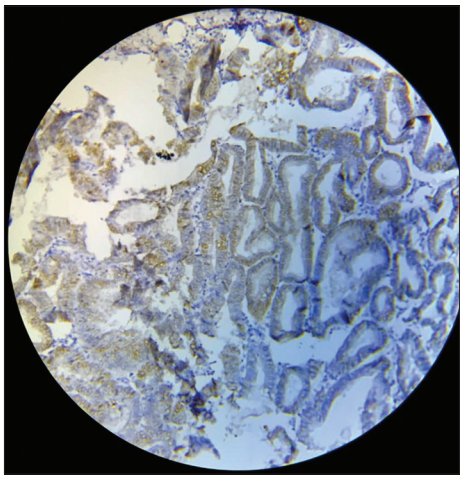

Figure 1: Endometrial hyperplasia without atypia estrogen receptor strong glandular positivity

ER and PR positivity rate in the present study was 98.5% and 100% for non-malignant cases as compared to 86.4% (ER) and 86.4% (PR) for malignant cases. Although Kumari *et al*.[20] too observed the expression of ER/PR to be significantly higher in hyperplasia as compared to malignant cases, in their study, the expression rate for ER and PR was 58% and 76%, respectively, in malignant as compared to 100% and 100%, respectively, in hyperplasia cases. In

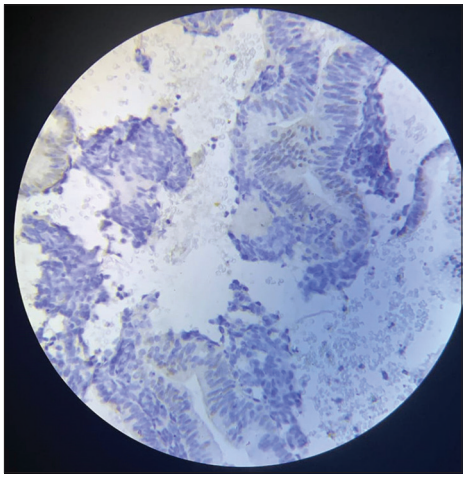

Figure 2: Atypical hyperplasia faint positivity progesterone receptor

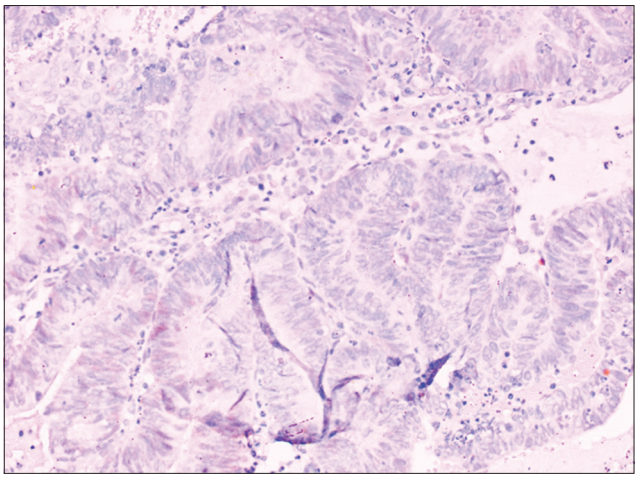

Figure 3: Endometrial CA Endometroid variantrp estrogen receptor (ER) ×20 faint positivity ER

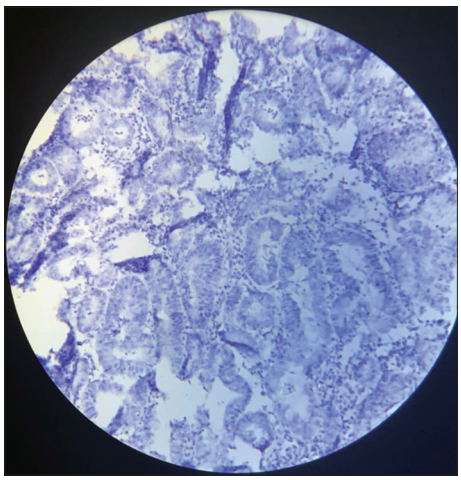

Figure 4: Serous endometrial Ca ×10 negative progesterone receptor

the present study, ER and PR positivity and ER and PR H SCORES in epithelium as well as stroma were higher in

non-malignant as compared to malignant. ER and PR H SCORES in epithelium and stroma, a decreasing trend is found from normal endometrium to complex hyperplasia with atypia, minimum in endometrial carcinoma and these trends were statistically significant too.

Panwar and Gangane[22] (2020) have found PR expression to hold a high discriminatory value with all the hyperplasia cases showing a positive expression as compared to only 50% of endometrial carcinoma. The present study do not find such a high discriminatory value on basis of ER and PR status only. In the present study, we used a semi-quantitative criteria, *i.e.,* H-score that looked beyond just positive or negative status but instead evaluated the expression of PR and ER by unifying the number of cells in which expression was seen and intensity of staining.

This quantitative measure has been used previously by some workers[20,23] and has been found to have a high discriminatory value too. With adaptation of a quantitative criteria like H-score, the discriminatory power of ER and PR expression increases substantially and it is able to serve to our primary purpose of differentiating between endometrial hyperplasia and endometrial carcinoma as well as between simple hyperplasia and hyperplasia with atypia cases effectively. These findings are in accordance with the observations of Kumari *et al.*[20] who also made similar observations. Kaur *et al.* too in their study, despite not using quantitative scores as used in the present study, emphasized that the intensity of expression of ER and PR was helpful in differentiating among histopathological grades of endometrial carcinoma.

CONCLUSION

ER and PR are the important prognostic biomarkers to predict response to the anti hormonal therapy.The findings of the present study showed that ER/PR expression, particularly quantification of their expression was helpful in not only differentiating between endometrial hyperplasia and endometrial carcinoma but also tended to provide further differentiation and characterization of different endometrial lesions. The study had limitation of sample size and disproportionate representation of different pathologies and grades of carcinoma. Further studies with a larger sample size with adequate representation of different pathologies and grades of carcinoma are recommended to highlight the role of ER/PR expression in differentiation between endometrial hyperplasia and different severity grades.

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