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Immunohistochemical Study of ER, PR, Ki67 and p53 in Endometrial Hyperplasia and Endometrial Carcinoma-An Institutional Study

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ABSTRACT

Background: Endometrial hyperplasia (EH) encompasses a range of proliferative endometrial disorders, often linked to unopposed estrogen exposure. Atypical EH is a recognized precursor to endometrial carcinoma (EC). Immunohistochemical (IHC) markers-estrogen receptor (ER), progesterone receptor (PR), p53, and Ki67—are pivotal in assessing tumour biology and guiding management. To evaluate and compare the immunohistochemical expression of ER, PR, Ki67, and p53 in endometrial hyperplasia and endometrial carcinoma and to correlate these markers with histological subtypes, tumour grades, and relevant clinical parameters.

Methods: A prospective observational study was conducted in the Department of Pathology, M.K.C.G. Medical College and Hospital, Berhampur, from June 2022 to June 2024. Thirty-five histologically confirmed cases (16 EH, 19 EC) underwent IHC evaluation for ER, PR, p53, and Ki67. Marker expression was correlated with histological subtype, tumour grade, and clinical parameters.

Results: ER and PR expression were significantly higher in EH than in EC, with lower positivity in high-grade and non-endometrioid carcinomas. Aberrant p53 expression predominated in serous and high-grade ECs. High Ki67 indices indicated increased proliferative activity and tumour aggressiveness. Hormone receptor negativity and elevated Ki67 correlated with advanced FIGO stage and deeper myometrial invasion.

Conclusion: IHC profiling of ER, PR, p53, and Ki67 offers diagnostic and prognostic value in EH and EC. Their expression aids in risk stratification, therapeutic decision-making, and predicting tumour behaviour.

Key-words: Endometrial hyperplasia, Endometrial carcinoma, Estrogen receptor, Immunohistochemistry, Progesterone receptor, p53, Ki67, Prognostic markers

INTRODUCTION

Endometrial hyperplasia (EH) includes a spectrum of proliferative disorders of the endometrial lining, primarily caused by prolonged unopposed estrogen stimulation [1]. It is clinically significant due to its potential to progress to endometrial carcinoma (EC), particularly when atypia is present [2].

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Endometrial carcinoma is one of the most prevalent gynecological malignancies, and early differentiation from its precursor lesions is essential for appropriate therapeutic intervention and prognosis [3].

Histopathological evaluation remains the gold standard for diagnosis, but it often lacks sufficient predictive power regarding disease progression and response to therapy. Hence, immunohistochemical (IHC) profiling has emerged as a valuable adjunct in the diagnostic algorithm. Estrogen receptor (ER) and progesterone receptor (PR) are hormone receptors whose expression reflects hormonal responsiveness and differentiation status of endometrial tissue [4]. The tumour suppressor gene product p53, when aberrantly expressed, indicates

genomic instability and is associated with aggressive histological variants and higher-grade endometrial carcinomas [5]. Ki67, a nuclear antigen expressed in proliferating cells, serves as a reliable marker of cellular proliferation and correlates with tumour aggressiveness and progression [6].

Integrating the expression profiles of these IHC markers with morphological and clinical parameters enhances diagnostic accuracy, assists in distinguishing between different categories of EH and EC, and provides prognostic insights. This is particularly useful in tailoring individualized therapeutic approaches, such as identifying patients who may benefit from hormone therapy.

MATERIALS AND METHODS

Place of study- This prospective observational study was conducted in the Department of Pathology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha. It included 35 histologically confirmed cases, comprising 16 cases of endometrial hyperplasia and 19 cases of endometrial carcinoma.

Paraffin-embedded tissue sections were subjected to immunohistochemical staining for ER, PR, p53, and Ki-67 [5]. The intensity and proportion of positively stained nuclei were recorded. Hyperplasia was categorized as non-atypical or atypical. Carcinomas were graded into grades 1 to 3 based on architectural and nuclear features [6].

Inclusion Criteria- All endometrial biopsy and hysterectomy specimens with features of EH or EC received in the department during the study period.

Exclusion Criteria

- Cases without valid patient consent.
- Specimens not received in formalin.
- Inadequate tissue samples unsuitable for IHC analysis.

Tissue Fixation and Processing- Tissues were fixed in 10% neutral buffered formalin (NBF) within 30 minutes of collection and processed after 12–24 hours of fixation. All specimens were processed using an automated tissue processor (Leica STP 120) and then embedded in paraffin. Sections of 4–5 µm thickness were prepared using a Leica semi-automated microtome (RM2245) and mounted on poly-L-lysine–coated slides.

Histological Staining- Routine hematoxylin and eosin (H&E) staining was performed to evaluate morphological features. The staining protocol followed standard steps of deparaffinization, hydration, nuclear staining with Harris hematoxylin, differentiation, bluing, counterstaining with eosin, dehydration, clearing, and mounting.

Immunohistochemistry (IHC)- Sections were subjected to antigen retrieval using heat-induced epitope retrieval in a pressure cooker with retrieval buffer (pH 8.5–9.0). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide. Primary antibodies for ER, PR, p53, and Ki-67 were applied under humid conditions and incubated for 20 minutes, followed by the application of secondary antibodies. Visualization was achieved using DAB chromogen. Slides were counterstained, dehydrated, and mounted for interpretation. IHC results were evaluated based on the percentage of positively stained nuclei and intensity, and were interpreted according to the College of American Pathologists (CAP) guidelines.

Statistical Analysis- Data were compiled in Microsoft Excel and analysed using SPSS version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize demographic and clinical variables. The Chi-square test or Fisher's exact test was applied to assess the association between IHC marker expression and clinicopathological parameters. A p-value < 0.05 was considered statistically significant.

Ethical Approval- Approval for the study was obtained from the Institutional Ethics Committee of M.K.C.G. Medical College & Hospital, Berhampur, Odisha. The Institutional Ethics Committee has approved this study vide No. 1385, Dt. 27.12.2022.

RESULTS

Fig. 1 illustrates the graphical representation of age distribution among the study subjects. The highest number of cases was seen in the 50–59 age group, followed by those aged 60 and above. This trend is consistent with the epidemiological understanding that endometrial abnormalities commonly arise during perimenopause and postmenopause.

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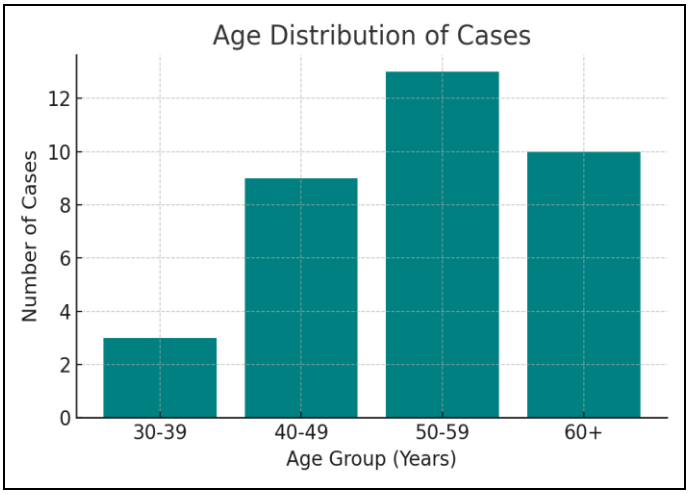

Fig. 1: Age Distribution of Cases

Table 1 compares the age-wise distribution of all 35 cases included in the study. Most patients were in the 50–59-year age group, followed by those aged 60 years and above. This pattern reflects the perimenopausal and postmenopausal hormonal shifts that contribute to endometrial pathology. A lower number of cases were reported in younger age groups, indicating reduced incidence in reproductive years. This distribution is crucial for understanding the demographic profile of patients at highest risk.

Table 1: Age Distribution of Cases

Age Group (Years)	Number of Cases	Percentage (%)
30-39	3	8.57
40-49	9	25.71
50-59	13	37.14
60+	10	28.57
Total	35	100

Table 2 summarizes the clinical complaints observed among the study population. Abnormal uterine bleeding was the predominant presenting symptom, particularly in hyperplasia cases, whereas postmenopausal bleeding was more frequent in carcinoma cases. A small number of patients presented with pelvic pain, while others were detected incidentally. The symptom profile varied based on lesion type and patient age. These findings emphasize the diagnostic value of early symptom recognition in endometrial diseases.

Table 2: Presenting Complaints

Complaint	Number of Cases	Percentage (%)
Abnormal Uterine Bleeding	20	57.14
Postmenopausal Bleeding	9	25.71
Pelvic Pain	4	11.43
Incidental Finding	2	5.71

Table 3 provides a detailed classification of endometrial lesions based on histopathological findings. The cases were grouped into non-atypical hyperplasia, atypical hyperplasia, and endometrial carcinoma (grades 1, 2, and 3). The distribution highlights the spectrum of disease progression from benign hyperplastic changes to malignant transformation. Notably, atypical hyperplasia and grade 1 carcinoma formed a substantial portion, supporting their transitional nature.

Table 3: Distribution of Endometrial Hyperplasia and Carcinoma

Lesion Types	Number of Cases	Percentage (%)
Endometrial Hyperplasia (non-atypical)	10	28.57
Endometrial Hyperplasia (atypical)	6	17.14
Endometrial Carcinoma (Grade 1)	7	20.00
Carcinoma (Grade 2)	6	17.14
Carcinoma (Grade 3)	6	17.14

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Table 4 compares the immunohistochemical expression of ER, PR, p53, and Ki-67 between endometrial hyperplasia and carcinoma. Hormone receptor (ER and PR) positivity was higher in hyperplastic lesions, whereas aberrant p53 expression and high Ki-67 index were significantly associated with carcinoma cases. These distinct expression patterns help differentiate benign from malignant endometrial changes.

Table 4: Comparison of ER, PR, p53 and Ki-67 Expression

Marker	Hyperplasia Positive (%)	Carcinoma Positive (%)
ER	94	58
PR	88	47
p53	0	32
Ki-67	12	38

Table 5 illustrates the relationship between tumour grade and immunohistochemical marker expression in endometrial carcinoma. A declining trend in ER and PR expression was observed from grade 1 to grade 3 tumours, suggesting a loss of hormonal responsiveness in higher grades. Conversely, p53 aberration and Ki-67 index showed a progressive increase, indicating greater proliferative activity and genomic instability. These marker-grade correlations are essential for prognosis and individualized treatment planning.

Table 5: Comparison of Marker Expression with Carcinoma Grades

Grade	ER Positive (%)	PR Positive (%)	p53 Aberrant (%)	Ki-67 Mean (%)
Grade 1	71	71	14	28
Grade 2	50	33	33	39
Grade 3	33	17	50	52

Table 6 presents the mean Ki-67 proliferation index across various endometrial lesions, showing a stepwise rise from non-atypical hyperplasia to high-grade carcinoma. Intermediate values in atypical hyperplasia and low-grade carcinoma support the continuum model of endometrial neoplasia. These findings highlight Ki-67 as a useful marker for tumour proliferation and prognostic assessment.

Table 6: Ki-67 Index in Various Lesions of Endometrium

Lesion	Mean Ki-67 Index (%)
Non-atypical Hyperplasia	8
Atypical Hyperplasia	18
Endometrial Carcinoma (Low Grade)	32
Endometrial Carcinoma (High Grade)	56

DISCUSSION

This study investigates the diagnostic and prognostic value of immunohistochemical markers—ER, PR, p53, and Ki-67—in endometrial hyperplasia and endometrial carcinoma. The age distribution showed that most patients belonged to the perimenopausal and postmenopausal groups, especially those between 50–59 years old, which corresponds with the hormonal transition phase known to influence endometrial proliferation [7]. The age trend also reflects findings from earlier population-based studies that identify this demographic as being at higher risk for both hyperplastic and neoplastic endometrial changes [8].

Among the 35 cases evaluated, the histopathological spectrum ranged from non-atypical hyperplasia to grade 3 endometrial carcinomas, highlighting the continuum of endometrial pathology. Atypical hyperplasia and grade 1 carcinoma, while distinct, share overlapping morphological and proliferative features, supporting the concept of endometrial intraepithelial neoplasia as a precursor lesion [9]. These groupings were key in analyzing biomarker expression patterns across lesion types and tumour grades.

Hormone receptor expression (ER and PR) was significantly higher in hyperplastic lesions and gradually declined in carcinomas, especially in higher-grade tumours. These findings are consistent with prior reports that associate ER/PR negativity with tumour dedifferentiation and poor hormone responsiveness [10,11]. The inverse relationship between ER/PR levels and tumour grade supports their utility in identifying low-

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grade carcinomas that may respond to progestin therapy. Studies have also shown that hormone receptor status may serve as an independent predictor of clinical outcome in endometrial carcinoma [12].

Aberrant p53 expression was observed exclusively in carcinoma cases, particularly among high-grade tumours, further emphasizing its association with genomic instability and tumour aggression. Previous literature has established that p53 mutation is strongly correlated with serous-type and high-grade endometrial carcinoma subtypes [13]. In our cases, increasing tumour grade corresponded with a higher percentage of p53 aberration, reinforcing its role as a poor prognostic indicator [14].

The Ki-67 index increased progressively from hyperplasia to carcinoma and was highest in high-grade carcinomas. This trend highlights the rising proliferative activity associated with neoplastic transformation. The stepwise increase in Ki-67 across lesion categories suggests its value in differentiating benign from malignant endometrial conditions and in gauging tumour aggression [15]. Several studies have validated Ki-67 as a surrogate marker for tumour growth, disease progression, and recurrence risk, particularly in early-stage carcinomas [16].

Together, the combined evaluation of ER, PR, p53, and Ki-67 provides a reliable framework for distinguishing hyperplasia from carcinoma, estimating tumour grade, and predicting prognosis. The expression patterns summarised in this study closely align with previously established immunohistochemistry (IHC)-based algorithms for endometrial pathology. This approach is particularly valuable in resource-limited settings where molecular profiling is not routinely available. Marker profiling not only enhances diagnostic precision but also supports individualized therapeutic planning, especially for cases at risk of progression or recurrence.

CONCLUSIONS

This study highlights the diagnostic and prognostic relevance of immunohistochemical markers—ER, PR, p53, and Ki-67—in endometrial hyperplasia and carcinoma. A progressive decline in ER and PR expression was observed from hyperplasia to high-grade carcinoma, indicating reduced hormonal responsiveness with disease advancement. Conversely, p53 aberration and elevated Ki-67 index correlated with high-grade, aggressive tumours, reflecting greater proliferative potential. These expression profiles aid in distinguishing benign from malignant lesions, grading tumours, and informing clinical decisions regarding hormone therapy and surgical management. Integrating these markers into routine histopathological evaluation enhances diagnostic accuracy, risk stratification, and treatment planning, particularly in settings where molecular diagnostics are unavailable. Their routine use can significantly enhance early detection and management outcomes in endometrial pathology.

Future studies should explore molecular correlations and validate marker thresholds in larger, multicentric cohorts to refine prognostic algorithms.

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