Original Article

Morphological Evaluation of the Endometrial Hyperplasia and Carcinoma with Overexpression of HE4

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Abstract

Objective: To determine endometrial carcinoma in our population and the significance of HE4 expression in malignant and normal endometrial tissue.

Methodology: This study was carried out in The Department of Pathology, Basic Medical Sciences Institute, Jinnah Post Graduate Medical Centre, Karachi from January 2014 to December 2020. Total of 330 endometrial cases were received over a period of seven years, out of which 103 cases of endometrial specimen were selected and analyzed for HE4 immuno-expression by immunohistochemistry.

Results: Out of 330 endometrial lesions, 103 were selected for immunostaining, with an average age of 44.27 ± 13.07 years. The most common finding was well-differentiated endometrioid adenocarcinoma (35.9%), followed by moderately (3.9%) and poorly differentiated (4.9%) endometrioid adenocarcinoma. Hyperplasia without atypia was present in 10.7% of cases, and hyperplasia with atypia in 7.8%. Normal endometrial phases included secretory phase endometrium (17.5%) and proliferative phase endometrium (19.4%). Endometrioid adenocarcinoma exhibited the highest intensity of HE4 expression (3+) in 37.9% of cases and the highest extent (19.4% at level 3 and 10.7% at level 4). Hyperplasia without atypia and other lesions showed lower HE4 intensity and extent, with significant differences (p=0.001). Strong positive HE4 expression was found in 83.3% of endometrioid adenocarcinoma cases, compared to lower levels in hyperplasia and normal endometrial phases.

Conclusion: Study revealed that the HE4 is a significant tissue biomarker, with strong immunointensity correlating with abnormal cellular proliferation, invasion, and tumor progression. Its expression levels may serve as a valuable predictor for evaluating the clinical behavior of endometrial tumors.

Keywords: Endometrium, Malignancy, HE4 expression, Immunohistochemistry.

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Introduction

Endometrial cancer is the 6th most common cancer of the female genital tract[1] and the 15th most common cancer in women worldwide. It is an epithelial malignancy originating from the uterine lining, ranking among the three most common cancers in women, alongside cervical and ovarian cancer, and represents 20–30% of all gynecologic malignancies.[2] The incidence and mortality rates of endometrial cancer have increased due to factors such as rising diabetes, hypertension, obesity, hypertension, and longer life expectancy, with a trend toward earlier onset in younger individuals.[3] Incidence of endometrial cancer (EC) varies significantly between industrialized and developing nations. In developed countries, EC is one of the most common gynecological malignancies, accounting for an estimated 20-30% of female cancers.[4] However, projected estimates are alarming which reveal an increase by more than 50% worldwide by 2040.[5] Incidence rate is highest in North America and Western Europe as compared to South Central Asia and Africa.[6] In Singapore this cancer emerged 19.1 per 100000 women. In Pakistan the number of uterine malignancies reported cases is 2881 and ranks 17th (1.7%) as of (2018). Shaukat Khanum Cancer

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Registry (2017) documented that cancers of corpus uteri and uterus were among 4th common malignancies comprising 3.7% of all tumors in females above 18 years of age. Total 111 uterine malignancies were reported out of which 64 were Endometrioid adenocarcinomas. According to American Cancer Society Endometrial Carcinoma is mostly encountered in post-menopausal females with a mean age of 60 years and uncommon below the age of 45 years.

According to a study conducted in Pakistan, 15% of endometrial cancers occur in women younger than 40 years of age with the mean age of 53.7 years. Endometrioid adenocarcinoma is more common than other endometrial cancer in women with the age ranging from 36 - 67 years. It is also more common in post-menopausal females7[5] Predisposing factors include obesity, hypertension, diabetes mellitus, nulli-parity, infertility, polycystic ovarian syndrome, unopposed estrogen therapy, estrogen producing tumors, Endometrial hyperplasia, early menarche, late menopause, breast cancer taking Tamoxifen, Lynch syndrome and hereditary non polyposis colon.[8] Type one tumors of endometrium carcinoma are more common and are estrogen dependent, predominantly endometrioid adenocarcinomas usually arising from precursor endometrial hyperplasia.

To enhance the prognosis and overall survival of EC patients, it is crucial to increase the rate of early diagnosis.[2] Several radiological technique and pathological biopsy remains the gold standard for diagnosing EC, with diagnostic curettage and hysteroscopic biopsy being the most commonly used procedures, both relying on histological findings for their diagnostic accuracy. However, the approaches has certain complications and invasive and often poorly tolerated by patients.[2] So far, several biomarkers for EC, including relative telomere length in cell-free DNA and CA125, have been identified.[2,9,10]

Serum HE4 is currently approved for diagnosing and monitoring ovarian cancer recurrence.[11] Growing interest surrounds its potential as a biomarker for endometrial cancer (EC), given that it is overexpressed in over 90% of EC cases. HE4 has shown higher sensitivity and specificity than serum cancer antigen 125 (CA125) in detecting EC and has been linked to histopathological indicators of disease severity, patient survival, and recurrence.[11] This makes HE4 a promising non-invasive biomarker for EC.[11,12] It is a member of the four WAP gene family.[13] Immunohistochemical analysis of HE4 in endometrial tissue samples showed that HE4 expression levels were higher in cases of endometrial hyperplasia compared to normal controls but lower than those observed in endometrial cancer patients.[13,14] Although this study aimed to assess the significance of HE4 expression in differentiating between malignant and normal endometrial tissues in our population to improve non-invasive diagnostic accuracy, enhance management methods, and potentially achieve better outcomes for individuals with endometrial carcinoma.

Methodology

This cross-sectional study was conducted at the Department of Pathology, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC), Karachi. The study involved histopathological analysis of endometrial specimens, including both curettage and hysterectomy samples received at the Department of Pathology, BMSI, JPMC, Karachi, over a period of three years from January 2017 to December 2020. A total of 103 diagnosed cases were selected for immunohistochemistry to evaluate and analyze HE4 expression. The limited number of cases was due to constraints related to the available staining kit and financial limitations. Formalin-fixed, paraffin-embedded specimens of normal endometrium, hyperplasia, and carcinoma received during the study period were included. Specimens with poor fixation, inadequate material, uterine fibroids, or other uterine diseases were excluded. Relevant clinical information and data were recorded on a designated proforma. Tissue sections were stained with Hematoxylin and Eosin (H&E) and immunohistochemical staining for HE4 was performed using a monoclonal rabbit antibody against HE4. All slides were examined under a light microscope using scanner (4X), low power (10X), and high power (40X) lenses in the presence of a supervisor.

Methods of Staining

Hematoxylin and Eosin

The sections were passed throught different solutions as follows:

- Xyline I for 10 minutes
- Xyline II for 10 minutes
- Absolute alcohol for five minutes
- 95% alcohol for five minutes
- 80% alcohol for five minutes
- 70% alcohal for five minutes

- Rinsed in tap water for two minutes
- Hematoxyline for five – 10 minutes
- Acid alcohal 1% 3 – 5 dips0only and then rinse in tap water for 10 – 15 minutes
- Ammonia water 3-5 quick dips only and then rinse in the tap water for 10 -15 minutes
- Eosin for 2 minutes
- 70% Alcohol five quick dips
- 80% alcohol five quick dips
- 95% alcohol five quick dips
- Absolute alcohol two changes five quick dips
- Xyline two changes for five mintes each
- Mount in DPX

Interpretation of Immune Reactivity

- HE4 expression was considered positive only if cell membrane and cytoplasm staining was present.
- The intensity of staining was graded as using Allred scoring system.
- 0 or unstained (negative)
- + Light yellow (weak staining)
- ++ yellow brown (moderate staining)
- +++ brown (Strong staining)
- The extent of staining was based on number of stained positive cells in most of the examined fields and scored as follows:
- <5% recorded as 0 for no positively stained cells
- 5% - 25% as 1
- 21% - 50% as 2
- 51% -75% as 3
- >75% as 4
- The final score was equal to the multiplication of the two scores
- 0-2 score is considered as negative, category 1.
- 3-4 score as weakly positive, category 11.
- 5-12 score as strongly positive. (2+/3+), category 111

All of the information was collected via study proforma and analyzed using SPSS version 26.

Results

Of total of 330 endometrial lesions 103 were selected for immuno-staining. The majority of cases were between 41-50 years (30.1%), with a mean age of 44.27 ± 13.07 years. On the distribution of various endometrial lesions and normal endometrial tissues among 103 cases, the most common lesion was well-differentiated endometrioid adenocarcinoma, which accounted for 37 cases (35.9%). Moderately differentiated endometrioid adenocarcinoma was observed in 4 cases (3.9%), while poorly differentiated endometrioid adenocarcinoma occurred in 5 cases (4.9%). Hyperplasia without atypia was found in 11 cases (10.7%), and hyperplasia with atypia in 8 cases (7.8%). Among the normal endometrial phases, the secretory phase endometrium was noted in 18 cases (17.5%), and the proliferative phase endometrium was seen in 20 cases (19.4%). Table I

Table I: Frequency of endometrial Lesions and Normal Endometria. (n=103)

Variables		N	%
Endometrioid adenocarcinoma	Well differentiated	37	35.9%
	Moderately differentiated	4	3.9%
	Poorly differentiated	5	4.9%
Hyperplasia without atypia		11	10.7%
Hyperplasia with atypia		8	7.8%
Secretory phase endometrium		18	17.5%
Proliferative phase endometrium		20	19.4%
Total		103	100.0%

Endometrioid adenocarcinoma showed the highest intensity (3+) in 39 cases (37.9%), while lower intensities (1+ and 2+) were more frequently observed in hyperplasia without atypia and proliferative phase endometrium. The extent of HE4 expression (measured per 100 cells) was highest for endometrioid

Table II: HE4 Immunohistochemistry in Endometrial Lesion and Normal Endometria in Term of Extent and Intensity. (n=103)

Intensity	ENDOMETRIAL LESIONS AND NORMAL ENDOMETRIUM					p-value
	Endometroid adenocarcinoma	Hyperplasia without atypia	Hyperplasia with atypia	Secretory phase endometrium	Proliferative phase endometrium	
0	0 (0.0%)	2(1.9%)	0(0.0%)	4(3.9%)	1	0.001
1+	1(1.0%)	3(2.9%)	0(0.0%)	4(3.9%)	7(6.8%)	
2+	6(5.8%)	4(3.9%)	3(2.9%)	8(7.8%)	11(10.7%)	
3+	39(37.9%)	2(1.9%)	5(4.9%)	2(1.9%)	1(1.0%)	
Total	46(44.7%)	11(10.7%)	8(7.8%)	18(17.5%)	20(19.4%)	
Extent/100 cells						
0	0(0.0%)	4(3.9%)	0(0.0%)	4(3.9%)	4(3.9%)	0.001
1	0(0.0%)	2(1.9%)	1(1.0%)	8(7.8%)	12(11.7%)	
2	15(14.6%)	2(1.9%)	5(4.9%)	6(5.8%)	4(3.9%)	
3	20(19.4%)	3(2.9%)	2(1.9%)	0(0.0%)	0(0.0%)	
4	11(10.7%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
Total	46(44.7%)	11(10.7%)	8(7.8%)	18(17.5%)	20(19.4%)	

adenocarcinoma, with 20 cases (19.4%) at an extent level of 3 and 11 cases (10.7%) at level 4. Although hyperplasia without atypia and other lesions displayed lower levels of both intensity and extent of HE4 expression with significant differences (p= 0.001). Table II

Endometrioid adenocarcinoma showed strong positive HE4 expression in 83.3% of cases, with a significant difference (p = 0.001). Hyperplasia without atypia was mainly negative or weakly positive, while hyperplasia with atypia had 75% strong positive expression. The secretory and proliferative phase endometria were mostly negative or weakly positive, reflecting lower HE4 expression compared to endometrial lesions. Table III

statistically significant (p = 0.039), but differences in intensity were not (p = 0.897) as shown in table IV

Discussion

Endometrial carcinoma (EC) is the most prevalent gynecological cancer. Over the past 30 years, its incidence has surged by 55%.In view of its common prevalence an effort has been made by this study to estimate the frequency of endometrial carcinoma among women of our population by analyzing the specimen receipt at the Department of Pathology, BMSI, Jinnah Postgraduate Medical Centre, Karachi.

An attempt was also made to appraise the immunohisto-chemical expression of HE4 in selected

Table III: Comparison of Cumulative Index (IHC Scoring) of HE4 Expression in Endometrial Lesions and Normal Endometria. (n=103)

Endometrial lesions and Normal endometrium	Cumulative index			Total	p-value
	Category-I (0-2) Negative	Category-II (3 -4) Weak Positive	Category-III (5-12) Strong Positive		
Endometroid adenocarcinoma	1(2.6%)	0(0.0%)	45(83.3%)	46(44.7%)	0.001
Hyperplasia without atypia	5(13.2%)	5(45.5%)	1(1.9%)	11(10.7%)	
Hyperplasia with atypia	0(0.0%)	2(18.2%)	6(11.1%)	8(7.8%)	
Secretory phase endometrium	15(39.5%)	2(18.2%)	1(1.9%)	18(17.5%)	
Proliferative phase endometrium	17(44.7%)	2(18.2%)	1(1.9%)	20(19.4%)	
Total	38(100.0%)	11(100.0%)	54(100.0%)	103(100.0%)	

In 46 cases of endometrioid adenocarcinoma, Grade I tumors predominantly showed strong positive HE4 staining intensity (3+) in 67.4% of cases, while Grade II and III tumors each had 8.7% with strong intensity. Grade I also had the highest staining extent (34.8% at level 3). The differences in staining extent were

Table IV: Intensity And Extent of He4 Immunostaining in Different Grades Of Endometrioid Adenocarcinoma. (n=46)

Intensity	HISTOLOGICAL GRADES			P value
	Grade-I	Grade-II	Grade-III	
1+	1	0	0	0.897
	2.2%	0.0%	0.0%	
2+	5	0	1	
	10.9%	0.0%	2.2%	
3+	31	4	4	
	67.4%	8.7%	8.7%	
Total	37	4	5	
	67.4%	8.7%	8.7%	
Extent/100 cells				
2	15	0	0	0.039
	32.6%	0.0%	0.0%	
3	16	1	3	
	34.8%	2.2%	6.5%	
4	6	3	2	
	13.0%	6.5%	4.3%	
Total	37	4	5	
	80.4%	8.7%	10.9%	

cases of normal phase endometrium, hyperplasia with and without atypia and endometrial carcinoma. Moreover, to the best of my knowledge the current study is the first to demonstrate the expression of HE4 in endometrial carcinoma in our population. In this study, out of 330 endometrial lesions, 103 were selected for immunostaining. The majority of cases were in the 41-50 age group (30.1%), with a mean age of 44.27 ± 13.07 years. In aligns to these findings Agarwal S et al[15] reported that the 73 were between 40 and 70 years old, with an average age of 54 years at the time of endometrial cancer diagnosis. However, Wasim T et al[16] reported some higher average age compared to this study as 58± 12.32 years of women with endometrial cancer in their 5 years systemic review. Furthermore, in this study among the 103 cases, the most common lesion was well-differentiated endometrioid adenocarcinoma, comprising 37 cases (35.9%). Moderately differentiated endometrioid adenocarcinoma was found in 4 cases (3.9%), and poorly differentiated endometrioid adenocarcinoma in 5 cases (4.9%). Hyperplasia without atypia was present in 11 cases (10.7%), and hyperplasia with atypia in 8 cases (7.8%). For normal endometrial phases, secretory phase endometrium was noted in 18 cases

(17.5%), and proliferative phase endometrium in 20 cases (19.4%). Similar findings were reported in Lahore, Pakistan by Tanvir I et al[15] who observed that 80% of cases were adenocarcinomas. Rashid et al.[7] and Pellerin GP et al[16] reported that well-differentiated endometrioid adenocarcinoma was observed in approximately 65.71% and 52.6% of cases, respectively. However, Pellerin GP et al also noted that 26.3% of their cases were moderately differentiated, and 21.1% were poorly differentiated endometrioid adenocarcinoma.[16] Some above findings differ from our study, which may be attributed to the difference in sample size of the studies and their sample selection criteria.

The focus of this study was to investigate the differential expression of HE4 in normal, hyperplastic, and malignant endometrial tissues. Out of 103 cases, 46 were identified as endometrioid adenocarcinoma. Of these, 37 cases were classified as well-differentiated endometrioid adenocarcinoma, which included three cases with squamoid differentiation and one with Villous Glandular type. Additionally, the study included four cases of moderately differentiated carcinoma and five cases of poorly differentiated carcinoma. The remaining cases consisted of twenty cases of proliferative phase endometrium, eighteen cases of secretory phase endometrium, eleven cases of hyperplasia without atypia, and eight cases of hyperplasia with atypia

In this study endometrioid adenocarcinoma showed strong positive HE4 expression in 83.3% of cases, with a significant difference (p = 0.001). Hyperplasia without atypia was mainly negative or weakly positive, while hyperplasia with atypia had 75% strong positive expression. The secretory and proliferative phase endometria were mostly negative or weakly positive, reflecting lower HE4 expression compared to endometrial lesions. Furthermore in 46 cases of endometrioid adenocarcinoma, Grade I tumors predominantly showed strong positive HE4 staining intensity (3+) in 67.4% of cases, while Grade II and III tumors each had 8.7% with strong intensity. Grade I also had the highest staining extent (34.8% at level 3).

The differences in staining extent were statistically significant (p = 0.039), but differences in intensity were not (p = 0.897). In aligns to this series, study by Das S et al[13] revealed that HE4 expression was strongly positive in cases of endometrial carcinoma, weakly positive in atypical endometrial hyperplasia, and negative in endometrial hyperplasia without atypia. Specifically, endometrioid adenocarcinoma classified as WHO grade 3 (50%) and grade 2 (29%) demonstrated strong HE4 positivity, with this result being statistically significant (p-value = 0.001). Recent research indicating that HE4-related gene overexpression is associated with increased malignant behaviors such as cell adhesion, invasion, and proliferation supports these findings. Furthermore, they observed strong HE4 positivity across all endometrial carcinoma groups, particularly at higher WHO grades. This suggests that HE4 could be a promising therapeutic target for advanced-stage endometrial carcinoma, warranting further investigation.[13] Deng et al[19] reported HE4 immunoreactivity at 48.8%, while the current study identified only one case of G1 endometrioid adenocarcinoma with complete absence of HE4 reactivity. Our findings are consistent with those of Drapkin et al.[20] However, there is limited literature addressing tumors with negative HE4 immunoreactivity, suggesting that other genetic or molecular mechanisms might be involved in these cases. Huiyu et al[21] found HE4 positivity in 93.33% of poorly differentiated ovarian cancers. Our findings were also supported by et al[23] where they reported that the endometrial endometrioid carcinoma showed considerably higher levels of HE4 overexpression compared to endometrial hyperplasia and non-atypical endometrium hypertrophy ($p < 0.05$).

Whereas 20% of atypical endometrial hyperplasia cases had high HE4 expression, there was no significant difference between atypical hyperplasia and endometrial cancer. Furthermore, HE4 overexpression demonstrated a statistically significant positive connection with FIGO grading and myometrium invasion depth.[23]

Conclusion

Endometrial adenocarcinoma was observed in 43.8% of cases and emerged as the most prevalent endometrial malignancy, with peak incidence occurring in the 6th to 7th decades of life. The study also revealed that HE4 is a significant tissue biomarker, with strong immunointensity correlated with abnormal cellular proliferation, invasion, and tumor progression. Its expression levels may serve as a valuable predictor for evaluating the clinical behavior of endometrial tumors. The study has several limitations, including a smaller sample size due to financial constraints, and a lack of correlation with patient prognosis and recurrence history due to insufficient follow-up and

patient awareness. Future research with larger sample sizes, detailed clinical histories, and extended follow-ups is recommended to further explore the prognostic and therapeutic significance of HE4 in our population.

References

1. Baker-Rand H, Kitson SJ. Recent advances in endometrial cancer prevention, early diagnosis and treatment. Cancers. 2024 Mar 1;16(5):1028.
2. Liu J, Han L, Jiao Z. The diagnostic value of human epididymis protein 4 for endometrial cancer is moderate. Scientific reports. 2021 Jan 12;11(1):575.
3. Abd El-Hamed AT, Mahmoud SA, Soliman AA, El-Yasergy DF. Immunohistochemical expression of "HE4" in endometrial hyperplasia versus endometrial endometrioid carcinoma. Open Access Macedonian Journal of Medical Sciences. 2021 Aug 7;9(A):669-75.
4. Jia, Liu. Endometrial Carcinoma. 2022. p. 43-52. doi: 10.1007/978-981-99-3644-1_9
5. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. The Lancet. 2016 Mar 12;387(10023):1094-108.
6. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. JNCI: Journal of the National Cancer Institute. 2018 Apr 1;110(4):354-61.*
7. Rashid MN, Fatima I, Ahmed F, Soomro AM, Noman B. The underuse of spirometry in routine medical practice for diagnosis and management of chronic obstructive pulmonary disease (COPD) patients in Karachi, Pakistan. Journal of Pulmonary Medicine. 2023;12(3):145-150.
8. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. International Journal of Gynecologic Cancer. 2016 Jan 1;26(1).
9. Benati M, et al. Aberrant telomere length in circulating cell-free DNA as possible blood biomarker with high diagnostic performance in endometrial cancer. Pathol. Oncol. Res. 2020;26(4):2281–2289
10. Omer B, et al. The diagnostic role of human epididymis protein 4 and serum amyloid—a in early-stage endometrial cancer patients. Tumor Biol. 2013;34:2645–2650
11. Behrouzi R, Barr CE, Crosbie EJ. HE4 as a Biomarker for Endometrial Cancer. Cancers. 2021 Sep 23;13(19):4764.
12. Degez M., Caillon H., Chauviré-Drouard A., Leroy M., Lair D., Winer N., Thubert T., Dochez V. Endometrial cancer: A systematic review of HE4, REM and REM-B. Clin. Chim. Acta. 2021;515:27–36.
13. Das S, Saha R, Das C, Deb M, Kamilya G. Prognostic Role of Human Epididymis Protein4 (HE4) in Endometrial Lesions: Study in a Tertiary Care Centre. Indian Journal of Surgical Oncology. 2023 Jun;14(2):428-33.
14. Lee KR. The Pathology of surface epithelial stromal tumors of ovary. In: Crum CP, Lee KR, editors. Diagnostic gynecological and obstetrical pathology. Saunders: Elsevier; 2006. pp. 839–903
15. Agarwal S, Melgandi W, Sonkar DR, Ansari FA, Arora S, Rathi AK, Singh K. Epidemiological characteristics of endometrial cancer patients treated at a tertiary health center in National Capital Territory of India. Journal of Cancer Research and Therapeutics. 2023 Jan 1;19(2):452-6.
16. Wasim T, Mushtaq J, Wasim AZ. Gynecological malignancies at tertiary care hospital, Pakistan: A five-year review. Pakistan journal of medical sciences. 2021 May;37(3):621.
17. Tanvir I, Riaz S, Hussain A, Mehboob R, Shams MU, Khan HA. Hospital-Based Study of Epithelial Malignancies of Endometrial Cancer Frequency in Lahore, Pakistan, and Common Diagnostic Pitfalls. Pathology research international. 2014;2014(1):179384.
18. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: a clinicopathological analysis. American journal of obstetrics and gynecology. 2005;1;193(5):1640-4.
19. Deng L, Gao Y, Li X, Cai M, Wang H, Zhuang H, Tan M, Liu S, Hao Y, Lin B. Expression and clinical significance of annexin A2 and human epididymis protein 4 in endometrial carcinoma. Journal of experimental & clinical cancer research. 2015;34:1-1.
20. Drapkin R, Von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, Hecht JL. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer research. 2005;15;65(6):2162-9.
21. Zhuang H, Gao J, Hu Z, Liu J, Liu D, Lin B. Co-expression of Lewis y antigen with human epididymis protein 4 in ovarian epithelial carcinoma. PloS one. 2013;22;8(7):e68994.
22. Abd El-Hamed AT, Mahmoud SA, Soliman AA, El-Yasergy DF. Immunohistochemical expression of "HE4" in endometrial hyperplasia versus endometrial endometrioid carcinoma. Open Access Macedonian Journal of Medical Sciences. 2021;7;9(A):669-75.