RESEARCH ARTICLE

F.U. Med.J.Health.Sci.
2023; 37 (1): 50 - 55
http://www.fusabil.org

The Role of Meteorin-Like Peptide and TRPM2 in Differential Diagnosis in Benign, Premalignant and Malignant Lesions of the Endometrium

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Objective: Endometrial cancer is the most common gynecological cancer in developed countries, and Type 1 endometrial adenocarcinoma develops from the background of atypical hyperplasia. Early diagnosis is effective on mortality and morbidity, and immunohistochemical biomarkers are the most helpful diagnostic method.

Materials and Methods: The samples of this retrospective study were obtained from the pathology laboratory of the Fırat University, School of Medicine, Department of Pathology. A total of 60 patient samples were used, with 10 samples in each group. The cases of proliferative endometrium, simple endometrial hyperplasia without atypia, simple atypical endometrial hyperplasia, complex endometrial hyperplasia without atypia, complex atypical endometrial hyperplasia, and endometrial endometrioid adenocarcinoma were included in the study. The tissue samples were treated and evaluated with Meteorin-like peptide (METRNL) and TRPM2 in all groups.

Results: Statistically significant relationships were detected between endometrial hyperplasia without complex atypia, endometrial hyperplasia with complex atypia, and Type-1 endometrial adenocarcinoma in terms of METRNL and TRPM2 immunoreactivity.

Conclusion: The study results support the presence of a significant association in terms of the expression of METRNL and TRPM2 in endometrial tumors. The results of the present study confirm that both markers have diagnostic value for endometrioid carcinoma.

Key Words: *Proliferative endometrium, endometrial hyperplasia, endometrial adenocarcinoma, meteorin-like peptide, TRPM2*

Endometriumun Benign, Premalign ve Malign Lezyonlarında Ayırıcı Tanıda Meteorin Benzeri Peptid ve TRPM2'nin Rolü

Amaç: Endometriyal kanser, gelişmiş ülkelerde en sık görülen jinekolojik kanserdir ve Tip 1 endometriyal adenokarsinom, atipik hiperplazi zemininden gelişir. Erken tanı mortalite ve morbidite üzerinde etkilidir ve immünohistokimyasal biyobelirteçler en yardımcı tanı yöntemidir.

Gereç ve Yöntem: Bu retrospektif çalışmanın örnekleri Fırat Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı patoloji laboratuvarından temin edildi. Her grupta 10 numune olmak üzere toplam 60 hasta numunesi kullanıldı. Proliferatif endometriyum, atipisiz basit endometrial hiperplazi, basit atipik endometrial hiperplazi, atipisiz kompleks endometrial hiperplazi, kompleks atipik endometrial hiperplazi ve endometrial endometrioid adenokarsinom olguları çalışmaya dahil edildi. Doku örnekleri tüm gruplarda Meteorin benzeri peptit (METRNL) ve TRPM2 ile işlendi ve değerlendirildi.

Bulgular: METRNL ve TRPM2 immünreaktivitesi açısından kompleks atipisiz endometrial hiperplazi, kompleks atipili endometrial hiperplazi ve Tip-1 endometrial adenokarsinom arasında istatistiksel olarak anlamlı ilişkiler saptandı.

Sonuç: Bu çalışmanın sonuçları, endometriyal tümörlerde METRNL ve TRPM2 ekspresyonu açısından anlamlı bir ilişkinin varlığını desteklemektedir. Her iki belirtecin de endometrioid karsinom için tanısal değere sahip olduğu doğrulanmaktadır.

Anahtar Kelimeler: *Proliferatif endometrium, endometriyal hiperplazi, endometriyal adenokarsinom, meteorin benzeri peptit, TRPM2*

Received : 01.10.2022
Accepted : 28.12.2022

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Introduction

Endometrial cancer is the most common gynecological malignancy as the fourth most common cancer in women in the United States, and its incidence has increased by 21% since 2008 with a mortality rate increasing by more than 100% over the past two decades (1, 2). When cancer cells grow uncontrollably, they might invade the myometrium and spread to other parts of the body. A total of 80-85% of patients who have endometrial cancer have Type I Endometrioid Cancer, which is usually estrogen-related and occurs in younger, obese, or perimenopausal women (3). These tumors are usually low-grade and develop from a background of hyperplasia (2). Endometrial Hyperplasia (EH) is a heterogeneous group of pathological lesions that range from mild, reversible glandular proliferations to direct cancer precursors (4). When compared to the normal proliferative endometrium, it is predominantly characterized by an increased

endometrial gland-stroma ratio. The clinical significance of EH lies in the risk of progression to associated endometrial cancer, and atypical forms of EH are considered premalignant lesions. According to the classical classification system, the progression of carcinoma in simple hyperplasia without atypia is 0-3%, with 0-8% in simple atypical hyperplasia, and 9-29% in complex atypical hyperplasia (5). The mechanisms involved in the pathological process of endometrial cancer and endometrial atypical hyperplasia are complex and multicentric. The diagnosis and treatment of endometrial lesions at an early stage have been promising for surgical treatments to preserve reproductive functions in recent years (1).

It has been understood in our present day that peptide and protein molecules involved in the energy balance play roles in the tumorigenesis and prognosis of cancer, and studies conducted on the subject have gained momentum (6, 7). Adipose tissue is an important endocrine organ secreting various hormones as well as chemokines modulating tumor behavior, inflammation, and tumor microenvironment (8). Meteorin-like Peptide (METRNL), which is an adipo-myokine secreted from adipose and muscle tissue, has started to be the subject of current studies on carcinogenesis (9, 7).

TRPM2 is one of the 8-channel proteins named after melastatin, which is a protein identified as a potential tumor suppressor. TRPM2 is permeable to calcium and activated by calcium. The changes in this channel may affect physiological functions and cause the formation of pathological processes (10).

The purpose of the present study was to evaluate the expression of METRNL and TRPM2 in the endometrial epithelial components of normal, atypical, hyperplastic, and neoplastic endometrial tissue and to determine the roles of these proteins in the diagnosis of endometrial carcinoma.

Materials and Methods

Research and Publication Ethics: The study was approved by the Local Ethics Committee of Firat University (Approval No: 2022/06-11).

The study was conducted with 60 cases taken in the pathology laboratory of Fırat University School of Medicine, Department of Pathology. The study included 10 proliferative endometrium (PE) cases, 10 simple EH without atypia, 10 simple atypical EH, 10 complex EH without atypia, 10 complex atypical EH, and 10 EAC cases. The tissue samples of the groups were treated with METRNL and TRPM2, and intra- and intergroup comparisons were made. Cases with PE were used as the control group.

Immunohistochemistry: Immunohistochemical procedures were used as described earlier by Kocaman and Artas (7). Immunohistochemistry (IHC) was performed using histological tissue microarray slides that were 3 µm thick. The following antibodies were used: anti-METRNL antibody (MBS7004241; MyBioSource, San Diego, CA) and Anti-TRPM2 antibody (rabbit Anti-TRPM2 antibody, ab101738, Abcam, Cambridge, UK). A histoscore was calculated for the measurement of tissue levels of meteorin like using indirect immunohistochemical staining.

Microscopic Evaluation of Staining Intensity: The data were evaluated and compared separately by 1 blinded independent pathologist and 1 blinded independent histologist based on the extent and intensity of the staining, and a histoscore was established

We scored the distribution of staining as 0.1, <25%; 0.4, 26-50%; 0.6, 51-75%; 0.9, 76-100%, and the intensity of staining as 0, no staining; 0.5, very little staining; 1, little staining; 2, moderate staining; 3, very strong staining. A histoscore was calculated as histoscore=distribution×intensity (7).

Statistical Analysis: Statistical analysis of the data was performed with the IBM SPSS 22 statistical package program. The Shapiro-Wilk test was used to examine whether or not the data showed a normal distribution. Descriptive statistics of the data are expressed as Median (min-max) for normally distributed variables in continuous data and as percentages [n (%)] for categorical variables. The Kruskal-Wallis test was performed in more than two independent group comparisons. After the Kruskal-Wallis test, the Post hoc Dunn's test was used for pairwise comparison of the groups.The Pearson Chi-Square test was used to compare the categorical variables. The significance level was determined as $p<0.05$.

Results

The demographic characteristics of the patients are given in Table 1. No statistically significant differences were detected between the groups in terms of menopausal status and age ($p>0.05$).

Table 1. Summary of patients' clinical data

Characteristic	PE	EH Without Simple Atypia	EH With Simple Atypia	EH Without Complex Atypia	EH With Complex Atypia	EAC
Age median (min-max)	36.0(23-48)	41.7(24-62)	44.3(27-56)	55.0(36-72)	45.4(23-65)	53.7(38-67)
Menopause n (%)						
Perimenopause	10(100.0%)	7(70.0%)	8(80.0%)	3(30.0%)	7(70.0%)	4(40.0%)
Postmenopause	0(0.0%)	3(30.0%)	2(20.0%)	7(70.0%)	3(30.0%)	6(60.0%)

Comparison of groups according to age and menopause ($p<0.05$). Descriptives are expressed as median (min-max). ($p<0.05$). Proliferative Endometrium (PE), Endometrial hyperplasia without simple atypia (EH) Endometrial hyperplasia with simple atypia (EH with simple atypia), Endometrial hyperplasia without complex atypia (EH without complex atypia), Endometrial hyperplasia with complex atypia (EH with complex atypia) Endometrial hyperplasia with complex atypia (EAC)

Table 2. Meteorin-like protein and TRPM2 Immunreactivity histoscore

Groups	Meteorin Like Protein	TRPM2
PE	0.08±0.074	0.07±0.06
EH without simple atypia	0.18±0.09	0.10±0.09
EH with simple atypia	0.29±0.17	0.22±0.19
EH without complex atypia	0.40±0.22[a]	0.15±0.12
EH with complex atypia	0.70±0.40[ab]	0.35±0.26[ab]
EAC	1.45±0.55[abc]	0.47±0.24[abc]

Values are given as mean±standard deviation. [a] Compared with the proliferative endometrium(PE) group, [b] Compared with the endometrial hyperplasia group without complex atypia, [c] Compared with the endometrial hyperplasia group with complex atypia (EAC) ($p<0.05$).

The median age of patients with proliferative endometrium (PE) was found to be 36 (23-48), the median age of patients with EH without simple atypia was 42 (24-62), the median age of patients with EH with simple atypia was 44 (27-56), and the median age of patients with EH without complex atypia was 44 (27-56). The median age of patients with EH was 55 (36-72), the median age of patients with EH was 45 (23-65), the median age of patients with EAC was 54 (38-67), and this difference was found to be statistically significant ($p<0.05$) (Table 1).

Also, when the distribution of the patients was examined, 100% of the patients were PE, 70% EH without simple atypia, 80% EH with simple atypia, 30% EH without complex atypia, 70% EH with complex atypia, and were 40% EAC premenopausal patients; however, there was no significant relationship in the inter-group comparison of premenopausal and postmenopausal status ($p<0.001$) (Table 1).

Immunohistochemical Findings

Meteorin-like protein immunoreactivity: As a result of the evaluation of the immunohistochemical staining for meteorin-like protein immunoreactivity under the light microscope;

When compared with the Proliferative endometrium (Figure 1A) group, METRNL immunoreactivity was found to be similar in the simple EH without atypia (Figure 1B) ($p=0.916$) and simple atypia EH (Figure 1C) ($p=0.254$) groups, with no statistically significant difference between the groups. Statistically significant increases were detected in METRNL immunoreactivity in complex EH without atypia (Figure 1D) ($p=0.016$), EH with complex atypia (Figure 1E) ($p<0.001$), and EAC (Figure 1F) ($p<0.001$) groups. However, no statistically significant differences were detected between EH without simple atypia and EH with simple atypia ($p=0.845$). When compared with EH without complex atypia, a statistically significant difference was detected between METRNL immunoreactivity in the EH with complex atypia ($p=0.018$) and EAC ($p<0.001$) groups. However, when compared with EH with complex atypia, it was found that the immunoreactivity of METRNL increased at a statistically significant level in the EAC group ($p<0.05$) (Table 2).

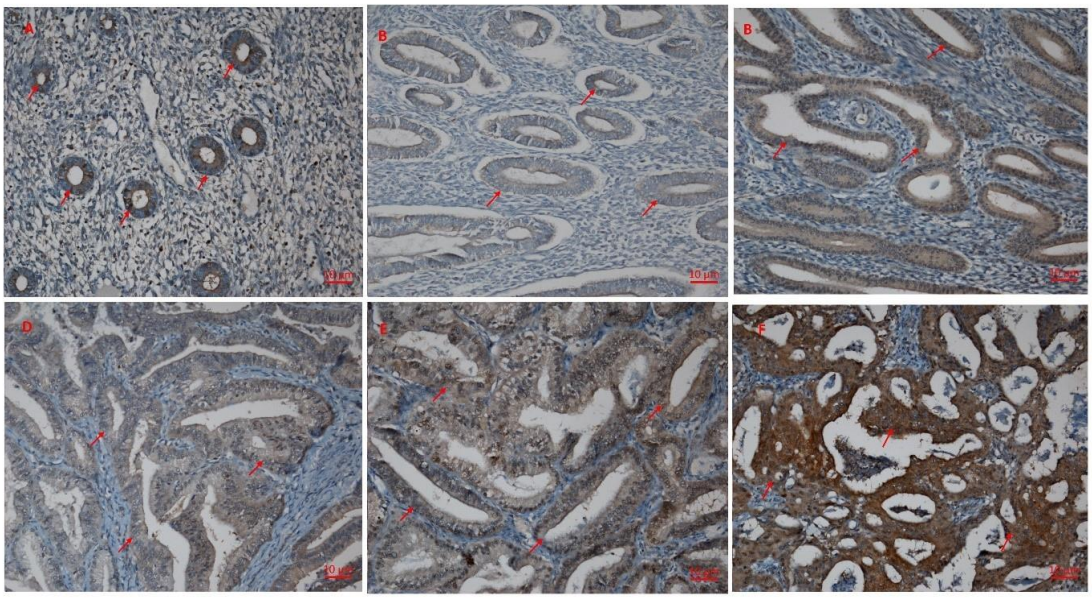

Figure 1. Immunohistochemical analysis of METRNL protein at lesion sites in proliferative endometrium, EH without simple atypia, EH with simple atypia, EH with complex atypia, EH with complex atypia and EAC. Proliferative endometrium group (A) METRNL immunoreactivity, EH without simple atypia (B) METRNL immunoreactivity, EH with simple atypia (C) METRNL immunoreactivity, EH without complex atypia (D) METRNL immunoreactivity, EH with complex atypia (E) METRNL immunoreactivity, EAC immunoreactivity

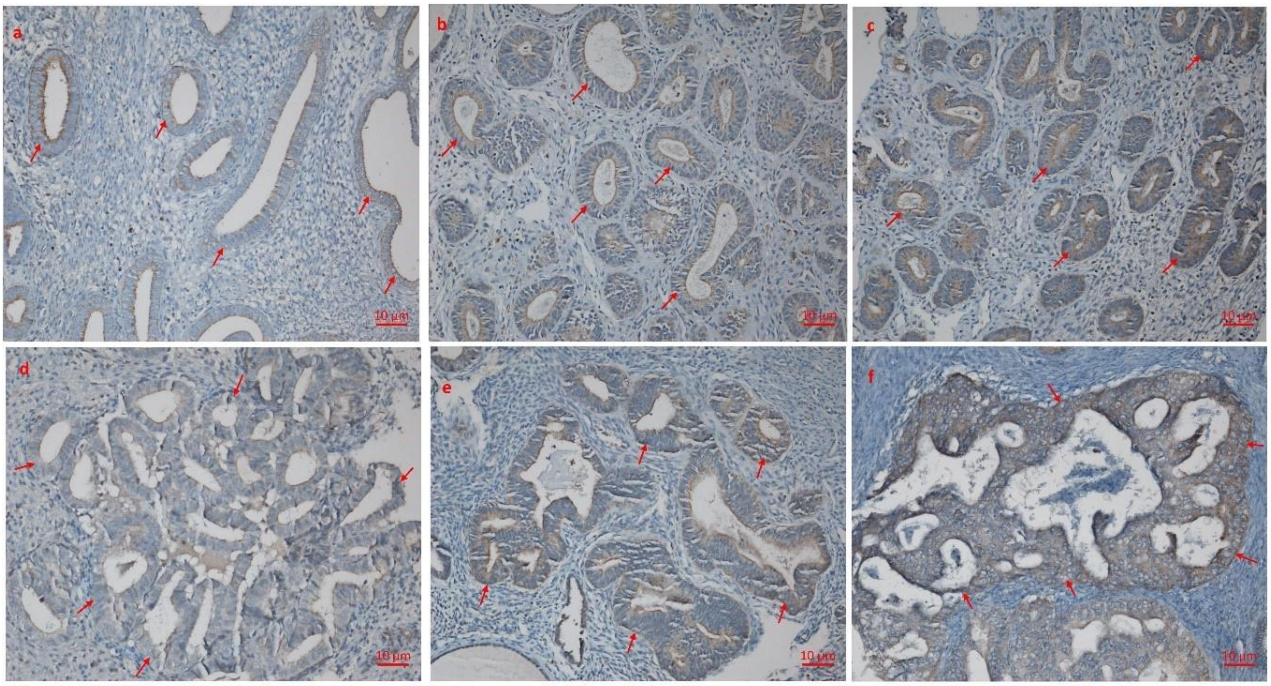

Figure 2. Immunohistochemical analysis of TRPM2 protein at lesion sites in proliferative endometrium, EH without simple atypia, EH with simple atypia, EH with complex atypia, EH with complex atypia and EAC. Proliferative endometrium group (a) TRPM2 immunoreactivity, EH without simple atypia (b) TRPM2 immunoreactivity, EH with simple atypia (c) TRPM2 immunoreactivity, EH without complex atypia (d) TRPM2 immunoreactivity, EH with complex atypia (e) TRPM2 immunoreactivity, EAC immunoreactivity

TRPM2 protein immunoreactivity: As a result of the evaluation of the immunohistochemical staining for TRPM2 immunoreactivity under the light microscope;

When compared with the proliferative endometrium group (Figure 2a), TRPM2 immunoreactivity was found to be similar in simple EH without atypia (Figure 2b) ($p=0.995$), EH with simple atypia (Figure 2c) ($p=0.075$), and EH without complex atypia (Figure 2d) ($p=0.651$) and there was no statistically significant difference between the groups. It was also determined that TRPM2 immunoreactivity was significantly increased in EH (Figure 2e) ($p<0.001$) and EAC (Figure 2f) ($p<0.001$) groups with complex atypia. However, no statistically significant differences were detected between EH without simple atypia and EH groups with simple atypia ($p=0.238$).

When compared with EH without complex atypia, TRPM2 immunoreactivity was increased at a statistically significant level in EH with complex atypia ($p=0.014$) and EAC ($p<0.001$) groups; and TRPM2 immunoreactivity was increased at a statistically significant level in EAC ($p<0.001$) group when compared with EH with complex atypia (Table 2).

Discussion

Various immunohistochemical biomarkers were proposed in the literature in the past to help the diagnosis and classification of Endometrial Hyperplasia (EH) and to predict the probability of transition from EH to Endometrial Adenocarcinoma (EAC). A good biomarker must be reliable and reproducible and must show the transition between groups in the differentiation process into normal, benign, premalignant, and malignant endometrium. However, studies continue and new biomarkers are proposed for many cancer types because no effective candidate has been found so far (11).

Endometrial carcinoma is one of the cancers that are associated with metabolic diseases most closely, and as the incidence of metabolic diseases increases, the incidence of endometrial cancer and endometrial atypical hyperplasia also increases (12, 13). In recent years, some adipokines such as METRNL have been shown to be involved in tumor development or progression aside from their endocrine functions. Adipokines are biologically active proteins with a small molecular weight produced by adipocytes. METRNL is a newly-identified adipo-myokine modulating energy expenditure and inflammation in adipose tissue, and there is no study in the literature evaluating its relationship with EAC (14).

The present study provided new insights into the association of METRNL and TRPM2 with well-differentiated EAC and atypical EHs. METRNL and TRPM2 reactivity were detected in tissue samples of all groups in the study. However, the expression of both molecules; It was increased in all atypical hyperplasias of the endometrium, whether simple or complex, compared to the PE group (especially at the highest level in EAC). METRNL uses different intracellular pathways in different tissues. For example, when it

exerts anti-inflammatory effects through the AMPK/PPARδ-linked pathway in adipose tissue, it also supports β-cell proliferation by activating the WNT/β-catenin pathway in the pancreas (15, 16). For this reason, its effects on EAC might occur through many different mechanisms. In a previous study, METRNL was associated with the cAMP/PKA signaling pathway, and its effect on oxidative stress and apoptosis was shown through the cAMP/PKA signal axis (17). Alicia et al. showed that METRNL has a protumor effect by reducing apoptosis and increasing cell proliferation in pancreatic cancer (18). METRNL also induces PPARy activity in white adipose tissue to increase preadipocyte differentiation and insulin sensitivity, which is also effective in carcinogenesis. It was shown in previous studies on the subject that METRN plays roles in the development of bladder, colon, and prostate cancers through AMPK and PPARδ signaling pathways (19). Glucose uptake and glycolytic pathway are activated by regulating AMPK/mTOR/S6 and MAPK signaling pathways in EAC, and therefore, increasing the invasion of endometrial cancer cells (20). Interestingly, as atypia increased in hyperplasia, METRNL expression also increased and a significant difference was detected between the groups in the present study. Staining was most severe in EAC when compared to other groups. In studies investigating the relationships between METRNL and cancer, it was shown to have a protumor effect in pancreatic cancer, and it has been emphasized that it might be a prognostic marker for bladder cancer, BCC, and malignant mesothelioma (7, 14, 18, 21). As is known, the PI3K/Akt pathway is among the pathways that are involved in carcinogenesis most frequently, regulating cell proliferation, growth, cell size, metabolism, and motility (15). The overactivation of the PI3K/Akt pathway has recently been associated with the pathogenesis of endometrial cancer, and thus inhibition of the PI3K/Akt pathway has therapeutic interest (16). However, the evidence for the association of METRNL with the PI3K/Akt/mTOR pathway is not yet at adequate levels and these drawbacks must be clarified with future research (22).

In this respect, the TRP superfamily represents a $Ca2^{+}$-permeable cation channel responding to various chemical and physical stimuli and playing key roles in signaling between the uterine epithelium and stromal cells. However, the data on the distribution of TRP channels in human endometrial epithelial and stromal cells is not adequate and is considered to be regulated by estrogen and progesterone hormones throughout the menstrual cycle (23, 24).

Tumor progression occurs as a result of the changes in the physiological processes (e.g. cell proliferation, apoptosis, migration, invasion, and angiogenesis), which are under the control of calcium homeostasis and Transient Receptor Potential (TRP) cation channels. TRP channels play a role in many physiological processes and are associated with some serious diseases such as cancer (25). Although it was reported in a previous study that the miRNA gene expression of TRPM2 was significantly downregulated in EH with atypia when compared to EH without atypia and proliferative endometrium, it was not demonstrated immunohistochemically (26). However, in the present study, it was found that TRPM2 expression increased as atypia increased in both simple and complex hyperplasia (most severe in adenocarcinoma). These findings suggest that TRPM2 may play a role in the process of endometrial carcinogenesis. TRP channels are expressed in different ways in different cancer types and have been associated with many cancers (e.g. bladder, breast, lung, liver, head, and neck cancer), which is consistent with the result found in the present study (27).

The current findings of the study show that METRNL and TRPM2 might play an important role in the transition from premalignant to malignant endometrial lesions. However, this study is the first to uncover the association of METRNL with endometrial lesions and needs further evidence (28).

As it is already known, obesity, diabetes, and hypertension are generally referred to as the metabolic triad that is effective in the development of endometrial cancer (29). Obesity and diabetes are high risk factors for EH and EAC with atypia because of the unopposed elevated circulating estrogen. Despite conflicting data, it was reported that hypertension doubles the risk of EAC, and women who have a Body Mass Index score above 30 kg/m^2 are also considered in the risk group for carcinomas (30).

In the present study, when the patients were evaluated in terms of premenopausal/postmenopausal status and age, no significant relationships were detected between the groups. However, the study has some limitations the most important of which is that the study had a retrospective design. For this reason, it was not possible to exclude patients who had chronic systemic diseases (i.e. diabetes, hypertension), and the effects of sex hormone profiles and Body Mass Indices on the development of carcinoma could not be determined. However, future studies to be conducted in a large prospective case series that might define the relationship between METRNL and TRPM2 proteins and the prediction of endometrial cancer, in which all these criteria will be considered, may yield better results.

In conclusion, METRNL and TRPM2 protein values may be effective markers in early-stage endometrial cancers for differentiating endometrial cancer from precancerous lesions. This result might also be a guide on how to plan treatment modalities, especially in patients who want to preserve their ovaries or fertility.

Funding: This research was not supported by any institution.

Declaration of Competing Interest: The authors declare no conflicts of interest.

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