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ORIGINAL PAPER

A new method that facilitates the diagnosis of endometrial cancer: the ratio of endometrial thickness to the full thickness of the uterine wall and subcutaneous adipose tissue measurements

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Abstract

Introduction: The aim of the present study was to investigate the association between some risk factors and endometrial pathologies determined by transvaginal sonography (TVS), as well as the diagnostic predictive values of serum oestradiol (E2) levels, subcutaneous adipose tissue (SAT) thickness, endometrium thickness (ET), and the ratio of ET to uterine wall full thickness (UWT) in differential diagnosis of malignant, precancerous, and benign pathologies of endometrium in patients with postmenopausal bleeding (PMB) or with asymptomatic increased endometrial thickness.

Material and methods: The study was conducted with 211 women who applied to the hospital with complaints of PMB or ET of 5 mm or more in their routine controls. Venous blood samples were taken for complete blood count and the measurement of E2 levels. Patients also underwent TVS; ET, UWT, and the ratio of ET to UWT were measured.

Results: Menopausal age and body mass index averages were significantly higher in atypical hyperplasia and endometrial cancer (EC) groups. Endometrial thickness and endometrial thickness/uterine wall full thickness ratio measured by TVS were significantly higher in all precancerous pathologies and EC. Subcutaneous adipose tissue thickness was significantly higher in all precancerous pathologies and EC. Oestradiol levels were higher in the atypical hyperplasia and EC groups.

Conclusions: Postmenopausal bleeding is a common symptom of EC, but in some cases this disease may occur asymptomatically. Measurement of the endometrium thickness, and the ratio of endometrium thickness/uterine wall full thickness and SAT thickness by sonography has a high predictive value for this disease.

Key words: endometrial cancer, sonography, PMB, endometrial hyperplasia, endometrial thickness, subcutaneous adipose tissue.

Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in Turkey, with an increasing incidence, similar to the data of many developed countries [1]. Although the aetiology of EC is still poorly clarified, there are several risk factors that are commonly associated with it. The most emphasised of these is unbalanced exposure of endometrium to the oestrogen hormone, including early menarche, late menopause, nulliparity, infertility/anovulation, and exogenous oestrogen use. The other risk factors are age, family history of gynaecological cancer, obesity, and some metabolic diseases including diabetes mellitus (DM) and hypertension (HT) [2, 3]. More than 90% of the patients are 50 years old or more, with a mode of 63 years, at the time of diagnosis [3]. Therefore, we can say that EC is commonly a cancer of postmenopausal women.

Postmenopausal bleeding (PMB) is one of the most common indicators of EC, and more than half of postmenopausal women suffer from this situation [4]. Approximately 10% of women with PMB are diagnosed with EC [5], so patients with this symptom should be examined by a gynaecologist as early as possible. On the other hand, 10% of EC cases are asymptomatic and are diagnosed with incidental during routine gynaecological examination with the presence of thickened endometrium in transvaginal sonography (TVS) [6]. In most cases, an endometrial biopsy is needed for a definitive diagnosis. There are also some markers that can be helpful for the prediction and follow-up of EC. Serum levels of tumour markers, such as cancer antigen 125 and cancer antigen 15-3, are the most

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commonly used ones that can also give an idea about the tumour stage, extrauterine spread, and response to medical treatment [7]. Several studies demonstrate that serum levels of some hormones, such as oestradiol (E2) and prolactin, may increase during the EC process, and these markers can be useful for the diagnosis and follow-up [7, 8].

Measurement of the endometrial thickness by TVS is a sensitive and less invasive method for EC diagnosis and can give an idea of the necessity of an endometrial biopsy [9]. In premenopausal women, the endometrium is thinnest (2–4 mm) during menstruation, becomes thicker during the proliferative phase, and reaches up to 16 mm thickness in the secretory phase. In healthy postmenopausal women, endometrial thickness is always measured as ≤ 5 mm [10]. Studies demonstrate that 6.7% of asymptomatic postmenopausal women with more than 11 mm endometrial thickness are diagnosed with EC [11]. The definitive diagnosis is usually made by endometrial sampling with an endometrial biopsy or by dilatation and curettage [12], but these methods usually cause anxiety, a feeling of discomfort, and a risk of perforation and anaesthesia complications in patients. There are many novel studies reporting TVS as a lower-risk method for detection of the EC risk and the need for endometrial biopsy [13, 14]. It was detected that 96% of EC and 92% of other endometrial pathologies can be diagnosed by TVS among postmenopausal women with > 5 mm endometrial thickness [15].

The aim of the present study was to investigate the association between some risk factors and endometrial pathologies determined by TVS, as well as the diagnostic predictive values of serum E2 levels, subcutaneous adipose tissue (SAT) thickness, endometrium thickness (ET), and the ratio of ET to uterine wall full thickness (UWT) in the differential diagnosis of malignant, precancerous, and benign pathologies of endometrium in patients with PMB or with asymptomatic increased endometrial thickness.

Material and method

Patients

This study was conducted on 211 women who applied to "Details blinded for peer review" Clinic between 10/10/2019 and 10/05/2021 with complaints of PMB or ET of 5 mm or more in their routine controls. The cases that had a period of at least one year or more since menopause were included in the study. Patients who take tamoxifen due to breast cancer, bleeding time-prolonging drugs, and external hormone replacement therapy, as well as patients with liver disease, congenital uterine anomalies, and uterine myomas, were excluded from the study. Endometrial sampling, a blood sample, ultrasonographic and anthropometric measurements were taken from all patients included in the study with the consent of the patients. Pathology reports of the patients were recorded in their files. According to the pathology report results, 7 subgroups were divided into 2 groups according to the expected prognosis. Atrophic endometrium, normal endometrial tissue, endometrial polyps, irregular proliferative endometrium, and non-atypical endometrial hyperplasia formed the benign group (n = 171). Endometrial cancer and atypical endometrial hyperplasia considered to be precancerous formed the premalignant/malignant group (n = 40).

Biochemical analysis

Venous blood samples were taken from all cases included in the study when they applied to the hospital, to measure E2, follicular-stimulation hormone (FSH), and luteinising hormone (LH) levels, and a complete blood count.

Ultrasonographic measurement

On the day of taking serum samples, patients underwent TVS. The Voluson S10 ultrasound device and the IC9-RS transvaginal probe were used for transvaginal ultrasonography. Endometrium thickness, UWT, and the ratio of ET to UWT were measured in all cases. The measurements were performed by following 3 layers in the sagittal plane of the uterus. These layers are, from the inside to the outside, endometrium, myometrium, and serosa. Uterine wall full thickness measurement includes the measurement of the anterior serosa, anterior myometrium, endometrium, posterior myometrium, and posterior serosa, respectively, while the uterus is in the sagittal plane.

Anthropometric measurements

On the day of taking serum samples, the body mass index (BMI) (kg/m^2) was calculated by measuring the height and weight of the cases, and the SAT thickness was measured by ultrasonography from 2 cm lateral and distal to the umbilicus. A Voluson S10 ultrasound device and C1-5 RS transabdominal probe were used for SAT measurement.

Endometrial sampling

Endometrial sampling was performed by obtaining informed consent from patients with endometrial sampling indications for PMB and/or increased endometrial thickness. Dilatation and curettage (D/C) was performed as an endometrial sampling procedure.

Table 1. Descriptive statistics

Parameters	*n*	Minimum	Maximum	Mean	SD
Age (years)	211	49	83	61.96	7.18
Parity	211	0	7	2.75	1.10
Height [cm]	211	150	175	161	4.9
Weight [kg]	211	56	120	77.11	11.24
BMI [kg/m^2]	211	21.30	46.88	29.771	4.41
Menarche age (years)	211	9	14	12.12	1.32
Menopausal age (years)	211	42	56	49.12	2.96
Postmenopausal period (years)	211	1	39	12.84	8.14
Age of first birth (years)	208	17	30	21.99	2.96
Age of last birth (years)	208	20	40	28.57	3.12
Endometrial thickness [mm]	211	2	39	11.69	8.54
Uterine wall full thickness [mm]	211	26	60	42.40	5.16
ET/UWT	211	0.06	0.78	0.265	0.174
Subcutaneous adipose tissue thickness [mm]	211	13	85	35.29	13.97
WBC [K/µl]	211	5.10	13.80	8.008	1.527
Neutrophil [K/µl]	211	3.5	7.9	5.30	0.74
Haemoglobin [g/dl]	211	8.9	15.7	12.96	1.11
FSH [IU/l]	211	11.1	167.0	56.81	16.76
LH [U/l]	211	3.9	115.0	42.10	15.45
FSH/LH	211	0.47	5.18	1.47	0.56
E2 [ng/l]	211	5.0	282.0	20.74	31.71

BMI – body mass index, E2 – 17 β-oestradiol, ET/UWT – thickness/uterine wall full thickness, FSH – follicular-stimulation hormone, LH – luteinising hormone, SD – standard deviation, WBC – white blood cell

Transvaginal sonography imaging, measurement of SAT thicknesses and endometrial sampling of all cases were done by the responsible researcher in the gynaecology clinic.

Ethical permission

Ethics Committee approval was obtained from the "Details blinded for peer review" (date 08/10/2019, number 17) for the study. Each patient was informed in detail, and informed consent forms were received. The ethical rules announced in the 2013 Helsinki Declaration were followed at every stage of the study.

Statistical analysis

SPSS v. 22 (IBM Inc. Armonk, NY) software was used for statistical analysis of the findings obtained in the study. The data of continuous variables were shown as mean, standard deviation (SD), minimum, maximum, and number (n), while the data of categorical variables were shown as numbers and percentages. The Shapiro-Wilk test was used to evaluate the normal distribution of data, and the Mann-Whitney *U* test was used for binary group comparisons. Significance value was accepted as $p < 0.05$.

Results

Descriptive statistics of the demographic, anthropometric, ultrasonographic, and biochemical data of the individuals participating in the research are shown in Table 1. Some average values are as follows; age 61.96 years, parity 2.75, height 1.61 m, weight 77.11 kg, BMI 29.78 kg/m^2, menarche age 12.12 years, menopausal age 49.12 years, postmenopausal period 12.84 years, age of first birth 21.99 years, age of last birth 28.57 years, endometrial thickness 11.69 mm, UWT 42.40 mm, endometrial thickness/uterine full thickness ratio 0.265, SAT thickness 35.29 mm, white blood cell 8.00 K/µl, neutrophil 5.30 K/µl, haemoglobin 12.96 g/dl, FSH 56.81 IU/L, LH 42.10 U/L, FSH/LH ratio 1.47, and E2 20.74 ng/l.

According to the data, 51.7% of the patients had no concomitant disease, 80.6% of those gave birth with spontaneous vaginal delivery, and 73.5% of those were consulted with complaints of PMB.

Concomitant disease rates in the endometrial sampling subgroups were highest in the EC group (DM, HT and DM + HT together: 63.6%), while the lowest rate was in the normal endometrial tissue group (DM, HT, and DM + HT together: 22.4%).

The mean values of the endometrial thickness/uterine wall full thickness (ET/UWT) ratio and SAT mea-

Table 2. The mean values of endometrial thickness/uterine wall full thickness ratio and subcutaneous adipose tissue measurements according to endometrial sampling subgroups

Endometrial sampling subgroups	*n*	Mean ±SD	
		ET/UWT	SAT thickness [mm]
Atrophic endometrium	47	0.10 ±0.018	22.77 ±6.39
Normal endometrial tissue	37	0.15 ±0.02	32.41 ±10.60
Endometrial polyp	32	0.28 ±0.086	36.44 ±13.06
Irregular proliferative endometrium	25	0.22 ±0.047	34.36 ±9.25
Non-atypical endometrial hyperplasia	30	0.27 ±.0042	35.90 ±9.71
Atypical endometrial hyperplasia	18	0.51 ±0.07	47.11 ±12.59
Endometrial cancer	22	0.61 ±0.11	55.77 ±11.49

ET/UWT – thickness/uterine wall full thickness, SD – standard deviation, SAT – subcutaneous adipose tissue

Table 3. Comparison between premalignant/malignant and benign groups

Parameters	Premalignant and malignant group (*n* = 40)	Benign group (*n* = 171)	*p*-value
	Mean ±SD		
Age (years)	62.80 ±5.02	61.77 ±7.60	0.167
Parity	2.13 ±0.64	2.90 ±1.14	< 0.001
Height [cm]	160 ±4.60	161 ±4.98	0.393
Weight [kg]	89.33 ±11.00	74.26 ±9.22	< 0.001
BMI [kg/m^2]	34.74 ±4.22	28.60 ±3.57	< 0.001
Menarche age (years)	10.68 ±0.88	12.46 ±1.17	< 0.001
Menopausal age (years)	52.10 ±2.02	48.42 ±2.70	< 0.001
Postmenopausal period (years)	10.70 ±4.72	13.35 ±8.69	0.209
Age of first birth (years)	23.40 ±2.72	21.65 ±2.92	0.001
Age of last birth (years)	27.33 ±2.67	28.86 ±3.15	0.012
Endometrial thickness [mm]	26.50 ±6.54	8.22 ±4.09	< 0.001
Uterine wall full thickness [mm]	46.28 ±5.18	41.49 ±4.72	< 0.001
ET/UWT ratio	0.56 ±0.11	0.19 ±0.08	< 0.001
Subcutaneous adipose tissue thickness [mm]	51.88 ±12.62	31.41 ±11.16	< 0.001
WBC [K/µl]	9.74 ±1.42	7.60 ±1.24	< 0.001
Neutrophil [K/µl]	6.20 ±0.64	5.09 ±0.59	< 0.001
Haemoglobin [g/dl]	12.11 ±1.35	13.16 ±0.95	< 0.001
FSH [IU/L]	47.71 ±12.59	58.94 ±16.93	< 0.001
LH [U/L]	36.31 ±9.16	43.46 ±16.30	0.004
FSH/LH ratio	1.34 ±0.31	1.50 ±0.60	0.188
E2 [ng/L]	40.34 ±39.20	16.16 ±27.89	< 0.001

BMI – body mass index, E2 – 17 β-oestradiol, ET/UWT – thickness/uterine wall full thickness, FSH – follicular-stimulation hormone, LH – luteinising hormone, SD – standard deviation, WBC – white blood cell

surements according to endometrial subgroups are presented in Table 2. The endometrial thickness/uterine wall full thickness ratio and SAT thickness were significantly lower in the benign group compared to the premalignant/malignant group. Endometrial thickness/uterine wall full thickness ratio and SAT thickness were lowest in atrophic endometrium and highest in EC.

Table 3 shows the differences in descriptive parameters between the benign and premalignant/malignant groups. While there was no age difference between the groups ($p > 0.05$), parity was higher in the benign group ($p < 0.001$**)**. And while there was no difference in height between the groups ($p > 0.05$), weight and BMI were significantly lower in the benign group ($p < 0.001$**)**.

There was no difference between the groups in terms of postmenopausal duration ($p > 0.05$). Age at last birth and at menarche were statistically greater in the benign group ($p = 0.012$ and < 0.001, respectively).

Age at first birth and at menopause were statistically greater in the premalignant/malignant group ($p = 0.001$ and < 0.001, respectively).

Ultrasonographic parameters such as ET, UWT, ET/UWT ratio, and SAT thickness were significantly higher in the premalignant/malignant group ($p < 0.001$**)**.

Blood values are presented in Table 3. White blood cell and E2 were statistically significantly higher in the premalignant/malignant group ($p < 0.001$**)**. Neutrophil, haemoglobin, FSH, and LH were statistically significantly higher in the benign group ($p < 0.001$**)**. There was no significant difference between the groups for the FSH/LH ratio ($p > 0.05$).

Discussion

Endometrial cancer was diagnosed in 22 (10.4%) of a total of 211 patients in our study. These results are compatible with the literature; the incidence of EC among women with PMB ranges from 3 to 25% worldwide, depending on the risk factors that affect the patient [16]. The Surveillance, Epidemiology, and End Result database demonstrates an increasing incidence of EC during the last decades, especially in developed countries [17]. These changes point to potential changes in risk factors for the disease over time. Therefore, the review of risk factors that are newly emerging or becoming more common is gaining importance.

More than 80% of EC cases are related to excessive oestrogen exposure [18]. Early menarche and late menopause are closely related to this situation. The Menopause and Osteoporosis Society of Turkey describe the average age of menopause as 49 years among Turkish women [19]. According to the results of this study, menopause age was 49.12 years among all participants. On the other hand, it was 51.44 and 52.64 years in the atypical endometrial hyperplasia and EC groups, respectively. Both were significantly higher than the average menopausal age. The younger age of menarche was statistically significant in the EC and precancerous groups compared to the benign group.

Obesity is known to be a remarkable risk factor for EC, and obese women (BMI > 30 kg/m^2) were shown to have a 2–4-fold increased risk of developing EC compared to women with normal body weight [20]. Novel observations demonstrate that a 5 kg/m^2 increase in BMI can cause about a 60% increase in the risk of EC [21]. Also, DM was found to be another conspicuous metabolic condition associated with EC [22]. Mechanisms of obesity and type-2 DM are closely related; they both cause hormonal imbalance in the body. Some of these hormones, including oestrogens, adipokines, insulin, and some growth factors, can cause endometrial tissue proliferation. Obesity is also an independent risk factor for type-2 DM and HT. In the present study, the mean values of BMI in the atypical endometrial hyperplasia and EC groups were over 30 kg/m^2 (the limit value for obesity), and the thickness of the SAT was significantly higher in EC and some precancerous diagnoses. Also, the rates of concomitant diseases were highest in the EC group (DM, HT, and DM + HT together: 63.6%). Obesity and related systemic diseases such as DM and HT are increasing society's health problems in developing countries as a result of sedentary lifestyles and improper nutrition habits. This may be one of the causes of the increasing incidence of EC, especially in developed countries.

The present study is in agreement with the literature stating that nulliparity, early menarche, and late menopause increase the risk of EC by extending the time of unopposed exposure of the endometrium to oestrogen [2, 23]. The effect of the low parity was found to be significant on the premalignant/malignant group.

Another controversial issue concerns the diagnosis of EC. Fast and correct diagnosis saves time for proper treatment and reduces the risk of unnecessary operations. Almost always, the first step of a gynaecological examination is a TVS both in women with PMB and in control patients. But invasive tests, such as an endometrial biopsy or D/C, are recommended for all symptomatic patients and patients with suspicious TVS results, for a definitive diagnosis [24]. The measurement of endometrial thickness is vital for the differential diagnosis of some endometrial pathologies. Five millimetres or less endometrial thickness in TVS was found to be related with atrophic endometrium in 96% of women with PMB [25], and in patients with endometrial thickness < 4 mm in TVS, the risk of EC falls below 1%4. However, most of the time it is not possible to differentiate the other endometrial pathologies that increase the endometrial thickness, such as hyperplasia and cancer. Our primary aim was to investigate whether the measurements of ET/UWT ratio and SAT thickness could help to improve the value of TVS diagnosis of endometrial pathologies. According to the results of our study, the mean values of ET, ET/UWT ratio, and SAT thickness were greater in patients with precancerous and EC lesions. As a result, measurements of ET, ET/UWT ratio, and SAT thickness helped us with the diagnosis of atrophic endometrium, normal endometrial tissue, precancerous endometrial pathologies, and EC.

Some other auxiliary tests, such as serum levels of E2, FSH, and LH hormones, can be used to support the preliminary diagnosis and follow-up of the disease. In many studies, serum E2 levels were shown to be higher in postmenopausal women with EC compared to normal controls and did not significantly decrease after ovariectomy [26]. As a result, E2 hormone is thought to be produced by the peripheral conversion of androgens, especially by adipose tissue. According to this theory, an increase in E2 levels is another risk factor for EC and a complication of obesity. Also, serum FSH and LH levels are affected by high levels of E2.

Conclusions

According to the results of our study, we can conclude that TVS is the primary evaluation method for women with PMB. Measurement of ET, ET/UWT ratio, and SAT thickness is a useful method for the differential diagnosis of EC and precancerous pathologies in normal or atrophic endometrium. Although D/C is the gold standard for the definitive diagnosis of EC, it is very important to evaluate the results of measurements by TVS properly to avoid unnecessary invasive procedures.

Disclosure

The authors report no conflict of interest.

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