

RELATION OF ENDOMETRIAL PATHOLOGICAL CHANGES WITH ENDOCRINE DISORDERS AND METABOLIC SYNDROME

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Abstract

Endometrial hyperplasia (EH) is an abnormal proliferation of endometrial glands and stroma and is associated with an increased risk of endometrial cancer (EC). Risk factors such as obesity, chronic anovulation, late menopause, hypertension, and diabetes lead to an increased risk of EH and EC.

Aim: to determine the association of pathological changes in the endometrium with endocrine disorders and metabolic syndrome in women in peri and postmenopause. This study including a total of 139 patients in peri and postmenopause. The examined group consisted of 104 women with fractional explorative curettage due to a medical indication and was divided into two subgroups: peri and postmenopausal. The control group included 35 healthy women. Anamnestic data, body weight, height, blood pressure measurement, were taken from all patients, and the following laboratory parameters were determined: glucose, TSH, thyroxine, glycosylated hemoglobin (HbA1c), and Vitamin D. The presence of metabolic syndrome (MetS) according to its diagnostic criteria was also determined.

In our study, significance was found in the comparison of the examined and the control group ($p = 0.0001$) in addition to the significantly higher BMI in the examined group. The comparison also indicated the existence of a significant difference in the level of glycemia in addition to a significantly higher level in the examined group ($p = 0.0001$).

The statistical analysis did not indicate a significant difference between the two subgroups of the examined group, nor between the examined and the control group in terms of TSH, thyroxine and HbA1c levels. The value of vit. D was significantly higher in the control than in the study group ($p = 0.0001$).

The analysis showed that patients with fractional explorative curettage had 4.982 times [OR = 4.982 (2.06–12.02) 99% CI] significantly more often MetS compared to women in the control group. Patients in the examined group had a significantly higher BMI, glycemia, and more frequent presence of MetS than those in the control group.

Keywords: endometrium, risk factors, fractional explorative curettage, metabolic syndrome

Introduction

Menopause is the period of a woman's life when menstrual cycles stop and the reproductive period ends. It is defined as the absence of menstrual bleeding for more than a year. It typically occurs between the ages of 49 and 52 [1].

A few years before menopause, menstrual cycles typically become irregular, last longer or shorter than normal or menstrual bleeding is reduced or increased [2].

The World Health Organization defines perimenopause as the period from two to eight years before menopause, as well as the first year after the last menstrual period [3].

Abnormal uterine bleeding is a complex gynecological problem, especially in the perimenopausal and postmenopausal period in women. The etiology may be organic (endometrial polyp, hyperplasia, fibroids, endometrial atrophy, cancer) or non-organic (dysfunctional uterine bleeding) [4].

Endometrial hyperplasia (EH) is an abnormal proliferation of the endometrial glands and stroma and is associated with a risk of endometrial cancer [5]. EH can be detected in about 10% of asymptomatic postmenopausal women, but it is rare in asymptomatic premenopausal women [6,7].

Obesity is the predominant risk factor for endometrial hyperplasia in younger women. Other risk factors include higher education, diabetes and the use of hormone replacement therapy [8].

Endometrial polyps (EPs) are benign growths of the endometrium, pedunculated or sessile in shape, containing varying amounts of glandular tissue, connective tissue and blood vessels. EH and EP are associated with the development of endometrial cancer and therefore these changes can be called premalignant changes, especially in the postmenopausal population.

Endometrial cancer (EC) occurs as a result of abnormal growth of endometrial cells that acquire the ability to invade and metastasize to other parts of the body [9]. Risk factors such as obesity, chronic anovulation, nulliparity, late menopause, unopposed estrogen (without progesterone), hypertension and diabetes increase the risk of endometrial hyperplasia and endometrial cancer [10].

The three main risk factors for endometrial cancer are obesity, diabetes and hypertension. They all have the same pathophysiological mechanism through insulin resistance and hyperinsulinemia. Insulin resistance and hyperinsulinemia increase the risk of multiple malignancies, especially colorectal and endometrial cancer [11,12].

Metabolic syndrome (MS) has been described as a cluster of diseases or conditions, including obesity, diabetes, glucose intolerance, dyslipidemia and hypertension [13].

The prevalence of the metabolic syndrome increases with menopause and may partially explain the apparent acceleration in cardiovascular disease after menopause. The transition from pre- to postmenopause is associated with the emergence of many features of the metabolic syndrome. Obesity, diabetes, metabolic syndrome, nulliparousness, late menopause, and unstoppable estrogen stimulation are established risk factors for endometrial cancer [14].

Also, hypertension and high glycemic levels are independent risk factors for this cancer [15].

The incidence of hypothyroidism in patients with endometrial cancer is significantly higher, and serum thyroid-stimulating hormone (TSH) levels before treatment are an independent risk factor for a worse EC prognosis [16].

Vitamin D receptor (VDR) is expressed in the ovaries, endometrium, and myometrium. There is also an expression in the endometrium of enzymes involved in Vitamin D metabolism. Alterations in Vitamin D metabolism (increased 24-hydroxylase mRNA activity and protein expression) have been demonstrated in endometrial cancer. In many lines of endometrial cancer, its anti-proliferative, pro-apoptotic, anti-inflammatory action has been demonstrated, as well as its action as a differentiation-inducing agent [17].

OBJECTIVES

The aim of the study was to determine the association of pathological changes of the endometrium with endocrine disorders and metabolic syndrome in women in perimenopause and postmenopause.

Material and Methods

This was a prospective observational clinical study conducted at the Special Hospital for Gynecology and Obstetrics "Mother Theresa" – Skopje.

The sample consisted of 139 patients in perimenopause and postmenopause.

The examined group consisted of 104 women with fractional explorative curettage due to medical indication (abnormal bleeding from the uterus or abnormally ultrasound findings), while the control group consisted of 35 healthy women.

The examined group was divided into two subgroups: perimenopausal and postmenopausal. We analyzed demographic and clinical parameters of interest for the research. We analyzed these laboratory parameters: serum glucose, thyroid-stimulating hormone (TSH), serum thyroxine, glycosylated hemoglobin (HbA1c) and Vitamin D - total (25-hydroxyvitamin D) in serum. Diagnostic criteria for metabolic syndrome included at least three of the following five criteria: a) central thickness: waist circumference ≥ 88 cm; b) fasting triglycerides ≥ 1.70 mmol/l or specific treatment for dyslipidemia; c) serum HDL cholesterol <1.29 mmol/l; d) elevated fasting blood glucose ≥ 5.6 mmol/l or previously diagnosed with type 2 diabetes or receiving diabetes therapy; e) hypertension (blood pressure $\geq 130 / \geq 85$ mmHg or receiving antihypertensive therapy). Blood pressure measurements were performed in a sitting position with three measurements at a distance of 1 hour. Weight and height were measured with a digital scale, with no clothing or footwear, only underwear. Waist circumference was measured by metro, at the level of the navel, before the end of the expiration. Body Mass Index (BMI) was calculated using the formula: $BMI = \text{body weight (kg)} / \text{body height (m}^2\text{)}$.

Results

The study included a total of 139 women, of which 104 (74.82%) from the examined group and 35 (25.18%) from the control group.

The examined group consisted of an equal number of 52 (50%) patients in perimenopause or postmenopause. In the examined group, the average age of patients with fractional exploratory curettage in perimenopause and postmenopause was 46.61 ± 4.23 years vs. 57.96 ± 7.27 years, respectively.. The analysis showed a significant difference between women with explorative curettage in the peri / post menopausal group (Mann-Whitney U test: $Z = -7.395$; $p = 0.00001$) in addition to significantly younger women in perimenopause. In the control group of healthy patients, the mean age was 50.20 ± 7.36 years and 50% of them under the age of 50 for Median (IQR) = 50 (44-53).

The analysis, for $p > 0.05$, did not indicate a significant difference between the examined and the control group in terms of age (Mann-Whitney U test: $Z = -1.300$; $p = 0.194$). According to the analysis presented in Table 1, there was no significant difference ($p = 0.085$) between the two subgroups of the examined group in terms of BMI, while significance was found in the comparison of the examined and the control group ($p = 0.0001$) in addition to a significantly higher BMI in the examined group.

Regarding the level of glycemia, no significant difference was found between the two subgroups of the examined group ($p = 0.085$). The comparison of the examined and the control group indicated the existence of a significant difference in the level of glycemia in addition to a significantly higher level in the examined group ($p = 0.0001$). The additional analysis did not indicate a significant difference between the two subgroups of the test group, nor between the test and control groups in terms of levels of TSH, thyroxine and HbA1c (Table 1). The value of vitamin D was significantly higher in the control compared to the examined group ($p = 0.0001$).

Table 1. Analysis of selected clinical parameters by groups

Parameter	N	Examined Group (EG)/ Control Group (CG)			Percentiles			¹ p	² p
		$\bar{X} \pm SD$	Min/Max		25th	Median	75th		
BMI									
EG perimenopausis	52	31.0±5.2	21/44		27	30	35	Z=-1.722; p=0.085	Z=-3.878; p=0.0001*
EG postmenopausis	52	28.7±4.0	19/35		27	29	31		
CG	35	26.5±3.4	18/33		24	28	29		
Glycaemia (mmol/L)									
EG perimenopausis	52	5.7±0.7	4.1/8.6		5.3	5.6	5.8	Z=-2.748; p=0.006*	Z=-4.306; p=0.0001*
EG postmenopausis	52	5.5±0.8	4.5/10		4.9	5.3	5.6		
CG	35	5.1±0.4	4.3/6.5		4.8	5.1	5.3		
TSH (mU/L)									
EG perimenopausis	52	2.4±1.7	0.6/8.9		1.3	1.9	2.9	Z=-0.348; p=0.728	Z=-0.854; p=0.393
EG postmenopausis	52	2.5±2.0	0.3/11.9		1.4	2.1	2.9		
CG	35	2.2±1.6	0.7/9.8		1.2	1.7	2.8		
Thyroxine (pmol/L)									
EG perimenopausis	52	15.4±3.6	9.8/24		12.7	14.7	18.2	Z=-0.101; p=0.920	Z=-0.529; p=0.597
EG postmenopausis	52	15.5±3.6	10.1/24.5		12.8	14.7	18.3		
CG	35	15.1±4.0	9.5/23.5		10.9	15.2	17.1		
HbA1c (%)									
EG perimenopausis	52	5.9±0.6	4.7/7.8		7.8	5.5	5.7	Z=-1.964; p=0.050	Z=-0.978; p=0.328
EG postmenopausis	52	5.7±0.6	4.8/7.8		7.8	5.3	5.6		
CG	35	5.7±0.6	4.8/7.5		7.5	5.3	5.3		
Витамин Д (ng/mL)									
EG perimenopausis	52	15.2±10.2	3/41.6		7.1	12.3	20.7	Z=-1.060; p=0.289	Z=4.188; p=0.0001*
EG postmenopausis	52	12.5±7.5	3/42.7		7.5	10.9	16.8		
CG	35	21.9±10.6	5.5/48.2		13.9	21.0	29.4		

¹Mann-Whitney U test: peri/post menopausis ²Mann-Whitney U test: examined/control group
*significant for p<0.05

Our analysis indicated that in both subgroups of the examined group (pre- and post-menopausal), the metabolic syndrome was present in 35 (67.31%) vs. 27 (51.92%) patients, respectively. We did not find a significant association between the presence of metabolic syndrome and belonging to any of the subgroups of the examined group (Pearson Chi-square test = 2.5561; df = 1; p = 0.1099).

Additionally, in the examined and control group, metabolic syndrome was present in 62 (52.62%) vs. 8 (22.86%) patients. The analysis showed that patients from the examined group had 4.982 times [OR = 4.982 (2.06–12.02) 99% CI] significantly more often metabolic syndrome compared to women in the control group (Fig. 1).

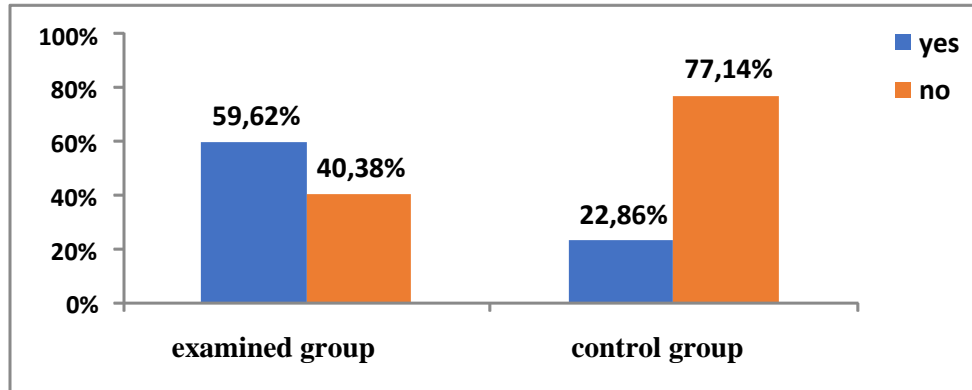


Fig. 1 Metabolic syndrome in the examined and control group

It was found: a) a significant linear strong negative correlation between changes in the endometrium and the level of vitamin D (Spearman Rank Order Correlations: $R = -0.3565$; $p = 0.00001$); b) a significant linear strong positive correlation between endometrial changes and glycemic level (Spearman Rank Order Correlations: $R = 0.3665$; $p = 0.00009$); and c) a significant linear positive correlation between endometrial changes and BMI (Spearman Rank Order Correlations: $R = 0.3311$; $p = 0.00007$).

Discussion

The incidence of endometrial cancer depends on age. In women aged 40 years the incidence is 12/100000, and in women aged 60 years the incidence is 84/100000 (14). Only 4% of these patients are under the age of 40, and 25% are premenopausal women. About 75% of EC cases occur in the postmenopausal period, and 50% of them are associated with risk factors [17].

In our study, in the examined group the average age of patients with fractionated explorative curettage in postmenopause was 57.96, and in perimenopause was 46.61 years. The analysis showed a significant difference between women with explorative curettage in the post / perimenopausal group in addition to significantly younger perimenopausal women. The mean age in the control group of healthy patients was 50.2 years.

Obesity and inactivity are two major risk factors associated with the development of endometrial cancer and endometrial hyperplasia. Other modifying risk factors include dietary habits, exercise, and the use of hormone therapy [18]. Regarding the height of BMI, in our study, significance was found in the comparison of the examined and the control group ($p = 0.0001$) in addition to a significantly higher BMI in the examined group (with fractional exploratory curettage).

The comparison of the examined and the control group indicated the existence of a significant difference in the level of glycemia in addition to a significantly higher level in the examined group ($p = 0.0001$). Several epidemiological studies have examined the association between type 2 diabetes and the incidence of cancer, and an increased risk of certain types of cancer has been detected, including endometrial cancer [19,20]. A meta-analysis by Zhang et al. found an increased risk of endometrial cancer in patients with diabetes [21]. The statistical analysis did not indicate a significant difference between the two subgroups of the test group, nor between the test and control groups in terms of TSH, thyroxine and

HbA1c levels. The value of vitamin D was significantly higher in the control compared to the examined group ($p = 0.0001$). Although, according to some studies, Vitamin D does not affect the risk of endometrial cancer, it suppresses obesity-induced premalignant lesions in animal models. Obesity is a significant risk factor for the EC. Yu et al., determined that dietary supplementation with vitamin D inhibited the carcinogenic effect of obesity on the endometrium [22].

Several studies have shown that metabolic syndrome (obesity, diabetes and hypertension), is strongly associated with the incidence and poor prognosis of endometrial cancer. A meta-analysis of six studies found that metabolic syndrome was strongly associated with an increased risk of EC in women (RR: 1.89, 95% CI 1.34-2.67) [23]. Our analysis showed that in both subgroups of the examined group, metabolic syndrome was present in 35 (67.31%) vs. 27 (51.92%) patients, respectively.

We did not find a significant association between the presence of metabolic syndrome and belonging to any of the subgroups of the examined group (Pearson Chi-square test = 2.5561; $df = 1$; $p = 0.1099$). In the examined group, 62 (52.62%) 8 (22.86%) of patients were with metabolic syndrome. In the control group only 8 (22.86%) were with metabolic syndrome. The analysis showed that patients with fractionated explorative curettage (from the examined group) had 4,982 times [OR = 4.982 (2.06–12.02) 99% CI] significantly more often metabolic syndrome compared to women in the control group.

Conclusion

Patients in the study group (with fractional explorative curettage) had a significantly higher Body Mass Index than those in the control group. Patients in the study group (with fractional explorative curettage) had significantly higher glycemic values than those in the control group.

The level of Vitamin D was significantly higher in the control compared to the examined group. Patients in the study group had 4.982 times more often metabolic syndrome compared to those in the control group. There was no significant difference between the examined and the control group in terms of the level of TSH, thyroxine and HbA1c.

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