

КЛИНИЧКИ ИСТРАЖУВАЊА

АНАЛИЗА НА ЕТИОЛОШКИ ФАКТОРИ ЗА ПОЈАВА НА ЕНДОМЕТРИЈАЛНА ХИПЕРПЛАЗИЈА ВО ПЕРИМЕНОПАУЗА

Анета Сима¹, Анита Арсовска², Слаѓана Симеонова-Крстевска¹, Ана Данева-Маркова¹, Драге Дабески¹

¹ Универзитетска клиника за гинекологија и акушерство, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, Република Северна Македонија

² Универзитетска клиника за неврологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, Република Северна Македонија

Извадок

Цитирање: Сима А, Арсовска А, Симеонова-Крстевска С, Данева-Маркова А, Дабески Д. Анализа на етиолошки фактори за појава на ендометријална хиперплазија во перименопауза. Arch J Здравје 2019;11(2):5-10.

Клучни зборови: ендометријална хиперплазија, ризик-фактори, перименопауза

***Кореспонденција:** Анета Сима, Универзитетска клиника за гинекологија и акушерство, Медицински факултет Универзитет „Св. Кирил и Методиј“ - Скопје, Е-mail: aneta_sima@yahoo.com

Примено: 21-јан-2019; **Ревидирано:** 25-апр-2019; **Прифатено:** 3-мај-2019; **Објавено:** 15-јун-2019

Печатарски права: © 2019 Анета Сима. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналните автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Целта на оваа студија беше да се евалуираат можните причини за појава на ендометријална хиперплазија во перименопауза. Материјал и методи: Беа анализирани 71 пациентка со неправилно крвавење, на возраст од 40-50 години, кај кои беше индицирана фракционирана киретажа. Зависно од хистопатолошкиот наод ги поделивме во 2 групи: група 1- со наод за ендометријална хиперплазија, група 2- атрофичен или ендометриум со дефицитни секреторни промени. Одредивме индекс на телесна маса (БМИ), обезитет дефиниран со БМИ > 30 kg/m², измеривме крвен притисок (cut-off вредност 135/90 mmHg), обем на струк (cut-off вредност 88 cm), како и податоци од анамнезата (возраст, физичка активност, тип на исхрана, пушење цигари). Сите овие податоци беа анализирани како етиолошки фактори во појавата на ендометријална хиперплазија. Резултати: Средна возраст на пациентките беше околу 47 години, а добиените резултати беа многу слични во двете испитувани групи. БМИ и обем на струк беа зголемени, хипертензија имаа повеќе од 60% од пациентките, но не беше утврдена статистичка значајност. Најголем дел беа со средно образование, а живењето во град статистички значајно го зголемува ризикот за ендометријална хиперплазија (p < 0,05). Што се однесува до животниот стил (физичка активност, калорична исхрана, пушење), резултатите покажаа дека мал дел се активни, речиси половина од нив конзумираат калорична храна и пушат, но без статистичка сигнификантност. Заклучок: Зголемената телесна тежина и покачениот крвен притисок имаат големо влијание врз започнување и прогресија на патолошки промени на ендометриумот. Како клинички доктори секогаш треба да помислиме на хиперплазија кај обезни и пациентки со хипертензија, кои неправилно крвават. Воедно треба и да ги едуцираме за промена на животниот стил, со цел спречување на гинеколошки и интернистички морбидитети.

CLINICAL SCIENCE

ANALYSIS OF ETIOLOGICAL FACTORS FOR EMERGENCE OF ENDOMETRIAL HYPERPLASIA IN PERIMENOPAUSE

Анета Сима¹, Анита Арсовска², Слаѓана Симеонова-Крстевска¹, Ана Данева-Маркова¹, Драге Дабески¹

¹ University Clinic of Gynecology and Obstetrics, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

² University Clinic of Neurology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

Abstract

Citation: Sima A, Arsovska A, Simeonova Krstevska S, Daneva Markova A, Dabeski D. Analysis of etiological factors for emergence of endometrial hyperplasia in perimenopause. Arch Pub Health 2019; 11(2): 5-10.

Key words: endometrial hyperplasia, risk factors, perimenopause

***Correspondence:** Aneta Sima, University Clinic of Gynecology and Obstetrics, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia. E-mail: aneta_sima@yahoo.com

Received: 21-Jan-2019; **Revised:** 25-Apr-2019; **Accepted:** 3-may-2019; **Published:** 15-Jun-2019

Copyright: © 2019. Aneta Sima. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Competing Interests: The author have declared that no competing interests

The aim of this study was to evaluate the possible reasons for the emergence of endometrial hyperplasia in perimenopause. Material and methods: A total of 71 patients with irregular bleeding were analyzed, at the age of 40-50 years, who should have undergone diagnostic curettage. Depending on the histopathological findings, we divided them into 2 groups: group 1-findings for endometrial hyperplasia, group 2 - atrophic or endometrium with deficient secretary changes. Body mass index (BMI) was determined (obesity defined with BMI >30 kg/m²); we measured blood pressure (cut-off value was 135/90 mmHg), waist circumference (cut-off value was 88 cm) as well as data of anamnesis (age, physical activity, type of diet, smoking cigarettes). All these data were analyzed as etiological factors in the emergence of endometrial hyperplasia. Results: The mean age of patients was 47 years, and the results obtained were very similar in both examined groups. BMI and waist circumference were increased, more than 60% of patients had hypertension, but not all had a statistical significance. Most of them were with completed secondary education, and city living statistically significantly increases the risk of endometrial hyperplasia (p < 0.05). As for the lifestyle (physical activity, caloric diet, smoking), the results have shown that a small number of patients are active, almost half of them consume caloric food and smoke, but without a statistical significance. Conclusion: Increased body weight and elevated blood pressure have a major impact on the onset and progression of pathological changes in the endometrium. As clinicians, we should always think of hyperplasia in obesity and patients with hypertension who are irregularly bleeding. At the same time, we should educate them to change the lifestyle in order to prevent gynecological and internistic morbidity.

Introduction

Endometrial hyperplasia is one of the common causes of irregular bleeding in the perimenopause period¹. The thickening of the endometrium occurs due to excess estrogen, progesterone deficiency (anovulation), and secretory transformation of the endometrium is avoided. Cut-off value of the perimenopausal endometrium is 11 mm; higher values suggest hyperplasia². Comparison of histological features is classified into 4 groups (by WHO): simplex, complex, simplex atypical and complex atypical hyperplasia³. This condition most commonly occurs around 50 years of age in women, but it is also possible in the reproductive period. By nature, it is benign, but a malignant transformation is possible too. In the etiology, several risk factors are mentioned: estrogen dominance, obesity, PCO syndrome, hypertension, diabetes, smoking, genetic predisposition, etc.⁴ Symptoms that indicate the presence of endometrial hyperplasia are irregular menstrual bleeding, bleeding in menopause. The diagnosis is made by ultrasound examination, hysteroscopy, endometrial biopsy, curettage⁵. Regarding treatment, depending on the type of hyperplasia, it can be conservative, with hormone therapy (gestagenic, oral, intrauterine device with gestagen) in hyperplasia without atypia, surgical removal (hysterectomy) in atypical hyperplasia, and in unsuccessful treatment with gestagens⁶. Obesity as a clinical entity is defined by overweight (BMI body mass index > 30), according to the World Health Organization⁷. The mechanism is carried out in several ways: it reduces the synthesis of sex hormone binding globulin (SHBG), increased conversion of androgens to estrogen in the peripheral fat tissue, then anovulation with low progesterone synthesis, etc.⁸

Unconcentrated estrogen action is a key point in the appearance of endometrial irregularities, including endometrial hyperplasia. According to the NHANES (National Health and Nutrition Survey), the age group of 40-59 years old is classified as obese, as a percentage of 68.1% of all respondents⁹. During this period, vis-

ceral fatty tissue, which is metabolic, is most active, increases insulin resistance, the risk of inflammatory, cardiovascular diseases, diabetes. The most suitable indicator of the amount of visceral fatty tissue is the waist circumference (up to 88 cm) and also the ratio of the waist circumference and hips (> 0.85). These values, together with BMI are the tools used in the diagnosis of obesity^{10,11}. The prevalence of hypertension (elevated blood pressure) in the total population is 30-33%¹². The diagnosis is made after several consecutive measurements of blood pressure, and the median is taken for consideration. If the values are 135 mm Hg for systolic and 90 mm Hg for diastolic pressure, hypertension is diagnosed¹³. According to Women's Health Study, in over 40,000 healthy women over 45 years of age, elevated blood pressure increases cardiovascular risk, as well as the risk of type 2 diabetes¹⁴. The increase in systolic blood pressure is mainly due to an increase in vascular resistance in arterial vessels combined with atherosclerotic changes in their wall. Hormonal changes in menopausal transition are also significantly affected¹⁵. Insulin resistance adversely affects blood pressure, body weight, lipid metabolism, and the onset of metabolic syndrome^{16,17}.

The aim of this study was to evaluate the possible reasons for the emergence of endometrial hyperplasia in perimenopause.

Material and methods

This study included 71 patients between the age of 40 and 50 who came to the University Gynecology and Obstetrics Clinic in Skopje because of irregular uterine bleeding. Medical history was obtained from all patients (type and amount of bleeding, age, physical activity, type of diet, BMI determination, blood pressure). Then a clinical examination followed (under a speculum, an ultrasound examination performed with Voluson 730 pro machine, vaginal device) and an indication for fractional curettage was set. After proper anesthesia preparation, short-term intravenous anesthesia was

performed by the curettage (the obtained material was placed separately in two vials - cervix and cavum uteri and sent to histological analysis). The histopathologic analyses were performed at the Institute of Oncology and Radiology- Skopje. After obtaining the results, patients were divided into two groups, depending on the histological finding: group 1 - with finding for endometrial hyperplasia, group 2 - atrophic or endometrium with deficient secretory changes. Possible etiological factors in the occurrence of endometrial hyperplasia (BMI, volume of structure, hypertension, age, place of residence, physical activity, type of diet, smoking of cigarettes, estrogen levels, reproductive history) were analyzed.

Inclusion criteria - patients between the age of 40 and 50 with irregular bleeding. Exclusion criteria - patients with hematological diseases, application of hormone therapy (contraceptives, replacement therapy, Tamoxifen).

Statistical analysis- The SPSS program, version 20 was used for analysis of the results in this study. Variables were analyzed with standard deviation (SD) and percent, t-test, chi-square test. Values of $p < 0.05$ were considered statistically significant.

Results

Table 1. Univariant analysis of variables - basic linear model

| Variables | With hyperplasia (N=39) | Without hyperplasia (N=32) | Statistical significance |
|---|--|---|--------------------------|
| BMI(kg/m ²) | 32.0±5.2 | 32.7±6.6 | NS |
| Waist circumference (cm) | 88.2±9.1 | 90.7±12.3 | NS |
| High blood pressure • systolic (mmHg) • diastolic(mmHg) | 28 (71.8%) • 138.9±16.6 • 88.2±9.7 | 20 (62.5%) • 138.7±12.0 • 87.8±6.7 | NS NS |
| Age | 46.9±1.6 | 47.7±1.5 | NS |
| Living in • city • village | • 17 (44%) • 22 (56%) | • 17 (22%) • 15 (78%) | P<0.05 P<0.05 |
| Physically active | 3 (7.7%) | 3 (9.3%) | NS |
| Caloric diet | 16 (41.0%) | 15 (46.8%) | NS |
| Education • primary • secondary • university | • 9 (23.1%) • 23 (58.9%) • 7 (17.9%) | • 11 (34.3%) • 17 (53.1%) • 4 (12.5%) | NS NS NS |
| Smokers | 20 (51.2%) | 15 (46.8%) | NS |

Table 1 shows the analyzed variables. Body mass index (BMI) in the hyperplasia group was median 32 ± 5.2 , and in the group without hyperplasia 32.7 ± 6.6 . The waist circumference was 88.2 ± 9.1 and 90.7 ± 12.3 in both groups, respectively. Hypertension was found in 71.8% of women in the hyperplasia group and 62.5% of the women without hyperplasia with a mean blood pressure value of 138.9 ± 16.6

/ 88.2 ± 9.7 mmHg vs. $138.7 \pm 12.0 / 87.8 \pm 6.7$ mmHg, respectively.

The mean age in the examined group was 46.9 ± 1.6 years versus 47.7 ± 1.5 years in the control group. Regarding the place of residence, 44% of women with hyperplasia live in the city, and 56% in the village vs. 22% of women in the control group who are from the city, and 78% from the village. Living in a city statistically

significantly increases the risk of endometrial hyperplasia ($p < 0.05$). Physically active were only 7.7% of women with hyperplasia, and non-significantly more than 9.3% of women without hyperplasia. Caloric diet was used by 41% of the investigated group versus 46.8% of the control group.

In terms of education, secondary educated women were dominant in both groups 58.9% vs. 53.1%, respectively. The percentage of smokers was high in both groups - 51.2% in the hyperplasia group versus 46.8% in the group of women without hyperplasia.

Table 2. Univariate analysis of hyperplasia

| Source | Type III Sum of Squares | Df | Mean Square | F | Sig. |
|---------------|-------------------------|----|-------------|-------|------|
| Model | 22,928 ^a | 11 | 2.084 | 8.159 | .000 |
| HTA | .049 | 1 | .049 | .192 | .663 |
| city | 1.112 | 1 | 1.112 | 4.353 | .041 |
| activity | .000 | 1 | .000 | .000 | .983 |
| diet | .056 | 1 | .056 | .217 | .643 |
| education | .198 | 2 | .099 | .388 | .680 |
| smoking | .089 | 1 | .089 | .350 | .556 |
| BMI | .005 | 1 | .005 | .018 | .894 |
| age | .444 | 1 | .444 | 1.737 | .193 |
| circumference | .006 | 1 | .006 | .023 | .880 |
| Error | 15.072 | 59 | .255 | | |
| Total | 38.000 | 70 | | | |

Table 2 shows the univariate analysis of hyperplasia as a dependent variable.

The results have shown that all variables have an independent impact on hyperplasia, other than the place of living, i.e. living in the city.

Discussion

Irregular uterine bleeding in the period of perimenopause is the most common symptom for which patients pay visit to a gynecologist. This is due to different diseases of the reproductive system, but also other diseases (internistic). Often these are benign conditions (polyps, hyperplasia, atrophic endometrium, deficient secretory phase, etc.), but premalignant and malignant conditions (atypical

hyperplasia, carcinoma) can occur¹⁸.

Patients need complex evaluation, to diagnose the condition, but also to detect additional risk factors that could lead to endometrial pathology (anovulatory cycles, age, parity, obesity, hypertension, diabetes, metabolic syndrome, etc.). In the study of Ozdemir et al. (2014), numerous non-gynecological factors were analyzed that affected the occurrence of endometrial pathology, including the occurrence of cancers. They proved the impact of obesity, hypertension, meta-

bolic syndrome, lipid imbalance on the endometrium⁵. The focus in this study was the analysis of endometrial hyperplasia and the risk factors for its appearance. Numerous studies in the world have also proven this association (along with increased BMI, increased waist circumference, waist/ hip ratio). Hormonal imbalance in the perimenopause period is crucial in the accumulation of adipose tissue, especially in the abdomen¹⁹. In our study the average age of patients was 47 years. The results confirmed hypertension as a risk factor, and this is most often associated with increased BMI, increased waist circumference, physical inactivity, caloric diet, and smoking. The incidence was similar in both examined groups and was also present in several cases of endometrial cancer (along with obesity, but this pathology was not the subject of our research), without statistical significance (Table 1). Life in the urban area significantly affects the occurrence of hyperplasia of the endometrium (Table 2). But, there is evidence in the world that all these factors are the cause of endometrial malignancies¹⁹.

Conclusion

Increased body weight and elevated blood pressure have a major impact on the onset and progression of pathological changes in the endometrium. In patients who are obese, with hypertension and irregular bleeding, we should proceed with further evaluation, searching for metabolic risk factors. Probably our area is responsible for the different phenotype of patients, as well as lifestyle and hence, we received different results in relation to similar studies conducted in America and Europe. In some future studies, the variables should be extended by analyzing additional metabolic parameters (glycemia, insulinemia, hormone and lipid status) in order to confirm the impact of impaired metabolism on reproductive organs. In order to reduce the prevalence of this pathology in perimenopause, it is necessary to educate patients to change their lifestyle, to lose weight, to increase physical activity, and to pay regular controls at gynecologist and internist offices. All these measures would help in preventing

serious gynecological and cardiovascular diseases, which would result in reducing morbidity and mortality in perimenopausal patients.

References

1. Zacur HA, Giuntoli RL, Jurema M. Endometrial Hyperplasia. UpToDate Online. Retrieved 2007; 5-26.
2. Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2006;32:588-592.
3. Emons G, Beckmann MW, Schmidt D, Mallmann P. Uterus commission of the Gynecological Oncology Working Group (AGO). New WHO Classification of Endometrial Hyperplasias. *Geburtshilfe Frauenheilkd* 2015; 75 (2):135-136.
4. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, et al. Risk factors for endometrial hyperplasia: results from a case-control study. *Int J Gynecol Cancer* 2002;12: 257-260.
5. Ozdemir S, Celik C, Gezginç K, Kireşi D, Esen H. Evaluation of endometrial thickness with transvaginal ultrasonography and histopathology in premenopausal women with abnormal vaginal bleeding. *Arch Gynecol Obstet* 2010; 282:395-399.
6. Trimble CL, Method M, Leitaio M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. *Obstet Gynecol* 2012; 120 (5):1160-1175.
7. World Health Organization Western Pacific Region. The Asia-Pacific perspective: redefining obesity and its treatment. Geneva: 2000.
8. Thurston RC, Sowers MR, Sutton-Tyrrell K, Everson-Rose SA, Lewis TT, Edmundowicz D, et al. Abdominal adiposity and hot flashes among midlife women. *Menopause* 2008;15:429-434.
9. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. *Ann Intern Med* 1978; 89:157-161.

10. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA* 2018; 319(16) : 1723–1725.
11. U.S. Preventive Services Task Force. Screening for obesity in children and adolescents: Recommendation statement. *Am Fam Physician* 2011; 83(6):739-740.
12. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension. An age-old debate. *Hypertension* 2008;51:952-959
13. Gierach GL, Johnson BD, BaireyMerz CN, Kelsey SF, Bittner V, Olson MB, et al. Hypertension, menopause and coronary artery disease risk in the Women's Ischemia Syndrome Evaluation (WISE) Study. *J Am Coll Cardiol* 2006;47:50S-58S.
14. Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: The Women's Health Study. *Eur Heart J* 2007;28:2937-2943.
15. Khalil RA. Sex hormones as potential modulators of vascular function in hypertension. *Hypertension* 2005;46:249-254.
16. Maas AHEM, Franke HR. Women's health in menopause with a focus on hypertension. *Netherlands Heart Journal* 2009;17(2):68-72.
17. Carr MC. The emerge of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88:2404-2411.
18. Wise, Michelle R. et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. *American Journal of Obstetrics & Gynecology* 2016; 214(6): 689.e1 - 689.e17
19. Paley CA, Johnson MI. Abdominal obesity and metabolic syndrome: exercise as medicine? *BMC Sports Sci Med Rehabil.* 2018;10:7.