RESEARCH ARTICLE

Evaluation of Endometrial Precancerous Lesions in Postmenopausal Obese Women - A High Risk Group?

Gokhan Acmaz[1]*, Huseyin Aksoy[2], Evrim Albayrak[3], Muruvet Baser[3], Sezin Ozyurt[1], Ulku Aksoy[1], Dilek Unal[4]

Abstract

Aim: To evaluate precancerous lesions such as hyperplasia and endometrial polyps in obese postmenopausal women. Materials and Methods: Women who were referred with abnormal uterine bleeding in postmenopausal period or the presence of endometrial cells on cervical cytology in our department were investigated. Anthropometric measurements such as height, weight, body mass index, waist/hip ratio and endometrial thickness were compared between a precancerous lesion (hyperplasia and endometrial polyp) group and a pathologically normal group. Results: We detected statistically significant thickening of endometrium in patients with precancerous lesions. Moreover patients with precancerous lesions had higher body mass index than the pathologically normal group. Conclusions: We found elevated precancerous lesion rates in overweight and obese women in the postmenopausal period, of interest given that the prevalence of obesity is increasing in most parts of the world. Although screening for endometrial cancer is not recommended for the general population, in high-risk populations like obese postmenopausal women, it may be very important.

Keywords: Endometrial hyperplasia - endometrial polyp - menopause - obesity - high risk group

Asian Pac J Cancer Prev, **15 (1)**, 195-198

Introduction

Obesity is defined as excessive body weight which represents the most important risk factor for endometrial precancerous lesions such as adenomatous and atypical hyperplasia of the endometrium in obese women. Adipose tissue, which increases with age and body weight, is the major conversion site of androstenedione to estrone (Gredmark et al., 1999; Reeves et al., 2007). The prevalence of obesity and excess weight increases with age. A study showed that 34.8% of adults 40 to 59 years old and 35.2% of 60 to 79 years old are obese (Ogden et al., 2007) and it is concluded that physical activities have protective effect on cancer (Kruk and Czerniak, 2013)

Endometrial hyperplasia (EH), which is thought to be caused by the prolonged, unopposed estrogenic stimulation of the endometrium, is a known risk factor for the development of endometrial cancer, particularly atypical EH, with a subsequent risk of up to 30% (Heller et al., 2011). It is established in literature that endometrial polyps (EP) and carcinoma may coexist in the same patient therefore sampling is necessary in patients with EP during menopausal period (Reinhold and Khalili 2002; Dubinsky et al., 2005).

Both EP and EH are related to the development of the endometrial carcinoma and therefore these situations can be accepted premalignant lesions in postmenopausal women. Screening for endometrial cancer is not recommended in general population. However, screening in high-risk population will be very important in the future (Milenković et al., 2005).

While obesity is increasing with the age, it is important to determine obesity related endometrial precancerous lesions in postmenopausal age for preventing patients from endometrial cancer. Therefore we aimed to evaluate the precancerous lesions such as EH and EP in risky postmenopausal patients.

Materials and Methods

A prospective study was conducted at the Kayseri Education and Research Hospital, Department of Obstetrics and Gynecology, Kayseri, Turkey, between March 2013 and September 2013. During a 6-month period all women (n=139) who were referred for abnormal uterine bleeding in postmenopausal period or the presence of endometrial cells on cervical cytology to the our department, were invited to participate in this

*[1]Department of Obstetrics and Gynecology, Kayseri Education and Research Hospital of Medicine, [2]Department of Obstetrics and Gynecology, Kayseri Military Hospital, [3]Department of Health Sciences, Erciyes University School of Medicine, [4]Department of Radiation Oncology, Kayseri Education and Research Hospital of Medicine, Kayseri, Turkey *For correspondence: gokhanacmaz@gmail.com*

study, and women ages 43-57 years, who fulfilled the inclusion criteria, were selected for inclusion. The Ethics Committee, Faculty of Medicine, Erciyes University, approved the study and informed consent was obtained from all the patients. After written consent was obtained, a structured in-person interview was conducted to elicit information on demographic factors, menstrual and reproductive history, hormone use, prior disease history, cigarette smoking and alcohol use, family history of cancer, and height and weight, past obstetric and medical history as well as ongoing pharmacological therapy was recorded. Hypertension or diabetes was registered if a woman reported treatment for the condition or said that a physician had diagnosed it.

A complete physical and gynecological examination was performed and routine laboratory tests were obtained to exclude systemic causes of bleeding. All patients underwent transvaginal ultrasound scanning to exclude the presence of other pathologies and to assess the endometrial thickness. All anthropometric measurements were recorded by a certified dietetic technician trained in anthropometry techniques. The technician obtained the measurements at the hospital.

Adiposity was estimated using both body weight and body mass index (BMI), which was computed as weight in kilograms divided by height in meters squared (kg/m^2). Body fat distribution was estimated using both waist circumference and waist hip ratio (WHR). BMI ≥ 30 kg/m^2 were considered obese for women (World Health Organization. WHO Technical Report Series 854. Geneva: 1995).

The inclusion criteria were following; BMI ≥ 30 kg/m^2 including symptoms of abnormal bleeding or the presence of endometrial cells on cervical cytology among women at postmenopausal age. Moreover patients who were administered our menopause clinic for routine control with thick endometrium >4mm, were included into the study. Ninety four women were excluded because of the presence of at least one of the exclusion criteria: BMI< 30 kg/m^2, use of steroid hormones during the 12 months prior to the study or use of oral contraceptives during their lifetime, patients with family history of endometrial cancer, liver disease, tamoxifen use, ovarian or endometrial tumor, endometriosis, bilateral oophorectomy or previous hysterectomy or endometrial ablation. The cases in which material was insufficient for biopsy were not considered in the analysis. At least we were capable of investigating 45 obese volunteers with postmenopausal bleeding (PMB) and the presence of endometrial cells on cervical cytology or thick endometrium.

Gynecologic pathologists assessed the histological samples and classified them using the 1994 World Health Organization classification of EH. This classification is comprised of four categories: (1) simple EH without atypia, (2) complex EH without atypia, (3) simple atypical EH and (4) complex atypical EH (Kleebkaow et al., 2008). We classified the findings as precancerous lesions (EH and EP) and normal results (secretuar endometrium, atrophic endometrium, proliferative endometrium and endometrial cells) then for the purpose of study women were divided into two groups as group 1 (women with precancerous lesions) and group 2 (pathologically normal group).

Diagnosis was based on outpatient endometrial curettage material. Dilatation and curettage was performed to according to our clinics description.

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution are presented as mean±SD. Median value is used where normal distribution is absent. Statistical analysis for the parametric variables was performed using the Student's t-test between two groups. The Mann-Whitney U test was used to compare nonparametric variables between two groups. Qualitative variables are given as percent and the correlation between categorical variables was investigated using the chi-square test. A p value of <0.05 was considered significant.

Results

This study examined only 45 obese postmenopausal women between the ages of 43-57. Table 1 shows comparison of demographic and clinical parameters between patient groups.

Table 1: Comparison of demographic and clinical parameters between patient groups

We detected statistically significant thick endometrium in patients with precancerous lesions (p<0.001). Moreover patients with precancerous lesions had higher BMI than pathologically normal group (p0.008). However, there was no significant difference between two groups in terms of other parameters (p>0.05).

Distribution of the patients according to their pathologic diagnose was illustrated in Table 2.

Table 2: Distribution of the patients according to pathological diagnose

Simple hyperplasia was the most common diagnose

Table 1. Comparison of Demographic and Clinical Parameters between Patient Groups

	Group 1	Group 2	p value
Age (years)	50.6±7.1	51.8±6.7	0.579
Gravida	4.41±2.19	5.83±2.55	0.051
Parity	3.0 (2.0-4.0)	4.0 (2.0-5.5)	0.338
Brest feeding (months)	16.0 (12.0-24.0)	12.0 (6.0-22.8)	0.507
Presence of diabetes mellitus (%)	3 (11.1)	5 (27.8)	0.151
Presence of hypertension (%)	8 (29.6)	7 (38.9)	0.371
Curettage time (minutes)	5.0 (5.0-10.0)	5.0 (5.0-10.0)	0.373
BMI (kg/m^2)	33.6±3.8	31.3±1.6	0.008
Waist/hip ratio	0.86±0.09	0.87±0.06	0.697
Endometrium (millimeter)	14.0 (2.0-80.0)	6.5 (4.0-20.0)	<0.001

Table 2. Distribution of the Patients According to Pathological Diagnose

Pathologic diagnose	n (%)
Simple hyperplasia without atipia	14 (31.1)
Complex hyperplasia without atipia	1 (2.2)
Simple hyperplasia with atipia	1 (2.2)
Complex hyperplasia with atipia	2 (4.4)
Endometrial polyp	9 (20.0)
Benign endometrial conditions	18 (40.0)

among patients with hyperplasia (14 of 18 patients). We detected simple EH without atipia in two of the 9 patients in EP patients.

Discussion

Endovaginal sonography is the initial imaging procedure of choice for evaluating PMB because of its ability to depict endometrial pathological conditions, its widespread availability, its excellent safety profile, and its cost-effectiveness (Bennett et al., 2011). In addition to evaluation for structural lesions, it is essential to repeat endometrial sampling to exclude EH or carcinoma. Reported rates of endometrial neoplasia in women evaluated for persistent or recurrent PMB vary widely, from 4 to 21 percent (Ronghe and Gaudoin, 2010).

EH is a common cause of PMB, which most often results from prolonged exposure of unopposed estrogen. The time course from a diagnosis of endometrial hyperplasia to carcinoma is not well known. A case control study reported that the average time to diagnosis of cancer was six years in women with all types of EH (Lacey et al., 2010).

EPs are more common in postmenopausal women. Patients with PMB and endometrial polyps usually undergo endometrial sampling and the removal of polyps because foci of atypical hyperplasia or carcinoma may be present at histopathology in a benign-seeming polyp, or endometrial polyps and carcinoma may coexist in the same patient (Dubinsky et al., 1995; Lacey et al., 2010).

Adenocarcinoma of the endometrium is the most common gynecological cancer (Turan et al., 2012). On the basis of this knowledge we aimed to investigate precancerous lesions in obese risky postmenopausal population and we found that ET was statistically thicker in patients with precancerous pathology than patients with normal pathologic results. Moreover patients with precancerous lesions (group 1) had significantly higher BMI than patients in group 2. Pathologic results of the patients revealed that EH were found 18 of 45 patients (40 %) and EP were found 9 of 45 patients (20%).

Several reports have revealed conflicting rates for EH in patients with obesity. Epplein et al. (2008) investigated EH in 57 obese (BMI 30-39.9) and 42 morbid obese (BMI≥40) patients. EH was found 35 of 57 patients (61.4%) in obese group and 35 of 42 (83.3%) patients in morbid obese group. They concluded that obesity is associated with increased levels of circulating estrogen relative to progesterone by several mechanisms including increased conversion of androstenedione to estrone within adipose stores, decreased circulating sex hormone-binding globulins, and increased rates of chronic anovulation. Moreover they found that 4-fold increase in the incidence of EH with atypia in women with obesity and 13-fold increased risk of EH with atypia and a 23-fold increased risk of EH without atypia in women with morbid obesity.

Van den Bosh et al. (1996) investigated 145 patients with PMB and 55 (37.9 %) of the patients were diagnosed pathologically as hyperplasia or polyp and 8 were diagnosed as endometrial cancer. Thus 63 patients (% 43) were diagnosed with precancerous or cancerous lesions. However they concluded that weight and BMI have little clinical relevance in the diagnosis of endometrial disease in postmenopausal women.

Anthony P et al. (2001) and Tingthanatikul Y et al. (2006) investigated EH in patients with PCOS in other words they investigated endometrial hyperplasia in risky population. The ET on ultrasound correlates positively with EH. In cases with day 3 ET on USG >7 mm, the prevalence of EH varies from 35.7% to 45.6%. Most cases were simple EH and only 1.75% was simple EH with atypia. Age, BMI and WHR did not predict EH, whereas the endometrial hyperechogenic pattern was a clinical predictor of EH with borderline significance. In conclusion, this study demonstrated that almost half of the anovulatory women with amenorrhea had EH. In view of these findings, an endometrial biopsy should be performed in all women with PCOS (Tingthanatikul et al., 2006). Viola et al., (2008) investigated 12 postmenopausal obese patients and hyperplasia was found 6 of 12 patients (50%) in their study group.

Rates of hyperplasia in our study were lower than those Epplein et al and Viola et al (2008). However there are some differences between our study and above mentioned studies. They did not exclude patients with family history of endometrial cancer. Moreover their study group was consisted of heterogeneous patients such as parity of the obese patients in postmenopausal group was significantly lower than control group. There were no significant differences between precancerous lesion and pathologically normal group for parity in our study. Our study group was not only obese but also they were in risky age for hyperplasia and their mean age was 48 (45-55) years old in precancerous group and 50.5 (45-52) in normal pathology group. Therefore we are of the opinion that both ages and BMIs of patients are responsible for high percentage of precancerous lesions.

It has been shown that estimated prevalence of EP is 13-50% of women with abnormal uterine bleeding (Lieng et al., 2009; Lasmar et al., 2010). The risk factors for malignancy are high BMI, arterial hypertension, advanced age, postmenopausal period, and use of tamoxifen.

Our results show that endometrial polyps were found 9 of 45 patients (20%) and 2 of the 9 polyps showed simple hyperplasia without atipia. In a study authors investigated EP size and polyp hyperplasia. They showed that endometrial polyps greater than 15 mm showed a hyperplasia rate of 14.8%, compared with 7.7% in the group with smaller polyps (Lasmar BP and Lasmar RB, 2013). Our results were similar with this study however we did not classified polyps according to their size.

In conclusion, we found serious precancerous lesion rates in overweight and obese women at the postmenopausal period, which so far had not been described extensively. Obesity bears a high social price and represents elevated costs for the health-care system. The prevalence of obesity is increasing in most parts of the world and in view of the associated health risks. Although screening for endometrial cancer is not recommended in general population, screening in an identified high-risk population is very important. Obese post-menopausal women could be one such group.

References

Anthony P (2001). Cheung Ultrasound and Menstrual History in Predicting Endometrial Hyperplasia in Polycystic Ovary Syndrome Obstetrics and Gynecology. *ACOG*, **98**, 325-31.

Bennett GL, Andreotti RF, Lee SI, et al (2011). ACR appropriateness criteria on abnormal vaginal bleeding. *J Am Coll Radiol*, **8**, 460-8.

Dubinsky TJ, Parvey HR, Gormaz G, et al (1995). Transvaginal hysterosonography: comparison with biopsy in the evaluation of postmenopausal bleeding. *J Ultrasound Med,* **14**, 887-93.

Epplein M, Susan D Reed, Lynda F Voigt, et al (2008). Weiss Risk of Complex and Atypical Endometrial Hyperplasia in Relation to Anthropometric Measures and Reproductive History. *Am J Epidemiol*, **168**, 563-70.

Gredmark T, Kvint S, Havel G, Mattsson LA (1999). Adipose tissue distribution in postmenopausal women with adenomatous hyperplasia of the endometrium. *Gynecol Oncol*, **72**, 138-42.

Heller DS, Mosquera C, Goldsmith LT, Cracchiolo B (2011). Body mass index of patients with endometrial hyperplasia: comparison to patients with proliferative endometrium and abnormal bleeding. *J Reprod Med*, **56**, 110-2.

Kleebkaow P, Maneetab S, Somboonporn W, et al (2008). Preoperative and Postoperative Agreement of Histopathological Findings in Cases of Endometrial Hyperplasia. *Asian Pac J Cancer Prev*, **9**, 89-91.

Kruk J, Czerniak U (2013). Physical Activity and its Relation to Cancer Risk: Updating the Evidence. *Asian Pac J Cancer Prev*, **14**, 3993-4003.

Lacey JV Jr, Sherman ME, Rush BB, et al (2010). Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol*, **28**, 788-92.

Lasmar RB, Barrozo PR, Parente RC, et al (2010). Hysteroscopic evaluation in patients with infertility. *Rev Bras Ginecol Obstet*, **32**, 393-7.

Lasmar BP, Lasmar RB (2013). Endometrial Polyp Size and Polyp Hyperplasia. *Int J Gynaecol Obstet*, 0020-7292, 00425-6. [Epub ahead of print]

Lieng M, Istre O, Sandvik L, et al (2009). Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. *J Minim Invasive Gynecol*, **16**, 465-71.

Milenković V, Sparić R, Atanacković J, et al (2005). Methods of screening for endometrial cancer. *Srp Arh Celok Lek*, **133**, 199-201.

Ogden CL, Yanovski SZ, Carroll MD, et al (2007). The epidemiology of obesity. *Gastroenterology*, **132**, 2087-102.

Reeves GK, Pirie K, Beral V, et al (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*, **335**, 1134-45.

Reinhold C, Khalili I (2002). Postmenopausal bleeding: value of imaging. *Radiol Clin North Am*, **40**, 527-62.

Ronghe R, Gaudoin M (2010). Women with recurrent postmenopausal bleeding should be re-investigated but are not more likely to have endometrial cancer. *Menopause Int*, **16**, 9-11.

Tingthanatikul Y, Choktanasiri W, Rochanawutanon M, et al (2006). Prevalence and clinical predictors of endometrial hyperplasia in anovulatory women presenting with amenorrhea. *Gynecol Endocrinol*, **22**, 101-5.

Turan T, Karadag B, Karabuk E et al (2012). Accuracy of frozen sections for intraoperative diagnosis of complex atypical endometrial hyperplasia. *Asian Pac J Cancer Prev*, **13**, 1953-56

Van den Bosch T, Vandendael A, Van Schoubroeck D, et al (1996). *Acta Obstet Gynecol Scand*, **75**, 181-2.

Viola AS, Gouveia D, Andrade L, et al (2008). Prevalence of endometrial cancer and hyperplasia in non-symptomatic overweight and obese women, *Aust N Z J Obstet Gynaecol*, **48**, 207-13.

World Health Organization. WHO *Technical Report Series 854*. Geneva: 1995. Physical Status: The use and interpretation of anthropometry. Report of a WHO Consultation. *World Health Organ Tech Rep Ser*, **854**, 1-452