Arch Gynecol Obstet
DOI 10.1007/s00404-016-4043-8

GYNECOLOGIC ONCOLOGY

Could body mass index be an indicator for endometrial biopsy in premenopausal women with heavy menstrual bleeding?

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Received: 26 November 2015 / Accepted: 9 February 2016

Abstract
Purpose To evaluate the role of body mass index (BMI) in women with premenopausal heavy menstrual bleeding (HMB) to identify patients who should undergo endometrial biopsy.
Methods This prospective cohort study included 1120 premenopausal women who presented to the Gynecology Clinic, Bakirkoy Dr. Sadi Konuk Training and Research Hospital in Istanbul, Turkey, due to HMB and who underwent endometrial sampling. The abnormal endometrial histopathological results were analyzed by separating patients into groups of all abnormal findings (hyperplasia without atypia + hyperplasia with atypia + carcinoma) and hyperplasia with atypia + carcinoma. Sensitivity and specificity of the abnormal histopathological results were calculated in both groups using BMI cut-off values as 25, 30 and 35 and age cut-offs as 40 and 45 years.
Results The rate of hyperplasia with atypia and carcinoma was sevenfold higher in women with a BMI ≥30 compared to those with a BMI ≤30 (95 % CI 2.4–17.9). In the analyses, BMI was a stronger risk factor in women younger than 45 years of age. The risk of endometrial carcinoma and atypical hyperplasia was twofold higher in patients older than 45 years when compared with patients younger than 45 years (95 % CI 1.1–5.1).
Conclusions All women with a BMI ≥30 and presenting premenopausal HMB should undergo endometrial biopsy regardless of age.

Keywords Body mass index · Endometrial carcinoma · Endometrial hyperplasia · Endometrial sampling · Premenopausal bleeding

Introduction

Endometrial carcinoma is the most common gynecological malignancy in developed countries, with a reported incidence of 12.9 per 100,000 [1]. The mean age at presentation is 61 years but between 5 and 30 % of women affected are younger than 50 years of age [2, 3]. The most common and earliest symptom of endometrial carcinoma is heavy menstrual bleeding (HMB). Although there is no doubt of the necessity for endometrial biopsy in postmenopausal women with HMB, the diagnostic approach and patient selection criteria for premenopausal women are still controversial [4].

Aside from age, several risk factors for endometrial cancer and endometrial hyperplasia have been identified, including obesity, nulliparity, late menopause, diabetes, hypertension and a history of polycystic ovary syndrome (PCOS) [2–6]. These risk factors have a strong relationship with premalignant and malignant endometrial lesions, especially when observed in the premenopausal period [2, 7–9]. As reported in several previous studies, obesity is one of the most important risk factors for endometrial hyperplasia and endometrial cancer [5, 8, 10–13]. Despite this strong relationship, only a few studies have evaluated the

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Published online: 20 February 2016

effect of obesity on the decision to perform endometrial biopsy in premenopausal patients with HMB. The majority of studies related to HMB have identified a cut-off age for endometrial evaluation. Most of these studies have been retrospectively designed and evaluation of obesity is based on self-reported values of height and weight, which are less accurate values than direct measurements [14, 15].

The aim of this prospective designed study was to find out a cut-off level of age and BMI in decision of endometrial biopsy for patients with premenopausal HMB.

Materials and methods

This prospective study was conducted after obtaining approval from local ethical committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (approval number 2014/08/10). 2618 women with heavy menstrual bleeding were admitted to our outpatient clinic during the time period between June 2014 and June 2015. A total of 1310 patients with juvenile/postmenopausal bleeding, using progesterone/estrogen treatment or positive β-human chorionic gonadotropin levels were excluded from the study population. 151 of the patients declined to participate. 37 of the patients lost to follow-up or discontinued intervention before the procedures. After all, endometrial sample results of 1120 premenopausal women with HMB were evaluated.

Data were recorded for the study population considering; age, height, weight, parity, familial history of endometrial and colon cancer, diabetes, hypertension and history of PCOS.

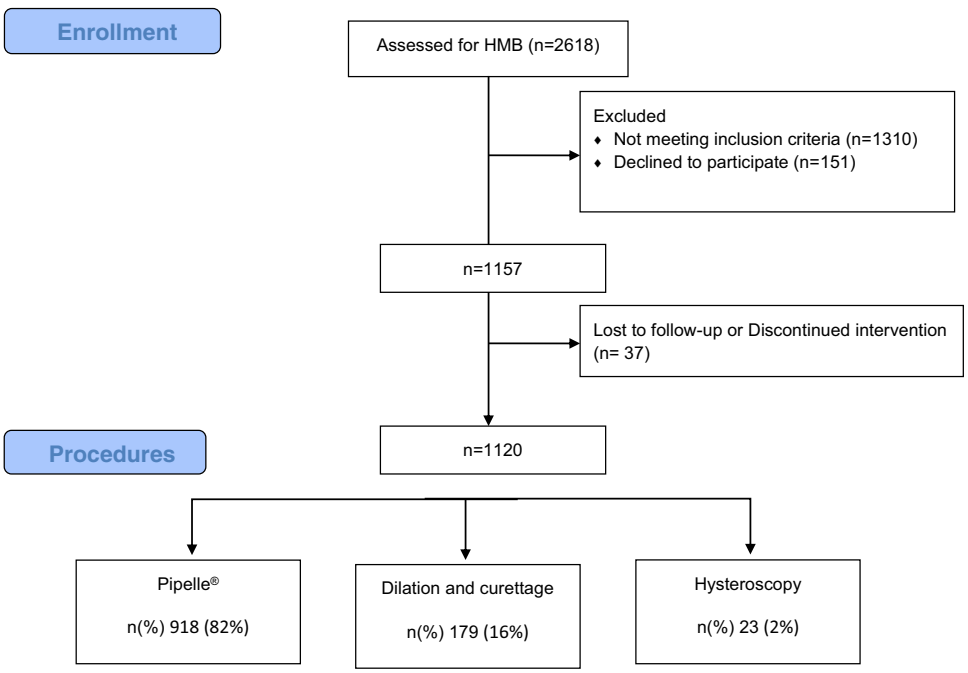
Most endometrial sampling was performed using a Pipelle curette (Pipelle® Endometrial Suction Currette, CooperSugical, Tuttlingen, Germany) without anesthesia. Dilation and curettage under general anesthesia was used for the patients when the material obtained with the Pipelle curette was insufficient for histological evaluation. In cases where sufficient material could not be obtained with dilation and curettage, biopsy was performed under hysteroscopy guidance.

Abnormal endometrial pathologies were defined as hyperplasia without atypia, hyperplasia with atypia and cancer, while benign pathologies included secretory and proliferative endometrium, irregular proliferation, inflammation, endometrial polyps and atrophic changes.

The abnormal endometrial histopathological results were analyzed by separating patients into the following two groups: all abnormal findings (hyperplasia without atypia + hyperplasia with atypia + carcinoma) and hyperplasia with atypia + carcinoma.

The patients were separated into four groups according to the BMI values: <25.0 (normal weight), 25.0–29.9 (overweight), 30.0–34.9 (class I obesity) and ≥35 (class II–III obesity) [16]. Sensitivity and specificity of the histopathological results were calculated for both groups using BMI cut-off values of 25, 30 and 35 and age cut-offs of 40 and 45 years. Independent risk factors were determined separately for the two groups with abnormal histopathological results.

Flow Diagram of the study population



The study data were analyzed using NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programs. The Pearson Chi square test and Fisher's exact test were used, as appropriate, to compare the qualitative data. The utility of using BMI to predict endometrial pathology was examined with receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity were calculated for different cut-off values of BMI and age. To identify independent risk factors for endometrial pathology, the potential risk factors identified in univariate analysis were evaluated with logistic regression analysis. Hosmer–Lemeshow goodness-of-fit statistics were used to assess model fit. A 5 % type-I error level was used to infer statistical significance.

Results

In 918 (82 %) cases, the endometrial sample was taken with a Pipelle curette without anesthesia. Dilation and curettage was performed under general anesthesia in 179 (16 %) cases, and 23 (2 %) cases by hysteroscopic guidance.

Table 1 Patient characteristics of the study population

	Mean ± SD (range) or *n* (%)
Age	44 ± 5 (19–53)
BMI	29 ± 5 (16–50)
Parity	2.7 ± 1.5 (0–12)
Nulliparity	59 (5.3 %)
Diabetes	184 (16.4 %)
Hypertension	285 (25.4 %)
PCOS	69 (6.2 %)
Family history of endometrial cancer	63 (5.6 %)
Family history of colon cancer	41 (3.7 %)

The mean age of the patients was 44 ± 5 years (range 19–53 years) and the mean BMI was 29 ± 5 (range 16–50). The characteristics of the study population are presented in Table 1. Two hundred and forty-nine (22 %) patients were with normal weight (BMI <25), 431 (38 %) were overweight (BMI 25–29.9), and 440 (39 %) were in obese category (BMI ≥30). Approximately half of the patients ($n = 547$, 49 %) were 45 years or older. The endometrial histological findings of 1120 premenopausal women with HMB stratified by age and BMI are shown in Table 2.

The vast majority ($n = 1060$, 94.6 %) had benign endometrial histology. A total of 60 (5.4 %) patients had abnormal histology; 28 (2.5 %) patients had hyperplasia without atypia, 20 (1.8 %) had hyperplasia with atypia, and 12 (1.1 %) had carcinoma. Of the 60 patients with abnormal endometrial histology, 47 (78 %) were obese (BMI ≥30 kg/m^2) and 13 were overweight (BMI 25–29.9). None of the normal weighted patients (BMI <25 kg/m^2) had abnormal histology. The majority of patients with hyperplasia with atypia and carcinoma histology ($n = 29$, 91 %) were ≥40 years, and 22 (69 %) were ≥45 years.

The distribution of risk factors among the study participants was as follows: age ≥40 years (81.5 %), age ≥45 years (48.8 %), BMI ≥30 (39.3 %), BMI ≥35 (14.2 %), diabetes (16.4 %), hypertension (25.4 %), nulliparity (5.3 %), history of PCOS (6.2 %), family history of colon cancer (3.7 %), and family history of endometrial cancer (5.6 %). In the univariate analysis, all abnormal findings including hyperplasia without atypia, hyperplasia with atypia, and carcinoma were found to be statistically significantly more frequent among patients with a BMI ≥30, those who were nulliparous, those with diabetes and those with a history of PCOS. When hyperplasia

Table 2 The endometrial histological findings of 1120 premenopausal women with heavy menstrual bleeding categorized according to age and BMI groups

	Benign histology (*n*)	Hyperplasia without atypia (*n*)	Hyperplasia with atypia (*n*)	Carcinoma (*n*)	Total (*n*)
BMI (kg/m$^{2)}$					
<25	249 (0)	0 (0)	0 (0)	0 (0)	249 (22.2)
25–29.9	418 (97.0)	8 (1.9)	4 (0.9)	1 (0.2)	431 (38.5)
30–34.9	260 (92.5)	9 (3.2)	8 (2.8)	4 (1.4)	281 (25.1)
≥35	133 (83.6)	11 (6.9)	8 (5.0)	7 (4.4)	159 (14.2)
Age (years)					
<35	47 (94.0)	2 (4.0)	1 (2.0)	0 (0.0)	50 (4.5)
35–39	150 (95.5)	5 (3.2)	1 (0.6)	1 (0.6)	157 (14.0)
40–44	351 (95.9)	8 (2.2)	6 (1.6)	1 (0.3)	366 (32.7)
≥45	512 (93.6)	13 (2.4)	12 (2.2)	10 (1.8)	547 (48.8)
Total	1060 (94.6)	28 (2.5)	20 (1.8)	12 (1.1)	1120 (100)

Values in parentheses indicate percentages

Table 3 Univariate analysis of risk factors for different histologic groups in premenopausal women

Risk factors	Total ($n = 1120$)	All abnormal findings[a] ($n = 60$)		Hyperplasia with atypia + carcinoma ($n = 32$)	
	N	*n* (%)	*p*	*n* (%)	*p*
Age (years)					
≥45	547	35 (6.4)	0.130	22 (4.0)	0.022
<45	573	25 (4.4)		10 (1.7)	
BMI (kg/m^2)					
≥30	440	47 (10.7)	0.001	27 (6.1)	0.001
<30	680	13 (1.9)		5 (0.7)	
Diabetes					
Yes	184	19 (10.3)	0.001	13 (7.1)	0.001
No	936	41 (4.4)		19 (2.0)	
Nulliparity					
Yes	59	9 (15.3)	0.003	5 (8.5)	0.023
No	1061	51 (4.8)		27 (2.5)	
PCOS					
Yes	69	8 (11.6)	0.026	4 (5.8)	0.129
No	1051	52 (4.9)		28 (2.7)	

[a] Hyperplasia without atypia + hyperplasia with atypia + carcinoma

without atypia was excluded, age of 45 years and older determined as a risk factor but PCOS was not a risk factor ($p = 0.022$ and 0.129, respectively) (Table 3). No statistically significant difference was found between patients aged ≥40 years and those aged ≤40 years with respect to endometrial pathologies ($p = 0.710$). The rates of endometrial hyperplasia and endometrial cancer were found to be similar in patients with a familial history of endometrial and colon cancer.

From the multivariate analysis, obesity and nulliparity were found to be independent risk factors in both groups with abnormal histology, and age ≥45 years and diabetes were independently related to the risk of hyperplasia with atypia and carcinoma. The rates of all abnormal findings (hyperplasia with and without atypia and carcinoma) were fivefold greater in obese patients than in nonobese patients (95 % CI 2.7–10.0), and when endometrial hyperplasia without atypia was excluded, a sevenfold increased risk was found (95 % CI 2.4–17.9). Nulliparity was associated with increased fourfold risk of hyperplasia with atypia and carcinoma (95 % CI 1.4–11.9), while diabetes and age ≥45 years were related to a twofold increase in risk (95 % CI 1.0–4.7 and 1.1–5.1, respectively) (Table 4).

In the ROC analysis, a significant relationship was found between abnormal endometrial histological results and BMI (AUC = 0.785 for all abnormal findings, AUC = 0.819 for hyperplasia with atypia + carcinoma). The ROC curves for each group are shown in Fig. 1. The sensitivity and specificity values of the various BMI cut-off values for both histopathology groups are shown in Table 4. With a BMI cut-off of 30, both histopathological groups had acceptable specificity and the highest sensitivity (Table 5).

Prevalence of endometrial hyperplasia and carcinoma stratified by age and BMI is shown in Table 6. BMI ≥30 is the strongest predictor of endometrial hyperplasia and carcinoma. A biopsy result indicative of hyperplasia or carcinoma was found in 11 % of obese patients compared with 5.4 % of the overall sample. The correlation between obesity and atypical hyperplasia and carcinoma was more evident among patients aged <45 years (0.3 vs 4.7 %; RR 17, 95 % CI 2.1–140.8). Patients aged ≥45 years and who had a BMI ≥30 kg/m^2 were at highest risk, while those aged <45 years and who had a BMI <30 were at lowest risk.

Discussion

The results of the current study showed abnormal endometrial histology in 5.4 % of 1120 premenopausal women with HMB. The major risk factors for endometrial hyperplasia and carcinoma in study were BMI ≥30 kg/m^2 and nulliparity. When hyperplasia without atypia was excluded from the analysis, age ≥45 years and diabetes were also independently associated with abnormal pathological findings. The current study revealed that the

Table 4 Independent risk factors for endometrial hyperplasia and carcinoma in premenopausal women with heavy menstrual bleeding

Risk factors	All abnormal findings[a]		Hyperplasia with atypia + carcinoma	
	RR (95 % CI)	*p*	RR (95 % CI)	*p*
Age ≥45 (years)	NS	NS	2.3 (1.1–5.1)	0.037
BMI ≥30 (kg/m^2)	5.2 (2.7–10.0)	0.001	6.6 (2.4–17.9)	0.001
Diabetes	1.6 (0.9–3.0)	0.126	2.2 (1.0–4.7)	0.048
Nulliparity	4.0 (1.8–9.1)	0.001	4.1 (1.4–11.9)	0.008

Results are from multivariate analyses

NS not significant

[a] Hyperplasia without atypia + hyperplasia with atypia + carcinoma

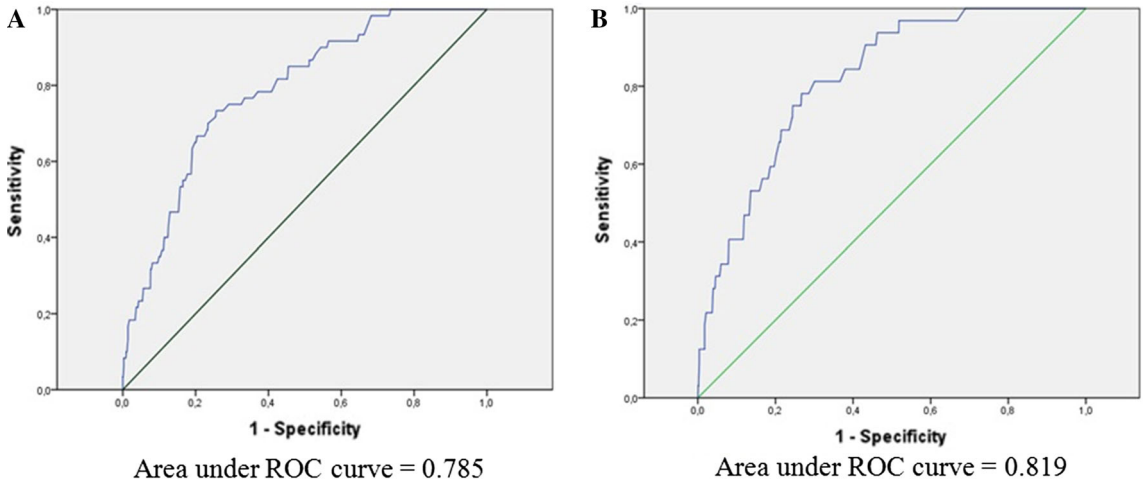


Fig. 1 ROC curves for BMI with all abnormal findings (**a**) and with endometrial hyperplasia with atypia and carcinoma (**b**)

Table 5 The sensitivity and specificity of different BMI cutoffs in different endometrial histopathology groups

Cut-off BMI (kg/m^2)	Sensitivity (%)	Specificity (%)	ROC (95 CI)	*p*
All abnormal findings[a]				
≥25	100	25.0	0.785 (0.731–0.839)	0.001
≥30	78.3	62.9		
≥35	43.3	87.5		
Hyperplasia with atypia + carcinoma				
≥25	100	25.0	0.819 (0.758–0.880)	0.001
≥30	84.4	62.0		
≥35	46.9	86.8		

[a] Hyperplasia without atypia + hyperplasia with atypia + carcinoma

Table 6 Prevalence of the endometrial hyperplasia and carcinoma according to different age and BMI groups

	All abnormal findings[a] Prevalence	Hyperplasia with atypia + carcinoma Prevalence
All patients	60/1120 (5.4 %)	32/1120 (2.9 %)
Age ≥45	35/547 (6.4 %)	22/547 (4 %)
BMI ≥30	47/440 (10.7 %)	27/440 (6.1 %)
Age <45		
BMI ≥30	18/190 (9.5 %)	9/190 (4.7 %)
BMI <30	7/383 (1.8 %)	1/383 (0.3 %)
Age ≥45		
BMI ≥30	29/250 (11.6 %)	18/250 (7.2 %)
BMI <30	6/297 (2.0 %)	4/297 (1.3 %)

[a] Hyperplasia without atypia + hyperplasia with atypia + carcinoma

prevalence of endometrial hyperplasia and carcinoma was significantly higher in obese (BMI ≥30) premenopausal women than in nonobese (BMI <30) premenopausal women with HMB, and the effect of a high BMI was more pronounced in patients below age 45.

There is a strong relationship between obesity and endometrial cancer according to previous published series in the literature [5, 10]. In a study by Farquar et al., which was based on important basic guidelines, body weight of ≥90 kg was reported to be the most significant risk factor for endometrial pathologies [5, 17]. However, the retrospective cohort study used body weight rather than BMI, which is a less reliable indicator of body fat. In a meta-analysis of 40 studies in 2015, Jenabi and Poorolajal reported a 1.5-fold

increased risk of endometrial carcinoma in overweight women and a 2.5-fold increased risk in obese women [10]. According to the results of that meta-analysis, cancer risk increased with increasing BMI and this provided evidence of a strong causal relationship between BMI and endometrial cancer. The results of another meta-analysis reported that with every 5 kg/m^2 increase in BMI, the risk of endometrial cancer was increased as 1.5-fold [12]. Similarly, the results of the current study showed endometrial cancer in 0.2 % of the overweight patients, in 1.4 % of the class I obese patients, and 4.4 % of the class II–III obese patients. Endometrial hyperplasia, especially hyperplasia with atypia, has been found to have similar risk factors to endometrial cancer and is similarly correlated with obesity [11, 13, 18]. In an Italian case–control study of 129 women with complex hyperplasia without atypia, obesity was defined as a BMI $\geq$30, and using those with a BMI <30 as the reference group, an odds ratio of 2.4 (95 % CI 1.0–5.9) was obtained for premenopausal women, though the data were self-reported [6]. Similarly, in an American case–control study of 440 cases of complex and endometrial hyperplasia with atypia, there was a 4.6-fold increase in complex hyperplasia (95 % CI 2.1–10.3) and a 3.7-fold increase in hyperplasia with atypia (95 % CI 1.0–13.8) in obese women compared with women with normal weight [11]. In morbidly obese women (BMI $\geq$40), the risk of complex hyperplasia increased 23-fold (95 % CI 6.6–79.8), and the risk of hyperplasia with atypia increased as 13-fold (95 % CI 1.9–86.9). In that study, the strongest correlation between increased BMI and endometrial hyperplasia was among patients aged <52 years. Consistent with both the above-mentioned studies, the results of the current study found the risk of endometrial hyperplasia with atypia and carcinoma to be approximately sevenfold greater in obese women with premenopausal HMB compared with nonobese women. As the study group was limited to premenopausal women, no comparison was made with postmenopausal women. However, it was observed that the relationship of obesity with endometrial hyperplasia and carcinoma was more stronger (RR 17, 95 % CI 2.1–140.8) in premenopausal patients younger than 45 years, which is consistent with several previous studies [2, 7–9, 11].

Although the relationship between obesity and endometrial pathologies has been reported several times, to the best of our knowledge, aside from the study by Farquar et al. that recommended endometrial biopsy for patients over 90 kg regardless of age, no study has recommended a cut-off BMI value for endometrial biopsy in women with premenopausal HMB [5]. In a Norwegian study of more than 35,000 women, approximately 60 % of whom were younger than 55 years, that had a mean follow-up period of 15.7 years and a strong correlation was reported between BMI and the risk of endometrial cancer [13]. According to the results of that study, while BMI showed a linear relationship with the risk of endometrial cancer in patients over 55 years of age, in those below the age of 55, increased risk was only in question for those with a BMI $\geq$35. It was reported that because of this threshold effect in young premenopausal women, BMI increased the risk of endometrial cancer through different mechanisms at different ages. This result showing that a cut-off BMI value can be defined for endometrial pathologies in premenopausal patients supports the hypothesis of our study. BMI values were found to be useful in prediction of abnormal endometrial pathologies in premenopausal women with respect to evaluation of ROC analysis in our study. The results of the current study were observed to be consistent with the Norwegian study, as 84 % sensitivity (with 62 % specificity) was shown with a BMI cut-off value of 30 kg/m^2 to differentiate cancer or atypical hyperplasia from benign endometrial pathologies. These results are also consistent with the guidelines of the Society of Obstetricians and Gynaecologists of Canada, which were revised in 2013 to include a BMI $\geq$30 instead of body weight for indications for endometrial biopsy in premenopausal women with HMB [17].

It has been reported that among women with endometrial cancer, 19 % are aged 45–54 years and 6 % are aged 35–44 years [19]. Due to this strong relationship with age, studies related to endometrial evaluation in women with premenopausal HMB have commonly been directed towards defining an age cut-off. Similarly in the guidelines, although age is reported as the most important indicator for the recommendation for endometrial biopsy, there are differences in the recommended cut-off ages. Some guidelines have recommended endometrial biopsy for all women with HMB who are older than 40 years, while others have recommended endometrial evaluation for women older than 45 years [17, 20, 21]. The results of the current study are consistent with those of Farquar et al., Iram et al. and Çorbacioglu et al. as the risk of endometrial carcinoma and hyperplasia with atypia in premenopausal women over 45 years in age with HMB was twofold greater than that of women younger than 45 years in age [5, 14, 15]. The cut-off level of 45 years is consistent with the guidelines of the American College of Obstetricians and Gynecologists and the National Institute for Health and Clinical Excellence [20, 21]. Similar to the other two studies, the sensitivity of the cut-off value of 45 years to predict endometrial hyperplasia with atypia and carcinoma was low (69 %) [14, 15].

As a result of the current study, almost all patients (97 %) with atypical hyperplasia and carcinoma histology could be identified if the patients older than 45 years old or younger than 45 years old with a BMI $\geq$30 underwent endometrial biopsy. In the lowest risk group of the patients,

who are less than 45 years old and have a BMI <30, while hyperplasia with atypia was found in 1 patient (0.3 %), there were no cases with cancer. In the light of these results, using BMI cut-offs in patients younger than 45 years who have HMB may be an appropriate approach for deciding to proceed with endometrial sampling.

The other risk factors in this study were nulliparity and diabetes mellitus. The risk of endometrial pathology was fourfold greater in nulliparous patients, which is consistent with previous studies [2, 7, 9]. Although in some studies the increased risk of endometrial cancer associated with diabetes has been considered to be due to comorbid factors, primarily obesity, in the current study, diabetes was independently related to endometrial hyperplasia with atypia and carcinoma [22]. This result is consistent with studies that have reported independent relationships of insulin resistance and a high carbohydrate diet with endometrial cancer [23].

As a limitation of the current study was the use of BMI to determine obesity. It has been suggested in the literature that BMI may not be the best predictor of obesity and could result in inaccurate calculations in the assessment of obesity and associated comorbidities [24]. Leitzmann et al. [25] reported that the inability of BMI to differentiate between fat and fat-free mass makes it an unreliable anthropometric measurement to determine obesity. There are increasing numbers of studies reporting that the measurement of subcutaneous visceral and retroperitoneal adipose tissue shows a more significant relationship with hypertension, impaired glucose tolerance, and diabetes than BMI [26, 27]. There may be a similar correlation with endometrial pathologies. Therefore, there is a need for future similar studies to include alternative methods of BMI measurement.

The results of the current study confirm that obesity is the most significant risk factor for endometrial hyperplasia and carcinoma in premenopausal patients with HMB. The effect of obesity is stronger in patients younger than 45 years. In addition, the results of this study support the use of 45 years as an age cut-off, despite the sensitivity being low for endometrial sampling. Biopsy for patients older than 45 years with premenopausal HMB and for all patients with a BMI >30 have the highest sensitivity for predicting endometrial hyperplasia and carcinoma.

Compliance with ethical standards

Funding The authors report no financial disclosure.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of Bakirkoy Dr Sadi Konuk Training and Research Hospital (approval number 2014/08/10) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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