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Assessment of Endometrial Thickness and Ovarian Volume as Risk Factors for Endometrial Carcinoma in Women with Recurrent Postmenopausal Bleeding

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ABSTRACT

Objective: To determine the prevalence of endometrial carcinoma and associated risk factors including endometrial thickness and ovarian volume in women with recurrent postmenopausal bleeding after initial benign tissue diagnosis.

Methods: A cross-sectional study was conducted on 148 consecutive women with recurrent PMB. All patients had transvaginal ultrasound for endometrial thickness and ovarian volume assessment, hysteroscopy and endometrial sampling was attempted.

Results: The time intervals between the first and recurrent episodes ranged from 5-31 months with mean 15.7± 6.7 months. The prevalence of endometrial cancer and hyperplasia was 6.8% and 9.5% respectively. Using logistic regression analysis, the best predictors of high risk lesions were, thick endometrium, and recurrent multiple episodes of vaginal bleeding than a single episode (p=<0.001, 0.018) respectively. Increased mean ovarian volume (MOV) were significantly more likely to be associated with endometrial cancer or hyperplasia (Odds ratio 2.13, 95%CI 1.12–4.21, p<0.001).

Conclusions: Our data support that substantial number of women presenting with recurrent postmenopausal bleeding was found to have endometrial carcinoma or hyperplasia. Hysteroscopy and entometrial biopsy should be advised in the selected cases based on endometrial thickness measurement of equal to or greater than 5 mm, increased ovarian volume and those with multiple episodes rather than heavy bleeding.

Keywords: recurrent postmenopausal bleeding, endometrial cancer, ovarian volume, endometrial thickness

Introduction

Postmenopausal vaginal bleeding is the presenting symptom in over 90% of women diagnosed with endometrial cancer[(1)]. So this symptom should always be carefully investigated. However, just 10-15% of women with postmenopausal bleeding have

endometrial carcinoma[2,3].

After management of the first episode of PMB, it is not uncommon for women initially assessed as negative to have recurrent episodes of bleeding and warrant further assessment. Among postmenopausal women, the prevalence of recurrent PMB ranges from 10 to 26%, whilst the proportion of these with significant endometrial pathology varies from a few percent with endometrial malignancy to over 20% with a variety of pathologies including endometrial cancer and hyperplasia[4,5].

All investigations for PMB carry a false-negative rate for malignancy[6]. There is a belief that women presenting with recurrent PMB are more likely to develop endometrial cancer than those with single episode of PMB, but there is no evidence in the literature to support this[5,7].

The objective of clinical prediction rules is to reduce the uncertainty inherent in medical practice by defining how to use clinical findings to make predictions. They can help physicians identify patients who require diagnostic tests, treatment, or hospitalization[8]. In particular, clinical studies have reported that ovarian stromal hyperplasia can predict endometrial cancer and often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among postmenopausal women[9]. The main objectives of this study were to estimate the prevalence for endometrial carcinoma or hyperplasia in women presenting with recurrent postmenopausal bleeding after initial benign tissue diagnosis and to determine the associated risk factors including endometrial thickness, ovarian volume and some clinical characteristics to identify the patients at high risk for malignancy.

Patients and methods

Consecutive postmenopausal women presenting with recurrent bleeding after initial negative evaluation in our hospital during the first episode of postmenopausal bleeding, were enrolled in a cross-sectional cohort study, conducted at department of Obstetrics and Gynecology, Ohud Hospital, one of the Taibah University Teaching Hospitals, Al-Madinah Al-Munawarah province, Saudi Arabia, between February, 2011 and June, 2013.

The exclusion criteria were use of hormonal replacement or anticoagulants therapy, and obvious cause of bleeding from cervix or vagina. Each patient gave informed consent to participate in the study. The study protocol was approved by "Medical and Health Sciences Research Committee Involving Human Subjects of our hospital" which conforms to the provisions of the Declaration of Helsinki.

All women underwent transvaginal ultrasound scanning using Toshiba SSA 270A/HG Tokyo Japan, vaginal probe 7.5 MHz as the initial investigation tool. Endometrial thickness was measured as the maximal distance between the two myometrial interfaces in a longitudinal scan. Meanwhile, Ovarian volume was calculated using the prolate ellipsoid formula ($V=D1 \times D2 \times D3 \times 0.523$)[10]. The mean ovarian volume (MOV) is defined as the average volume of the two ovaries. When only one ovary could be measured by ultrasound, its measurement was considered to be the patient's ovarian volume[11].

Hysteroscopy was performed in our Gynecologic Endoscopic Unit with a Storz Hamou II continuous flow, micro-hysteroscope (4 mm diameter, 30 Co angle and 5.0 mm sheath). Guided biopsies were performed in all patients with suspected alterations. Four samples were taken (one for each uterine wall) when the endometrium had homogeneous characteristics using a 3 mm stainless steel Novak curette attached to 20 ml disposable syringe after removal of the scope regardless of the ultrasound endometrial thickness (ET).

One-hundred and fifty-seven women with recurrent postmenopausal bleeding were evaluated for eligibility in this study, hysteroscopy was failed to perform in 6 women due to cervical stenosis and 3 patients abandoned the study; only 148 women had completed the protocol.

SPSS 14.0 Statistics Package (SPSS Inc., Chicago, IL, 2004) was used for analysis. Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number and percentage. Statistical significance for differences was analyzed using

Independent sample t test, Wilcoxon rank sum (Mann–Whitney) test, Kruskal-Wallis test, and Chi-squared test where appropriate. Further, Multiple logistic regression analysis was used to estimate the Odds ratio (95% CI) of cancer and endometrial hyperplasia associated with various variables. A value of $p<0.05$ was considered significant.

Table 1. Stratification of ultrasound endometrial thickness at the time of recurrent postmenopausal bleeding and the final diagnosis

Ultrasound	Histology							Total
Endometrial thickness (mm)	No abnormality	Atrophy	Benign polyp	Hyperplasia	Carcinoma	Endometritis	Insufficient endometrium	N(%)
< 5	28	16	-	-	-	2	6	52 (35.1)
5-10	26	16	6	10	2	8	2	70 (47.3)
>10	-	-	6	4	8	8	-	26 (17.6)
Total	54 (36.5)	32 (21.6)	12 (8.1)	14 (9.5)	10 (6.8)	18 (12.1)	8 (5.4)	148 (100)

Table 2. Univariate comparison of the variables according to final histologic diagnosis*

Characteristics	Begnin lesions (n=124)	endometrial carcinoma or hyperplasia (n=24)	p
Age (years)	58.1±5.2	61.3±6.8	0.011
Time interval between first and recurrent PMB (months)	16.4±7.0	14.0±0.7	0.102
BMI (kg/m^2)	26.0±2.1	27.1±2.4	0.020
Diabetes			
Yes	26 (72.2)	10 (27.8)	0.031
No	98 (87.5)	14 (12.5)	
Hypertension			
Yes	32 (76.1)	10 (23.9)	0.116
No	92 (86.8)	14 (13.2)	
Amount of bleeding			
Spotting	30 (83.3)	6 (16.7)	0.892
Light	78 (84.8)	14 (15.2)	
Heavy	16 (80)	4 (20)	
Episodes of recurrent bleeding			
Multiple	44 (71)	18 (29)	< 0.001
Single	80 (93)	6 (7)	
ET (mm)			
During the first episode	2.8±0.7	3.0±0.8	0.246
At time of recurrent bleeding	5.9±2.1	11.2± 2.7	< 0.001
MOV (cm^3) (range)	1.3±0.10 (0.90-1.52)	1.8±0.17 (1.45-2.00)	< 0.001

* Values are given as number (percentage) or mean±SD unless otherwise indicated.

BMI, body mass index; ET, endometrial thickness; MOV, mean ovarian volume

Table 3. Multiple Logistic regression analysis for predictors of endometrial carcinoma and hyperplasia in women with recurrent postmenopausal bleeding

Factors	Odds ratio (95%CI)	p
ET (mm)		
At time of recurrent bleeding	1.17 (1.15 – 1.20)	< 0.001
Episodes of recurrent bleeding		
Multiple	1.04(1.00-1.07)	0.018
Single	1	
MOV (cm^3)	2.13 (1.12–4.21)	< 0.001

ET, endometrial thickness; MOV, mean ovarian volume

Results

During a 28-month interval, 148 women were investigated for recurrent postmenopausal vaginal bleeding. Age distribution ranged from 52 to 80 years with a mean age, 64.3±6.1 years.

The time intervals between the first and recurrent episodes ranged from 5-31 months with mean 15.7± 6.7 months. Fifteen women underwent hysterectomy due to recurrent prolonged attack of postmenopausal bleeding or according to patient request, but they were included in our study after they had definitive histologic diagnosis.

The stratification of ultrasound ET at the time of recurrent postmenopausal bleeding and final diagnoses are shown in Table 1. There were 10 cases with endometrial cancer (6.8%) and 14 cases of endometrial hyperplasia (9.5%); 2 were simple, 4 were complex without atypia and 8 complex with atypia. of note, one of 10 cases with endometrial cancer and endometrial thickness of 5 mm was returned within 5 months after the first episode and most likely missed at initial investigation. Endometrial thickness < 5 not associated with endometrial cancer or hyperplasia. For the purposes of the study women diagnosed as endometrial carcinoma or hyperplasia 24 (16.2%) were included as one group and the remaining 124 (83.8%) included in the benign group.

Table 2 shows a univariate comparison of clinical variables between endometrial carcinoma or hyperplasia group and benign group. Women diagnosed with endometrial carcinoma or hyperplasia were significantly older (p=0.011) and had higher body mass index (p 0.020) compared with women who had benign lesions. Similarly, they were more likely to have a history of diabetes (p=0.031). In addition, Women with recurrent PMB and having endometrial cancer or hyperplasia usually presented with thick endometrium (p<0.001), multiple episodes of bleeding (p<0.001) and large ovaries (p<0.001)compared with those with benign lesions.

On multiple logistic regression analysis, the factors considered the best predictors of endometrial malignancy or hyperplasia in recurrent postmenopausal bleeding and help in classifying the women as high risk group, were presence of thick endometrium at time of recurrence (OR 1.17, 95% CI 1.15–1.20, p<0.001), and multiple episodes of vaginal bleeding than a single episode (OR 1.04, 95% CI 1.00-1.07, p=0.018). Increased MOV were more likely to be associated with endometrial cancer or hyperplasia (OR 2.13, 95% CI 1.12–4.21, p<0.001) (Table 3).

Discussion

The objective of this current study is to discriminate patients at high risk of endometrial cancer or hyperplasia in postmenopausal women presenting with recurrent vaginal bleeding after initial negative investigation during the first episode. It is essential to re-investigate women presenting with recurrent PMB and no ET threshold on ultrasound can completely rule out early endometrial carcinoma[12]. Moreover, all endometrial biopsy techniques carry false-negative

rates and can miss cancers[13,14]. Surprisingly, in this current study even if we did not take into account the initial histopathologic diagnosis, we still found a low risk of endometrial cancer or hyperplasia in women with recurrent bleeding and a thin ET. However, with increasing ET, the risk increased significantly.

In our series, endometrial thickness <5 not associated with endometrial cancer or hyperplasia. Many studies have suggested that an endometrial thickness of <5 mm is infrequently associated with endometrial cancer[15–17]. A large multi-centre study, which included 1,168 women with PMB, found no endometrial cancer to be associated with thickness <5 mm, and concluded that it would be warranted to avoid doing curettage in these cases[15]. A meta-analysis, including 35 studies with 5,892 women with PMB, documented that on using a 5 mm threshold to define abnormal ET, 96% of women with endometrial cancer and 92% of women with endometrial pathology including cancer, polyp, or atypical hyperplasia had an abnormal TVS result. The risk of endometrial cancer was about 7.3% with an ET of >5 mm, and was only <0.07% if it was ≤5 mm[18].

Our patients contact the hospital in case of repeated bleeding after initial negative assessment as they were clearly instructed. In this study, the incidence of endometrial cancer or hyperplasia in women developed recurrent PMB were 6.8%, and 9.5%, respectively. A retrospective study scheduled 1,536 women with PMB, of whom 126 (8.2%) developed recurrent PMB. Among the latter group, there were 5 (4%) with endometrial cancer. Two of them were probably missed cases; one returned within 6 months of the first visit and the other had endometrial cancer diagnosed 8 months later. Both had increased ET and negative hysteroscopies at their initial assessment[4]. In other study done with 257 women followed for 10 years after referral for postmenopausal bleeding. Out of 66 women who developed recurrent bleeding, the prevalence of endometrial cancer and atypical hyperplasia were 10.6% and 12.1%, respectively and they concluded that, women with recurrent PMB were at higher risk of developing endometrial cancer or atypia, nonetheless, those women with ET of ≤4 mm at initial scan did not have increased risk of endometrial cancer regardless of recurrent PMB[5]. These inconsistent results may have been due to the difference in the study type, studied population, sample size and regular follow-up for a longer period of time may detect more women harbouring endometrial cancer or hyperplasia, when they experience recurrent PMB.

The potential inaccuracy of invasive techniques was also well illustrated in the current study in which one case with ET of 5 mm and negative histological assessment was found to have endometrial cancer on hysteroscopy and biopsy performed 5 months later because of recurrent bleeding. Accepting that all investigations have a false negative rate, women with recurrent PMB should be re-investigated after 6 months and those with persistent bleeding should be investigated earlier[6].

To the best of our knowledge, there are no studies that differentiate between low and high risk for endometrial cancer or hyperplasia in postmenopausal women presenting with recurrent vaginal bleeding after initial negative investigation. The presented data showed associations between the increases in age, BMI, diabetes, increased endometrial thickness, high MOV, multiple episodes of bleeding and the incidence of endometrial carcinoma or hyperplasia. Nonetheless, there was no association with the severity of bleeding. On multiple logistic regression models, we further analyzed the ability of these variables to classify an individual as either low or high risk of endometrial cancer or hyperplasia. There is an evidence that increased endometrial thickness, high MOV, multiple episodes of bleeding ($p=0.001$, <0.001 and 0.018 respectively) simultaneously correctly classifies an individual as high risk with respect to logistic discriminant analysis.

The cut-off value for endometrial thickness beyond which further investigation can be recommended is beyond 5 mm[19]. A thick endometrium is a nonspecific finding; most current protocols include use of hysteroscopy or endometrial office biopsy for histologic diagnosis[20,21]. However, about 90% of women with postmenopausal bleeding will finally be found to have a nonmalignant condition. Therefore, women who

are at increased cancer risk should further be distinguished[22]. The introduction of integrated MOV with endometrial thickness in clinical practice can improve the accuracy and efficiency of diagnostic work-up. For women at high risk of malignancy further diagnostic evaluation is indicated even if the initial tests were negative.

Previous analyses had considered large postmenopausal ovaries as a marker of risk for endometrial carcinoma[23, 24]. Ovarian enlargement in women who present with postmenopausal bleeding and a thick endometrium may represent a sign of hormonal imbalance mostly higher androgen levels (current, past or at both times), which indicates a greater availability of substrate for estrogen production in peripheral adipose tissue and is a factor that could increase the prospect for endometrial cancer[25].

In this analysis, multiple episodes of recurrent postmenopausal bleeding rather than heavy bleeding were associated with endometrial carcinoma or hyperplasia. Similarly, a cross-sectional study, including 2,348 women with PMB showed that the amount of bleeding (defined in the study as heavy, light or spotting) did not correlate with the risk of endometrial cancer. Women with a single episode of bleeding and endometrial thickness between 5 and 10 mm had a 0.4% risk of endometrial carcinoma compared to 4.6% for multiple episodes of bleeding and same endometrial thickness ($p<0.05$). The authors concluded that, postmenopausal women with a single episode of vaginal bleeding and ET between 5 and 10 mm a very low risk of endometrial carcinoma might be considered[26].

The present data revealed that, thickened endometrium (≥ 5mm), increased MOV and multiple episodes of recurrent postmenopausal bleeding can help in classifying patients at high and low risk of malignant and premalignant lesions. Women with recurrent postmenopausal bleeding and at high risk can be referred urgently to specialist clinics that have the facilities for hysteroscopic evaluation of the endometrium, tissue biopsy for definitive tissue diagnosis.

In conclusion, our data support that substantial number of women presenting with recurrent postmenopausal vaginal bleeding was found to have endometrial carcinoma or hyperplasia. Further diagnostic evaluation is indicated even if the initial tests were negative in women with thickened endometrium, increased ovarian volume and those with multiple episodes of bleeding. A combination of repeat endometrial biopsy or hysteroscopy should be pursued.

Conflict of interest

The authors have no conflict of interest to declare

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