Evaluation of Recurrent Postmenopausal Bleeding

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Objectives: This study was undertaken to examine the prevalence and predictors of endometrial cancer or endometrial hyperplasia in women with recurrent postmenopausal bleeding after an initial negative assessment.
Methods: This was a retrospective study of 1931 women who had investigations in our Postmenopausal Bleeding Clinic for single or recurrent postmenopausal bleeding from 1 September 2007 to 30 June 2011. Their basic characteristics, the causes of bleeding, and time of recurrence were analysed.
Results: In women with postmenopausal bleeding for the first time, the prevalence of endometrial cancer and endometrial hyperplasia were 3.1% and 1.2%, respectively. After initial negative assessment, 262 (10.6%) women had recurrent postmenopausal bleeding. Among them, 5 (1.9%) turned out to have endometrial cancer, 4 (1.5%) had endometrial hyperplasia, and 1 (0.4%) had cervical cancer. The time interval between the initial negative assessment and the final diagnosis of endometrial cancer or hyperplasia ranged from 6 to 73 months with a median of 17 months. Women with endometrial thickness of more than 4 mm at the initial assessment were more likely to have endometrial cancer or hyperplasia if they experienced recurrent postmenopausal bleeding (odds ratio=10.1; 95% confidence interval, 2.0-51.8; p=0.003) when compared to those with less endometrial thickness. The greater the endometrial thickness (>5 mm) at the initial assessment, the higher was the risk (odds ratio=13.6; 95% confidence interval, 3.0-60.7; p=0.001). Women with initial histopathology showing proliferative or secretory endometrium were also more likely to have endometrial cancer or hyperplasia when they experienced recurrent postmenopausal bleeding (odds ratio=7.4; 95% confidence interval, 1.7-32.4; p=0.021) than those with other histopathology (including insufficient sample, atrophic endometrium, endometrial polyp and pyometra). A case of suboptimal hysteroscopic examination with insufficient tissue from endometrial biopsy for histopathological diagnosis with increased endometrial thickness had endometrial cancer diagnosed 6 months after the initial 'negative' assessment.
Conclusion: Women with recurrent postmenopausal bleeding after initial negative assessment should be re-investigated because they still have the risk of significant genital tract malignancy. Those with endometrial thickness of more than 4 mm or a proliferative or secretory endometrium at the initial assessment are especially at risk. Whenever a woman presents with postmenopausal bleeding and increased endometrial thickness but the hysteroscopic assessment is suboptimal and there is insufficient tissue for diagnosis from the endometrial biopsy, a more thorough examination and specific management should be considered.
Hong Kong J Gynaecol Obstet Midwifery 2012; 12:69-79

Keywords: Biopsy; Endometrial hyperplasia; Endometrial neoplasms; Postmenopause; Ultrasonography

Introduction

Postmenopausal bleeding (PMB) is any vaginal bleeding that occurs 1 year after cessation of normal menstrual periods due to menopause. It can be caused by lesions in the genital tract (vulva, vagina, cervix, uterus, fallopian tubes, or related to the ovaries). It is mostly due to benign conditions, such as atrophic vaginitis. However, it can also be a sinister symptom of genital tract malignancy.

Prompt assessment with a detailed history, clinical examination and investigations is required to find out the cause. In the past, examination under anaesthesia (EUA) with dilatation and curettage (D&C) was considered the gold standard for excluding endometrial cancer. Because of the cost and risks of general anaesthesia and D&C, simple, safe, and non-invasive procedures under local or no anaesthesia were introduced. These included transvaginal ultrasound imaging of the endometrium, endometrial sampling, and hysteroscopy. A number of independent studies were performed to determine the accuracy of these procedures, and still there is no consensus on the sequence of diagnostic tests[1]. Every investigation has its own sensitivity and false-negative rate for malignancy. In a meta-analysis of endometrial thickness (ET) measurements using transvaginal ultrasound for detection of endometrial cancer, the sensitivity was 97.9% and the specificity was 35.4% at a cut-off of ≤3 mm[1,2]. Therefore, a cut-off value of 3 mm was recommended[1]. In a meta-analysis of endometrial sampling for detection of endometrial cancer,

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the sensitivity was 95.0% and the specificity was 99.5%[3]. A recent study on the use of hysteroscopy in women with PMB showed that it was a safe and reliable diagnostic procedure for evaluating benign endometrial lesions, such as endometrial polyp and submucosal fibroids with a sensitivity of 94.7% and specificity of 97.8%[4]. On the other hand, its sensitivity and specificity for endometrial hyperplasia were only 56.5% and 91.6%, respectively; and for endometrial cancer, 50.0% and 94.2%, respectively[4]. Therefore, it should be complemented by endometrial biopsy.

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, of whom, a considerable proportion had significant endometrial disease, including malignancy and hyperplasia. Among postmenopausal women, the prevalence of recurrent PMB ranges from 10 to 26%, whilst the proportion of these with significant endometrial disease varies from a few percent with endometrial malignancy to over 20% with a variety of pathologies including endometrial malignancy and hyperplasia[5-12].

As a common gynaecological problem, PMB accounted for 9% of referrals to our gynaecological clinic in the New Territories West Cluster in 2010. As the elderly population in our community grows, both the workload of managing patients with new onset of PMB as well as dealing with those suffering from recurrent bleeding are expected to increase. The objectives of this study were to examine the prevalence and predictors of endometrial cancer or endometrial hyperplasia in women with recurrent PMB after an initial negative assessment.

Methods

This was a retrospective observational study carried out in the Pok Oi Ambulatory Gynaecology Centre Postmenopausal Bleeding Clinic in the New Territories West Cluster. This clinic is a one-stop postmenopausal assessment clinic established since September 2007 by the Department of Obstetrics and Gynaecology, Tuen Mun Hospital. It is a half-day clinic running once a week, and staffed by a team of gynaecologists, registered nurses, and health care assistants. A total of 1931 women presenting with a single or recurrent episodes of PMB attending our clinic between 1 September 2007 and 30 June 2011 were included in this study.

A detailed history of symptoms based on a standard questionnaire was obtained from each attendee by a registered nurse. With the help of patient information, the nurse then counselled them on the causes of PMB and the investigations necessary. A gynaecologist then checked the medical history and the understanding of the counselling by the patient. Physical examination included a speculum examination performed by the gynaecologist. A cervical smear was taken if none had been obtained within 1 year, and a cervical biopsy was carried out if the cervix looked suspicious. Transvaginal grey-scale ultrasound examination of the uterus (using Prosound Alpha 7 ultrasound machine equipped with high-frequency vaginal transducers of 5-7.5 MHz, Aloka, Japan) was then performed to assess the morphology of the endometrial lining and measure ET. ET was measured as a double layer at its thickest part in the longitudinal plane from one basal layer to the other. When the endometrial layers were separated by intracavity fluid, both layers were measured and the sum recorded. Ultrasound via the transrectal or transabdominal approach was adopted for virgins. The women were counselled for outpatient hysteroscopy if the ultrasound scan was suboptimal (including unclear ET) or suggestive of endometrial pathology (e.g. ET >3 mm, or suspicion of an endometrial polyp). Endometrial biopsy using Vabra aspirator was performed for histopathological examination regardless of the ultrasound ET or morphology. EUA, hysteroscopy, and D&C were arranged if the patients were virgins, if they refused outpatient hysteroscopy, or if endometrial biopsy failed. Gynaecologists who performed the ultrasounds, hysteroscopies, and endometrial biopsies were either Fellow gynaecologists or trainees under supervision.

When the PMB clinic was first set up in Pok Oi Hospital, our department adopted the protocol of diagnostic hysteroscopy together with endometrial biopsy for PMB patients with an ET of >3 mm. There were several reasons for using ET of >3 mm to triage our patients for hysteroscopy. First, while any test has its own sensitivity and false-negativity rate, we would rather start with a lower threshold in order not to miss significant endometrial pathology. Second, we had to take into account the interobserver error in measuring ET since different operators were performing the measurements. Third, we wanted to collect more data about the assessment of PMB in our locality, in order to plan and guide the clinical management of women with PMB in the future. Lastly, hysteroscopy was a reasonably simple and safe procedure that most patients could tolerate well without complications.

All clinical information and investigation results were collected and entered into the Clinical Management

System, an electronic medical record system of the Tuen Mun Hospital. Thereafter a management plan was developed. If there was no abnormality, the patient was seen by the registered nurse once every 3 months. Women presenting with recurrent PMB underwent the same sequence of investigations (after their previous investigation results and diagnosis were traced). Women with endometrial biopsies showing either a proliferative or secretory endometrium had blood tests for hormonal profiles (follicle-stimulating hormone and oestradiol levels to confirm menopausal status and to look for any exogenous or endogenous source of estrogen).

The medical records were reviewed and analysed. The data included age, parity, age of menopause, recurrent episodes of PMB (if any), and the time interval to recurrence. Age of menopause was defined as the age at the last menstrual period, followed by at least 12 months of amenorrhoea. Any history of diabetes mellitus, hypertension, and current use of hormonal medications such as hormonal replacement or tamoxifen were noted. Any personal history and family history of gynaecological cancer, breast or colorectal cancers in any first-degree relatives were documented. This information, together with body weight and height, pelvic examination findings, ET on ultrasound assessment, cervical smear result, hysteroscopic findings and histopathology of endometrial biopsy were also recorded.

The target group of this study included all women who had recurrent PMB after initial negative assessment. The 'initial assessment' was the first assessment which the woman with PMB sought, irrespective of the number of prior episodes. Results of that assessment showing malignant or pre-malignant pathologies were regarded as 'positive'. By contrast, all those without such findings were regarded as 'negative'.

Statistical analysis was undertaken using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US). Fisher's exact test was used for categorical variables. The Mann-Whitney *U* test was used for continuous variables that were not normally distributed. The level of significance was set at a p value of less than 0.05.

Results

From 1 September 2007 to 30 June 2011, a total of 2155 women attended our clinic, of whom 1931 were included in this study. From the latter, 224 were excluded as 23 had already had a hysterectomy, 3 had already had investigations in the private sector, 149 refused investigation, and 49 did not have genuine PMB after detailed review of the menstrual history.

In women who presented with PMB for the first time, the prevalence of endometrial cancer and endometrial hyperplasia were 3.1% and 1.2%, respectively (Table 1). Cervical cancer accounted for 0.8% of cases. Two patients were incidentally found to have ovarian cancer, of whom one had stage IIIC clear cell carcinoma and the other had stage IC mucinous carcinoma. 262 Women had recurrent bleeding, among whom, 185 had investigations of both their first and recurrent episode(s) of PMB in our clinic. The remaining 77 attended our clinic for the first time because of recurrent PMB, having had their initial assessment for that first episode of PMB completed in Tuen Mun Hospital outside the study period, but with the same sequence of investigations. All the investigation results of their initial assessment were traced and reviewed. In evaluating the point prevalence of recurrent PMB in women with initial negative assessments, the denominator used excluded the aforementioned 77 cases and all cases whose initial assessment showed malignant or pre-malignant pathology. Therefore, the prevalence of recurrent PMB was 10.6% (185 / [1931-77-106]).

The Prevalence of Endometrial Cancer or Endometrial Hyperplasia in Women with Recurrent Postmenopausal Bleeding after an Initial Negative Assessment

Among all the 262 women with recurrent PMB, 39 had only one recurrent episode of bleeding and 16 had more than two episodes. The median time interval between the first and next recurrent episode of PMB was 14 (range, 1-133) months; 68 (26%) women had recurrent PMB within 6 months of their first PMB. The median ET revealed by the assessment for recurrent PMB was 2.6 mm (interquartile range, 2.0-3.6 mm). The final diagnoses in these women are shown in Table 1. There were five cases with endometrial cancer, yielding a prevalence of 1.9% (5/262) for women with recurrent PMB after initial negative assessment. This figure was lower than that of women with first PMB (3.1%) but the difference was not statistically significant (p=0.2). There were four cases of endometrial hyperplasia (1.5%); two were simple without atypia and two were complex endometrial hyperplasia without atypia. There was one case (0.4%) of cervical cancer.

Women Presenting with Recurrent Postmenopausal Bleeding after an Initial Negative Assessment

The group of women with recurrent PMB and the final diagnoses of either endometrial cancer or hyperplasia

Table 1. Diagnoses in women with an initial assessment for first postmenopausal bleeding (PMB) and subsequent assessment for recurrent PMB

Diagnosis	No. (%) of patients	
	Initial assessment for first PMB	Subsequent assessment for recurrent PMB
Malignant		
Endometrial cancer	59 (3.1)	5 (1.9)
Cervical cancer	16 (0.8)	1 (0.4)
Ovarian cancer	2 (0.1)	0
Vulval cancer	1 (0.1)	0
Premalignant		
Endometrial hyperplasia	24 (1.2)	4 (1.5)
Carcinoma in situ cervix	4 (0.2)	0
Benign		
Atrophic endometrium	759 (39.3)	110 (42.0)
Atrophic vaginitis	354 (18.3)	52 (19.8)
Endometrial polyp	301 (15.6)	20 (7.6)
Proliferative endometrium	95 (4.9)	11 (4.2)
Cervical polyp	84 (4.4)	7 (2.7)
Uterovaginal prolapse	74 (3.8)	22 (8.4)
Submucosal fibroid	44 (2.3)	5 (1.9)
Endometritis	24 (1.2)	4 (1.5)
Secretory endometrium	9 (0.5)	2 (0.8)
Cervical ectopy	8 (0.4)	0
Urethral caruncle	2 (0.1)	0
Vulval dermatitis	1 (0.1)	0
No known pathology	70 (3.6)	19 (7.3)
Total	**1931 (100)**	**262 (100)**

were compared with those having other pathologies (Table 2). The body mass index (BMI) was higher in those suffering from endometrial cancer or hyperplasia (median of 27.2 kg/m^2 vs. 22.2 kg/m^2 ; p=0.010). The odds ratio (OR) of either endometrial cancer or hyperplasia for a BMI of ≥25 kg/m^2 was 5.0 (95% confidence interval [CI], 1.2-21.6; p=0.029). Higher percentages of women with endometrial cancer or hyperplasia had diabetes mellitus, hypertension, breast cancer, colorectal cancer, used tamoxifen, and had a positive family history; although none of these differences were statistically significant. Nor was there any significant difference between these two groups of women in terms of age and age at menopause. The time intervals between the first and recurrent episode of PMB were also similar (median values of having endometrial cancer or hyperplasia and other pathologies being 12 months vs 14 months, respectively; p=0.693), as were the time intervals between initial and subsequent assessments (median values being 17 months vs 15 months, respectively; p=0.542).

Among the 262 women presenting with recurrent PMB after an initial negative assessment, five had endometrial cancer (Table 3). The median time interval between the first bleeding episode and the recurrent episode was 30 months (range, 7-74 months). The median time interval between the initial negative assessment and the final diagnosis of endometrial cancer was 37 months (range, 6-73 months).

In the five cases with endometrial cancer, more than 2 years had elapsed after the initial negative assessment, except in case 2. In this case, endometrial cancer was diagnosed only 6 months after the initial negative assessment. During the first visit, a thickened ET (6 mm) was found on ultrasound examination. Hysteroscopy was performed, but was suboptimal because of blood obscuring the view. Endometrial biopsy was done but the material was insufficient for assessment. PMB recurred 5 months later, at which time a fragile mass protruding from the cervix

Table 2. Univariate comparison of the characteristics of women with recurrent postmenopausal bleeding (PMB) and the final diagnoses of endometrial cancer or hyperplasia and those with other diagnoses

	No. (%) or median (interquartile range)		p Value
	Recurrent PMB with other diagnoses (n=253)	Recurrent PMB with endometrial cancer or endometrial hyperplasia (n=9)	
Age (years)	56 (53-62)	60 (56-62)	0.200‡
Menopausal age (years)	50 (48-52)	51 (49-53)	0.834‡
Time interval between first and recurrent PMB (months)	14 (6-29)	12 (9-35)	0.693‡
Time interval between initial and subsequent assessment (months)	15 (8-31)	17 (10-38)	0.542‡
BMI (kg/m^2)*	22.2 (20.0-25.3)	27.2 (23.1-28.1)	0.010‡
Parity (nulliparity)*			
Yes	5 (2.0%)	0	1.000§
No	245 (98.0%)	9 (100.0%)	
Diabetes mellitus			
Yes	37 (14.6%)	2 (22.2%)	0.627§
No	216 (85.4%)	7 (77.8%)	
Hypertension			
Yes	100 (39.5%)	4 (44.4%)	0.744§
No	153 (60.5%)	5 (55.6%)	
Breast cancer			
Yes	13 (5.1%)	2 (22.2%)	0.087§
No	240 (94.9%)	7 (77.8%)	
Tamoxifen use			
Yes	9 (3.6%)	1 (11.1%)	0.299§
No	244 (96.4%)	8 (88.9%)	
HRT			
Yes	4 (1.6%)	0	1.000§
No	249 (98.4%)	9 (100.0%)	
Colorectal cancer			
Yes	3 (1.2%)	1 (11.1%)	0.131§
No	250 (98.8%)	8 (88.9%)	
Positive family history†			
Yes	29 (11.5%)	2 (22.2%)	0.289§
No	224 (88.5%)	7 (77.8%)	
ET (mm)			
At initial assessment*	3.0 (2.0-4.0)	5.5 (3.0-6.8)	0.035‡
At subsequent assessment*	2.5 (2.0-3.3)	10.5 (5.3-17.8)	<0.0001‡
Change of ET (mm)*	-0.3 (-1.3 to 0.6)	2.4 (-0.6 to 9.6)	0.030‡

Abbreviations: BMI = body mass index; HRT = hormonal replacement therapy; ET = endometrial thickness

* Statistics worked on less numbers from overall due to missing information (BMI: missing data in 82 cases of recurrent PMB with other diagnoses; parity: missing data in 3 cases of recurrent PMB with other diagnoses; ET at initial and subsequent assessment: missing data in 53 and 30 cases respectively because of unclear ET; change of ET: missing data in 1 case of recurrent PMB with the final diagnosis of endometrial cancer/hyperplasia and 62 cases of recurrent PMB with other diagnoses because of unclear ET in initial or/and subsequent assessment)

† Positive family history of gynaecological cancer, breast and colorectal cancer in the first-degree relatives

‡ Two-sample Mann-Whitney test

§ Fisher's exact test

Table 3. Details of the 5 cases of recurrent postmenopausal bleeding (PMB) with final diagnosis of endometrial cancer

Details	Case No.				
	1	2	3	4	5
Age of the first episode of PMB (years)	54	50	56	53	59
Menopausal age (years)	50	49	53	52	40
Initial assessment					
ET (mm)	6.2	6	7	5	0.6
Hysteroscopy	Atrophic	Suboptimal	Normal	Normal	Atrophic
Pathology (EB)	Insufficient	Insufficient	Secretory	Proliferative	Insufficient
Subsequent assessment					
ET (mm)	19	5	14	4.2	11
Hysteroscopy	Cancer	Cancer	Cancer	Cancer	Cancer
Pathology (EB)	Cancer	Cancer	Cancer	Cancer	Cancer
Final diagnosis (staging according to FIGO 2009)	Endometrioid adenocarcinoma (IA)	Endometrioid adenocarcinoma (II)	Endometrioid adenocarcinoma (IB)	Endometrioid adenocarcinoma (IB)	Endometrial carcinosarcoma (II)
Time interval between the first PMB and the final diagnosis	6 years and 5 months	8 months	3 years and 4 months	3 years and 1 month	2 years and 9 months
Time interval between the initial assessment and the final diagnosis	6 years and 1 month	6 months	3 years and 3 months	3 years and 1 month	2 years and 4 months

Abbreviations: ET = endometrial thickness; EB = endometrial biopsy

was noted and the biopsy showed poorly differentiated carcinoma. Hysteroscopy was performed again, showing tumour growth arising from the fundus extending down to the internal cervical os. The final diagnosis was stage II endometrioid adenocarcinoma.

In case 1, despite the ultrasound finding of a thickened endometrium (6.2 mm), hysteroscopy at the first episode of PMB showed atrophic endometrium. The material obtained on endometrial biopsy was insufficient for a histopathological diagnosis. More than 6 years later, PMB recurred and the patient turned out to have early-stage endometrial carcinoma.

In cases 3 and 4, histopathologies of the endometrial biopsy after the first episode of PMB were secretory and proliferative endometrium, respectively. Both women denied any intake of hormones or Chinese herbs with oestrogenic components. Their hormonal profiles including follicle-stimulating hormone and oestradiol levels were checked and their menopausal status was confirmed. PMB recurred more than 3 years after the initial negative assessment. Both women had an early-stage endometrial carcinoma.

In case 5, during assessment of the initial PMB episode, the ultrasound revealed a very thin ET and hysteroscopy yielded atrophic change, although the tissue obtained on endometrial biopsy was insufficient for histopathological diagnosis. She had a history of pelvic irradiation for colon cancer. PMB recurred almost 3 years later and the final pathology was endometrial carcinosarcoma.

Among the 262 women presenting with recurrent PMB after initial negative assessment, four others were found to have endometrial hyperplasia, of which two had simple endometrial hyperplasia without atypia and two had complex endometrial hyperplasia without atypia. The median time interval between the initial negative assessment and the final diagnosis of endometrial hyperplasia was 12 months (range, 8-17 months). Two women had initial histopathology showing atrophic endometrium. One woman had an initial ET of 2.3 mm and the final diagnosis of complex hyperplasia was made 8 months after the initial negative assessment. Another had unclear ET at initial assessment and underwent hysteroscopy which showed an atrophic endometrium. She was found to have simple hyperplasia 17 months after the initial negative

assessment. Both the remaining two cases of endometrial hyperplasia were diagnosed 12 months after their initial negative assessment. One woman had breast cancer and received tamoxifen treatment when she had her first PMB. An endometrial polyp was found and a hysteroscopic polypectomy revealed it to be benign. The final assessment for recurrent PMB showed complex hyperplasia. The last case had initial histopathology yielding proliferative endometrium. She denied intake of hormones or Chinese herbs with oestrogenic components. Her hormonal profiles including follicle-stimulating hormone and oestradiol levels were checked and her menopausal status was confirmed. The subsequent diagnosis was simple hyperplasia. Eventually all except the last case underwent hysterectomy. The histopathology of the hysterectomy specimens confirmed endometrial hyperplasia without atypia or co-existing cancer. The outcome of the last case was unknown because she defaulted subsequent follow-up and treatment.

Among the 262 women with recurrent PMB, there was a 74-year-old patient with cervical cancer. The diagnosis was made 2.5 years after the initial negative assessment. At that time, the cervical smear was normal. Two years later, she presented with recurrent PMB. Cervical smear was repeated and showed atypical cells of undetermined significance. Another cervical smear was taken 6 months later and showed a high-grade squamous intraepithelial lesion. Colposcopy was performed and a 1-cm lesion suspicious of malignancy was seen. Cervical biopsy was then taken, and the histopathology showed squamous cell carcinoma. The clinical staging was IB1 (FIGO 2009). In view of her old age, radiotherapy was opted for instead of radical hysterectomy.

The Predictors for Endometrial Cancer or Hyperplasia in Women with Recurrent Postmenopausal Bleeding after Initial Negative Assessment

Sonographic Measurement of Endometrial Thickness

Table 2 shows that the endometrium was significantly thicker on ultrasound assessment of recurrent PMB in women with endometrial cancer or hyperplasia than in those with other diagnoses (median of 10.5 mm vs 2.5 mm; p<0.0001). The increase of ET from the initial to subsequent assessment was also greater than in women without endometrial cancer or hyperplasia (median of 2.4 mm vs -0.3 mm; p=0.030). In the women with recurrent PMB with other pathologies, ET had scarcely changed.

Table 2 also reveals that there was a significant difference (p=0.035) between the initial ETs in the two groups of women, median values being 5.5 mm (interquartile range, 3.0-6.8 mm) and 3.0 mm (interquartile range, 2.0-4.0 mm).

The greater the initial ET, the higher was the risk of having endometrial cancer or hyperplasia if the women experienced recurrent PMB (Table 4). Among the nine cases of endometrial cancer or hyperplasia diagnosed after the investigation for recurrent PMB, six had initial ETs of >4 mm and five had initial ETs of >5 mm. The OR of endometrial hyperplasia or cancer for women with recurrent PMB and an initial ET of >3 mm, >4 mm, and >5 mm were 4.7, 10.1, and 13.6, respectively (respective p values being 0.063, 0.003, and 0.001). Both the ORs in those with ETs >4 mm and >5 mm were statistically significant.

Histopathology of Endometrial Biopsy

The association between various histopathological

Table 4. Risk of endometrial cancer and hyperplasia in women with recurrent postmenopausal bleeding, grouped according to endometrial thickness at their initial assessment (n=262)

Initial ET (mm)	No. of cases with recurrent bleeding (n=262)	No. of endometrial hyperplasia (n=4, 1.5%)	No. of endometrial cancer (n=5, 1.9%)	OR* (95% CI); p value
Unclear†	53	1	0	-
≤3	125	1	1	-
>3	84	2 (2.4%)	4 (4.8%)	4.7 (0.9-24.0); 0.063
>4	52	2 (3.8%)	4 (7.7%)	10.1 (2.0-51.8); 0.003
>5	27	2 (7.4%)	3 (11.1%)	13.6 (3.0-60.7); 0.001

Abbreviations: ET = endometrial thickness; OR = odds ratio; CI = confidence interval

* OR for the final diagnosis of endometrial hyperplasia or cancer

† Unclear ET: reasons included unsatisfactory ultrasound image, distortion of endometrial lining (due to uterine fibroid, intra-uterine device); reasons were not documented in some cases

diagnoses based on the initial endometrial biopsy and the risk of endometrial cancer or hyperplasia at the time of recurrent PMB is shown in Table 5. Women with initial histopathology showing either a proliferative or secretory endometrium were more likely to have endometrial cancer or hyperplasia when they experienced recurrent PMB compared to women with other histopathological findings, including insufficient sample, atrophic endometrium,

Table 5. The relationship between the histopathological diagnosis of endometrial biopsy on initial assessment and the final diagnosis of endometrial cancer or hyperplasia at the time of recurrent postmenopausal bleeding

Initial histopathological diagnosis	No. of cases with recurrent bleeding (n=262)	No. of endometrial hyperplasia (n=4, 1.5%)	No. of endometrial cancer (n=5, 1.9%)	OR* (95% CI); p value
Insufficient sampling	88	0	3	1.0 (0.2-4.0); 1.000
Inactive / atrophic	118	2	0	0.3 (0.1-1.7); 0.192
Proliferative / secretory	19	1	2	7.4 (1.7-32.4); 0.021
Endometrial polyp	35	1	0	0.8 (0.1-6.6); 1.000
Pyometra	2	0	0	-

Abbreviations: OR = odds ratio; CI = confidence interval

* OR for the final diagnosis of endometrial hyperplasia or cancer

Table 6. The relationship between the histopathological diagnosis of endometrial biopsy and endometrial thickness (ET) on initial assessment and the final diagnoses of endometrial cancer or hyperplasia at the time of recurrent postmenopausal bleeding (PMB)

Initial histopathological diagnosis and ET (mm)	No. (%) of endometrial hyperplasia at the time of recurrent PMB	No. (%) of endometrial cancer at the time of recurrent PMB
Insufficient sampling		
ET ≤3	0/46	1/46 (2.2)
ET >3	0/22	2/22 (9.1)
Unclear	0/20	0/20
Inactive / atrophic		
ET ≤3	1/70 (1.4)	0/70
ET >3	0/30	0/30
Unclear	1/18 (5.6)	0/18
Proliferative		
ET ≤3	0/5	0/5
ET >3	1/12 (8.3)	1/12 (8.3)
Unclear	0/1	0/1
Secretory		
ET ≤3	0/0	0/0
ET >3	0/1	1/1 (100)
Endometrial polyp		
ET ≤3	0/5	0/5
ET >3	1/18 (5.6)	0/18
Unclear	0/12	0/12
Pyometra		
ET ≤3	0/0	0/0
ET >3	0/0	0/0
Unclear	0/2	0/2

endometrial polyp and pyometra (OR=7.4; 95% CI, 1.7-32.4; p=0.021). Among the 88 women whose initial endometrial samples were insufficient for histological assessment, three had endometrial cancer when assessed for recurrent PMB (3/88). In contrast, none of the women (0/118) with an initial histopathology showing atrophic endometrium had endometrial cancer when they had recurrent PMB.

The prediction of endometrial cancer in women with recurrent PMB based on the initial histopathological diagnoses was further enhanced by having a thickened endometrium (initial ET >3 mm; Table 6). Women with a thick initial ET (>3 mm) during the initial assessment for first PMB but with insufficient tissue obtained from endometrial biopsy for histological diagnosis had a risk of having endometrial cancer of 9.1% (2/22) when they had recurrent PMB. The risk was lower (2.2%, 1/46) when the initial ET was thinner (≤3 mm). Women with initial assessment endometrial biopsies showing either a proliferative or secretory endometrium were also at higher risk if they had a thick initial ET (>3 mm), compared to their counterparts with initial ETs ≤3 mm. The respective risks for proliferative and secretory histology at the second assessment were 8.3% (1/12) and 100% (1/1).

Discussion

The Prevalence of Significant Genital Tract Pathology in Women with Recurrent Postmenopausal Bleeding after Initial Negative Assessment

In this study, the prevalence of endometrial cancer, cervical cancer, and endometrial hyperplasia in women who presented with PMB for the first time were 3.1%, 0.8%, and 1.2%, respectively. In comparison to those who developed recurrent PMB after initial negative assessment, the values were 1.9%, 0.4% and 1.5%, respectively. There was no statistically significant difference in the percentages of women with endometrial cancer in the two groups. Women with recurrent PMB after initial negative assessment should be re-investigated because they still bear a risk of significant genital tract pathology.

The Risk of Endometrial Cancer after Initial Negative Assessment and the 'Missed Cases'

Ronghe and Gaudoin[5] undertook a retrospective study on 1536 women with PMB, of whom 126 (8.2%) developed recurrent PMB. Among the latter, there were five (4%) with endometrial cancer. Two of these five women were probably missed cases; one returned within 6 months of the initial visit and the other had endometrial cancer diagnosed 8 months later. Both had increased ET and negative hysteroscopies at their initial assessment. In these two patients, endometrial biopsy failed, evidently due to difficulty inserting the Pipelle in one case, and intolerance of speculum examination in the other. Both patients were scheduled for re-investigation after 6 months[5].

Gull et al[6] followed up 339 women for 10 years, three of whom had endometrial cancer diagnosed after the first episode of recurrence (the point prevalence being approximately 1%). At the first examination, their ET values were 5 mm, 22 mm, and 29 mm. Their histopathological diagnoses of uterine curettage at the first examination were atrophic, hyperplasia, and insufficient tissue. The time intervals from the first bleeding to diagnosis of cancer were 5 years, 2 months, and 3 months. In the latter two cases, it was likely that cancer was already present at the primary curettage but not detected. The authors concluded that increased ET values at the initial scan indicated higher risk of endometrial diseases even with an atrophic endometrium[6].

In our study, there were five patients with endometrial cancer after initial negative assessment, giving a point prevalence of 1.9%, which was similar to the two aforementioned studies. It is also likely that case 2 of our series was missed during the initial assessment. In contrast to Ronghe and Gaudoin's suggestion to restart investigation after 6 months[5], we do not advocate such a policy after suboptimal or incomplete assessment. In the setting of a thick ET, instead of waiting for recurrence of symptoms a more thorough examination like EUA, hysteroscopy, and D&C or a discussion of hysterectomy should be recommended.

Excluding this likely 'missed' case of endometrial cancer in the initial assessment, we encountered eight others with either endometrial cancer or hyperplasia in women with recurrent PMB after an initial negative assessment. The shortest interval between the initial negative assessment and the final diagnosis of significant endometrial pathology was 8 months, which was in a patient with complex hyperplasia who had an initial ET of 2.3 mm and an atrophic endometrium. Based on such data, for women with recurrent PMB after initial negative assessment, re-investigation after 8 months was deemed justified.

The Predictive Factors for Endometrial Cancer or Hyperplasia

Sonographic Measurement of Endometrial Thickness

Various studies have been performed to assess the relationship between the transvaginal sonographic measurement of ET and endometrial cancer in recurrent

PMB. In Gull et al's study of 339 women over 10 years[6], three patients had endometrial cancer diagnosed after the first episode of recurrence, with ET values ranging from 5 to 29 mm, whilst no endometrial cancer was diagnosed in cases of recurrent PMB with ET values of 4 mm or less at the initial scan[6].

Gull et al[7] also followed up 163 women with PMB and ET values of less than 4 mm for 1 year. Endometrial biopsy was performed because of recurrent bleeding in 6% of these cases. No cancer or hyperplasia was diagnosed in their series[7].

On the contrary, Van Doorn et al[8] followed up 249 women with PMB and ET values of 4 mm or less for a median of 174 weeks (range, 4-250 weeks). During follow-up, 25 (10%) of the women had recurrent bleeding, two (8%) of whom had endometrial cancer. The times to recurrent bleeding in these women were 44 weeks and 16 weeks[8].

Timmermans et al[9] followed up 222 women with ET values of greater than 4 mm and benign pathology, for a median duration of 176 weeks (range, 50-260 weeks). During follow-up, 47 (21%) of the women had recurrent bleeding, two (4%) of whom had atypical endometrial hyperplasia. The times to recurrent bleeding were 49 weeks and 3.5 years[9].

In our series, nine patients had either endometrial cancer or hyperplasia at the time of recurrent PMB. Not only were their initial ET values greater, but with respect to the final diagnosis of endometrial cancer or hyperplasia when they experienced recurrent PMB, the greater the initial ET, the higher was the risk of having either endometrial cancer or hyperplasia. The OR in the group of women having an initial ET >3 mm, >4 mm, and >5 mm showed a trend for increasing risk (OR=4.7, 10.1 and 13.6, respectively). Moreover, they also had greater increases in ET from the initial to subsequent assessment (p=0.030).

Consistent with the finding of Van Doorn's study[8], neither did our study show that a very thin ET at the initial scan was 'protective' of subsequent development of significant endometrial pathologies for PMB cases with initial negative assessment. Two of the nine cases suffering from either endometrial cancer or hyperplasia had initial ETs of 3 mm or less. Case 5 had carcinosarcoma of the endometrium and a very thin initial ET (<1 mm). This woman had had irradiation of pelvis for carcinoma of the colon which might have predispose to the development of such an aggressive tumour.

Histopathology of Endometrial Biopsy

Few studies have tried to evaluate the association between the histopathology of initial endometrial biopsy for the first PMB and the risk of subsequent endometrial cancer or hyperplasia after initial negative assessment. In our study, women with initial histopathology showing either proliferative or secretory endometrium, or insufficient tissue for histological diagnosis were more likely to have endometrial cancer or hyperplasia when they experienced recurrent PMB, especially if the initial ET was thick (>3 mm). Despite this observation, the risk shown in Table 6 has to be cautiously interpreted in very small subgroups, such as those with a secretory endometrium. When subgroups are larger, as for women with a proliferative endometrium, the associations are less liable to bias. On the other hand, the negative association between an atrophic endometrium at initial assessment and subsequent low risk of endometrial cancer at the time of recurrent PMB seems more reassuring, especially as the sample (118 women) in this subgroup was reasonable.

Proliferative endometrium in the initial pathology suggests a high level of unopposed oestogen stimulation, which can be endogenous or exogenous and lead to rapid progression to endometrial hyperplasia or cancer. Besides, a secretory endometrium indicates either reactivation of residual ovarian activity leading to delayed menopausal age, or an un-noticed intake of hormones. In our society, this might be due to intake of adulterated traditional Chinese or other herbal medicine. The endometrial biopsy showing insufficient tissue for histopathological diagnosis in the setting of a thick ET alerts us to the possibility of a 'missed case'.

Limitations of this Study

One limitation of this study is that women with an initial negative assessment were not given a long-term follow-up appointment, unless they had other gynaecological symptoms. However, they were all seen once more by a registered nurse 3 months after completion of all investigations and advised to contact us if they developed recurrent PMB. A telephone line for calling back was provided. Nevertheless, the number of patients with recurrent PMB might be underestimated. Some women who initially tested negative might just choose observation without seeking help from or might attend the private sector. Routine sharing of patient information between private doctors and Tuen Mun or Pok Oi Hospitals is not yet established. Because of the small patient numbers with endometrial diseases, either cancer or hyperplasia noted after recurrent PMB with an initial negative assessment,

multivariate analysis was not feasible. Regular follow-up of all women for a longer period of time may detect more women harbouring endometrial cancer or hyperplasia, when they experience recurrent PMB. Such a policy may improve the ability to predict these diseases.

Conclusion

Women with recurrent PMB after an initial negative assessment should be re-investigated because they may still have significant genital tract pathology. Those with a thick ET (>4 mm) or histopathology showing a proliferative or secretory endometrium at the initial assessment are especially at risk. A more thorough examination and specific management should be carried out for a woman who presents with PMB and increased ET if hysteroscopic assessment is suboptimal and endometrial sampling provides insufficient tissue for histopathology.

Acknowledgements

The author would like to thank Dr CP Pang, Dr YF Kwok, Dr YM Leung, Dr Stephen Yong, and Dr WK Lam for the advice. The author would also like to thank Dr SC Ling, Dr CK Cheng, Dr FY Leung, Dr SY Tse, and Dr YC Li for the data retrieval.

References

1. van Hanegem N, Breijer MC, Khan KS, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. *Maturitas* 2011; 68:155-64.
2. Timmermans A, Opmeer BC, Khan KS, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2010; 116:160-7.
3. Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer* 2000; 89:1765-72.
4. Elfayomy AK, Habib FA, Alkabalawy MA. Role of hysteroscopy in the detection of endometrial pathologies in women presenting with postmenopausal bleeding and thickened endometrium. *Arch Gynecol Obstet* 2012; 285:839-43.
5. Ronghe R, Gaudoin M. Women with recurrent postmenopausal bleeding should be re-investigated but are not more likely to have endometrial cancer. *Menopause Int* 2010; 16:9-11.
6. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as the predictors of endometrial cancer. *Am J Obstet Gynecol* 2003; 188:401-8.
7. Gull B, Carlsson S, Karlsson B, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding: is it always necessary to perform an endometrial biopsy? *Am J Obstet Gynecol* 2000; 182:509-15.
8. Van Doorn HC, Timmermans A, Opmeer BC, et al. What is the recurrence rate of postmenopausal bleeding in women who have a thin endometrium during a first episode of postmenopausal bleeding? *Acta Obstet Gynecol Scand* 2008; 87:89-93.
9. Timmermans A, van Doorn LC, Opmeer BC, et al. Follow-up of women after a first episode of postmenopausal bleeding and endometrial thickness greater than 4 millimeters. *Obstet Gynecol* 2008; 111:137-43.
10. Kaplan E. Recurrent postmenopausal bleeding. *S Afr Med J* 1977; 52:1121-3.
11. Twu NF, Chen SS. Five-year follow-up of patients with recurrent postmenopausal bleeding. *Zhonghua Yi Xue Za Zhi (Taipei)* 2000; 63:628-33.
12. Feldman S, Shapter A, Welch WR, Berkowitz RS. Two-year follow-up of 263 patients with post/perimenopausal vaginal bleeding and negative initial biopsy. *Gynecol Oncol* 1994; 55:56-9.