Original Article

Etiologies for Postmenopausal Bleeding and Diagnostic Values of Endometrial Biopsy

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Objective: To define the etiologies of postmenopausal bleeding [PMB] categorized by clinical finding and endometrial histopathology and explore the diagnostic performance of endometrial biopsy compared to either fractional curettage [F&C] or hysteroscopic biopsy or hysterectomy.

Materials and Methods: The retrospective study of 100 consecutive postmenopausal women presenting with PMB at the out-patient department, Ramathibodi Hospital between January 1 and June 30, 2015. They were investigated for the causes of bleeding by vaginal examination and endometrial biopsy for histopathologic examination. Some patients received additional investigations or operations for final diagnosis, either F&C, directed hysteroscopic biopsy, or hysterectomy. The accuracy, sensitivity, and specificity of the endometrial biopsy was analyzed.

Results: From 100 consecutive PMB patients, the bleeding sources were vagina (3%), cervix (2%), and endometrium (95%). The etiologies of PMB were mostly from endometrial sources, including proliferative and other benign endometrial pathology (45%), atrophic endometrium (22%), endometrial polyp (12%), endometrial hyperplasia (7%), and endometrial carcinoma (9%). Besides, a small part of PMB resulted from atrophic vaginitis (3%) and cervical polyp (2%). The pathologic reports of 68 endometrial samplings revealed proliferative and other benign endometrium (48.5%), atrophic endometrium (14.7%), endometrial polyp (7.3%), endometrial hyperplasia (8.8%), endometrial cancer (7.3%), and inadequate endometrial tissue (13.2%). Some patients received further investigations or operations, either F&C, or directed hysteroscopic biopsy or hysterectomy. The discrepancy of the pathology, between endometrial sampling and further investigation or operations, was found in 37.5% (6 in 16 of patients). The sensitivity and specificity of endometrial biopsy for benign and malignant endometrial lesions were 62.5% and 100%, respectively. The positive predictive value [PPV], the negative predictive value [NPV], and the accuracy were 100%, 72.73%, and 81.25%, respectively.

Conclusion: The most common causes of PMB were benign in nature, however, endometrial carcinoma accounted around 9%. The diagnostic performance of endometrial biopsy for PMB was relatively low, demonstrated by low sensitivity and some risks of undetectable endometrial precancerous and cancerous lesion.

Keywords: Postmenopausal bleeding, Endometrial biopsy, Endometrial hyperplasia, Endometrial cancer

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Postmenopausal bleeding [PMB] refers to any bleeding from genital area after one year since last menstrual period in menopausal women. PMB is a common gynecologic problem and responsible for approximately 10% of postmenopausal women visiting gynecological practice. Despite permanent cessation of the ovarian hormone production, any unexpected vaginal bleeding in postmenopausal women, even in women receiving menopausal hormone therapy [MHT] should be promptly evaluated for gynecologic malignancy, not only endometrial and cervical cancer but also ovarian cancer. The sources of bleeding can be varied from vulvar, vagina, cervix, and uterine lesions, as a result of either trauma, infection, inflammation, atrophic change, benign tumor, or malignancy[1,2]. However, the endometrial cancer is the most significant and lethal conditions, with an approximate prevalence of 5% to 10% in PMB. More than 90% of the first diagnosed endometrial cancer patients presented with PMB[3]. An early stage endometrial cancer can be cured by hysterectomy, therefore, early, prompt, and accurate diagnosis is recommended.

The clinical approach to PMB aims to exclude

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or diagnose the endometrial intraepithelial neoplasia or hyperplasia and endometrial carcinoma. In the gynecologic practice, the evaluation of PMB patient includes history taking for the risk factors of bleeding and vaginal examination for local or organic lesion, such as vaginal tear, vaginal atrophy, cervicitis, cervical polyps, precancerous lesion, and cancerous lesion of cervix. At present, transvaginal sonography is a common investigation for PMB because it is non-invasive and convenient for out-patient setting. Furthermore, it can evaluate the endometrial echo complex or endometrial thickness, and even perform endometrial biopsy for histopathologic examination[4]. According to the American College of Obstetrics and Gynecology [ACOG] Committee Opinion, PMB with thin endometrial echo complex, defined as less than or equal to 4 mm, has a less than 1% of probability of endometrial cancer. Therefore, the endometrial biopsy is unnecessary, unless in persistent or recurrent bleeding patients[5]. From the meta-analysis study in 2000, the diagnostic accuracy of endometrial biopsy in the detection of endometrial carcinoma and hyperplasia, compared to either fractional curettage [F&C], hysteroscopy or hysterectomy, had shown a sensitivity of 95% and a specificity of 99.5%[6]. However, some studies reported the inadequate sampling as high as 50%. Furthermore, the present study of the insufficient sampling tissue from PMB demonstrated that one fifth of the cases had uterine pathology, and after further investigation the obscure malignancies were found in 3%[7].

In Thailand, there is still lacking the data of etiologies of PMB and the accuracy of endometrial biopsy in the authors settings. Moreover, the present practice is more familiar with prompt endometrial biopsy for the first bleeding episode because there is an insufficiency of gynecologist and transvaginal ultrasound in rural areas. The authors performed this retrospective study to determine the etiologies of PMB, categorized by clinical finding and endometrial histopathology. The aim of the current study is to evaluate the diagnostic values of endometrial sampling compared to either F&C, directed hysteroscopic biopsy, or hysterectomy.

Materials and Methods

Patients

The present study included the data of 100 consecutive Thai postmenopausal women visiting the gynecologic outpatient department or emergency department, Ramathibodi Hospital, with the symptom of PMB between January 1 and June 30, 2015. The present study was approved by the Ramathibodi Hospital Ethics Committee on Human research, Faculty of medicine, Ramathibodi Hospital by IRB. Number (MURA) 2016/682 (20-04-2017).

Methods

The retrospective medical charts review was performed to collect the data that included baseline characteristics, clinical diagnosis, and the pathological report from the endometrial biopsy. When necessary for the final diagnosis, further investigations or operations were performed for the definite pathological reports, either from F&C, hysteroscopic biopsy, or hysterectomy. The final pathologic reports and the final diagnosis were collected. The diagnostic performance of endometrial biopsy was performed, correlating to the final standard pathological diagnosis.

Statistical analysis

Statistical analysis was done using Stata Statistical Software version 14 (College Station, Texas: StataCrop LP, USA). The baseline characteristics were presented as the mean ± SD or median (minimum value to maximum value) in continuous data and the percentage in categorical data. Student's t-test was used for normal distribution and Mann-Whitney U test was used for non-normal distribution. The diagnostic performance of endometrial biopsy pathology comparing to gold standard procedure pathology, either from F&C or directed hysteroscopic biopsy or hysterectomy. The sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and the accuracy were calculated.

Results

Data of 100 consecutive Thai postmenopausal women presenting with PMB was collected. The baseline characteristics of the patients are summarized in Table 1. The median age was 57 years (range from 45 to 96 years), median time since menopause was five years (range from 1 to 40 years) and median body mass index [BMI] was 25.80 kg/m^2 (range from 16.03 to 43.06 kg/m^2). Most of the patients have an underlying disease such as hypertension, dyslipidemia, or diabetes mellitus. Only one patient had used the MHT.

The most common PMB sources was endometrium 95% and a small portion came from the vagina 3% and the cervix 2%. From the vaginal examination and clinical finding, the diagnosis were atrophic vaginitis in three cases, cervical polyp in two cases, and one case

of atrophic endometrium. At the pelvic examination, 26 patients experienced technical failure of the endometrial biopsy due to pain and cervical stenosis. Those patients underwent F&C or hysteroscopic biopsy under general anesthesia or hysterectomy. Apart from that, most of the patients received the endometrial biopsy at the out-patient setting and got the final diagnosis of PMB without any further investigations or operations. The pathology reports of 68 endometrial samplings, nearly half of samplings, revealed proliferative and other benign endometrium (48.5%), atrophic endometrium (14.7%), endometrial polyp (7.3%), endometrial hyperplasia without atypia (8.8%), endometrial cancer (7.3%), and inadequate endometrial tissue (13.2%), as shown on Table 2. Sixteen of 68 patients needed further investigations, either F&C, directed hysteroscopic biopsy, or hysterectomy, to confirm the final diagnosis as shown in Figure 1. From 16 cases data, most of them got concomitant findings between endometrial biopsy and the final pathologic report from additional investigation. Nevertheless, the authors discovered six discrepancy outcome cases (37.5%). The endometrial biopsy could not detect the endometrial polyp in three cases. Moreover, this procedure missed the one case of endometrial hyperplasia and two cases of endometrial cancer, as shown on Table 3. From the present study,

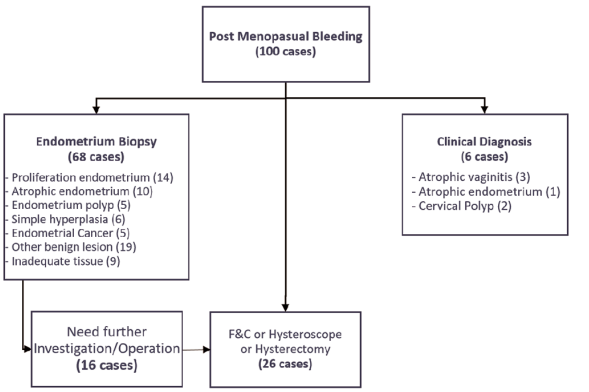

Figure 1. Diagnostic work up flow of the PMB patient in this study.

the diagnostic performances of the endometrial biopsy yielded sensitivity of 62.5% (95% CI 24.5 to 91.5), specificity of 100% (95% CI 63.1 to 100.0), PPV 100% (95% CI 47.8 to 100.0), NPV of 72.73% (95% CI 39.0 to 94.0), accuracy of 81.25%, negative likelihood ratio [LR^-] of 0.375 (95% CI 0.153 to 0.917), and the positive likelihood ratio [LR^+] was infinity due to no false positive case. However, if we estimated LR^+ with at least one case with a false positive result, then the calculate LR^+ would be 10.91 (95% CI 0.71 to 171). The area of receiver operation characteristic [ROC] was 0.813 (95% CI 0.633 to 0.992) for the diagnosis of benign and malignant endometrial lesions.

Summation from the final pathologic and clinical diagnosis, the etiologies of PMB were mostly from the endometrial sources, aside from the atrophic vaginitis 3% and cervical polyp 2%. The most common causes of PMB was proliferative endometrium and other benign endometrial pathology in 45%. The second most common cause was atrophic endometrium 22%. The

Table 1. Baseline characteristics of the PMB women

Characteristics	Total = 100, n (%)
Age (years), median (range)	57 (45 to 96)
Nulliparous	29 (29)
BMI (kg/m^2), median (range)	25.8 (16.03 to 43.06)
Time since menopause (years), median (range)	5 (1 to 40)
History of MHT use	1 (1)
Underlying disease	
Hypertension	34 (34)
Dyslipidemia	32 (32)
Diabetes mellitus	12 (12)
Breast cancer	9 (9)
Liver cirrhosis	3 (3)

PMB = postmenopausal bleeding; MHT = menopausal hormonal therapy

Table 2. The pathological report of 68 endometrial samplings

Endometrial sampling	n (%)
Proliferative endometrium	14 (20.59)
Atrophic endometrium	10 (14.71)
Endometrial polyp	5 (7.35)
Inadequate	9 (13.24)
Simple hyperplasia	6 (8.82)
Endometrial cancer	5 (7.35)
Other benign endometrial	19 (27.94)

Table 3. The comparison of the pathologic outcome of the endometrial biopsy and the final pathology, either from fractional curettage or directed hysteroscopic biopsy or hysterectomy

Endometrial sampling pathology	Final pathology	n (total 16 cases)
Endometrial polyp	Endometrial polyp	1
Benign or proliferative endometrium	Endometrial polyp	2
Inadequate specimen	Atrophic endometrium	2
Inadequate specimen	Inadequate specimen	2
Inadequate specimen	Endometrial polyp	1
Endometrial cancer	Endometrial cancer	5
Endometrial polyp	Endometrial hyperplasia	1
Inadequate specimen	Endometrial cancer	1
Endometrial hyperplasia	Endometrial cancer	1

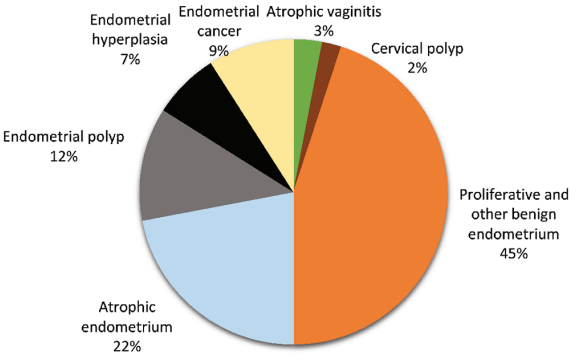

Figure 2. Etiologies of post-menopausal bleeding in this study.

endometrial polyp was found in 12%. The endometrial hyperplasia and endometrial cancer were detected in 7% and 9%, respectively, as shown in Figure 2.

Discussion

From the present study, the most common causes of PMB were benign pathologies including proliferative, other benign endometrium, and atrophic endometrium. However, PMB resulting from endometrial hyperplasia in 7% and endometrial cancer in 9%, without any finding of cervical carcinoma. Similar to the prior studies[7-11], the most common pathology of PMB was benign in nature. However, the studies from Lee et al (1995)[7], Kaur et al (2009)[8], and Tariq et al (2015)[9], revealed the frequent incidence of cervical carcinoma, which ranged from 7.6% to 14%, endometrial cancer, which ranged from 11% to 15.9%, and endometrial hyperplasia that ranged around 13% in PMB women. Those incidences of malignancy were much higher than in the present study, especially the cervical carcinoma, which imply to the effective and pervasive policy of cervical cancer screening programs. Besides, the endometrial cancer incidence in the present study was consistent with studies of Van den Bosch et al (2105)[10] and Burbos et al (2010)[11], which reported the endometrial cancer incidence of 5% to 7% in PMB. Additionally, the peak incidence occurred at the age 60 to 64 years.

The main managements of PMB are to exclude the malignancy by vaginal examination, cervical cytology examination, transvaginal sonography for endometrial thickness measurement, and endometrial biopsy for tissue pathology. According to the ACOG Committee Opinion of 2018, they recommend transvaginal ultrasonography [TVS] as the initial evaluation of PMB. Cases of TVS reveal thin endometrial echo (less than or equal to 4 mm). Therefore, the endometrial sampling could be exempted due to greater than 99% NPV for endometrial cancer. However, rare type II endometrial carcinoma can be found in even endometrial thickness of less than 3 mm. Therefore, recurrent, or persistent PMB are indicated for the endometrial histopathological diagnosis, even in cases of thin endometrium[4]. In the present study, the TVS were not included, due to the incomplete medical records. Furthermore, some of our patients had not been investigated by the TVS because it is not routinely recommended in the authors practice. The present study discovered that the diagnostic performance of endometrial biopsy for detecting benign and malignant endometrial lesions, was sensitivity 62.5% and specificity 100%, compared to either F&C or directed hysteroscopic biopsy or hysterectomy. This is in contrast with the prior meta-analysis of 2000 that reported the pooled sensitivity of 95% and specificity of 99.5% for accuracy of endometrial biopsy to detect endometrial carcinoma and atypical hyperplasia, compared to dilation & curettage [D&C], hysteroscopy, and/or hysterectomy[5]. In line with the recent meta-analysis of 2016, they revealed the weighted sensitivity and specificity of 100% and 92%, respectively, of endometrial sampling in PMB for the diagnosis of endometrial hyperplasia. The meta-analysis included 12 studies on 1,029 PMB women, which endometrial biopsy diagnostic performance were compared to dilatation & curettage in five studies and hysteroscopy in seven studies. However, the diagnostic performance of endometrial biopsy was reduced to 90% sensitivity (range from 50 to 100) and 82% specificity (range from 56 to 94) for the diagnosis of endometrial cancer, endometrial hyperplasia, and other benign endometrial lesions, such as endometrial polyp, comparing to the hysteroscopy. The weighted failure rate of endometrial sampling was 11% (range from 1% to 53%) and the inadequate samples were found in 31% (range from 7% to 76%). Those became to premalignant endometrial lesion around 7%[12]. This imply that the sensitivity of endometrial biopsy was lower, comparing to hysteroscopy than the blind investigation technique, like D&C or F&C. Another supported information from Gungorduk et al (2014)[13], revealed that the concordance of endometrial pathology between endometrial biopsy and hysterectomy in patient undergoing hysterectomy in various condition was 62%. Moreover, the sensitivity of endometrial biopsy in detecting the endometrial hyperplasia was only 41.7%[13].

The present study showed the relatively low sensitivity and good specificity of endometrial biopsy

for detecting both benign and malignant endometrial lesions. When applying endometrial biopsy in large population of post-menopausal bleeding, because of low or high prevalence, incidence will affect values of sense and specificity, the authors needed to use LR^+/LR^- from the present study and used prior probability (odds) of 50% from prevalence found from this sample of population. The authors applied the Fagan nomogram for evaluate post-test probability. Based on LR^+, the results showed that the posterior probability (odds) was 92% (95% CI 42% to 99%) increasing from 50% of pretest or prior probability, and LR^- showed that the posterior probability (odds) was 29% (95% CI 15% to 49%) from Fagan nomogram, as shown in Figure 3. Although the LR^+ values give rise to higher probability of post-test probability, they are likely to be used in endometrial biopsy as a means of detection. However, the follow-up might be necessary and important in the present setting, even in the case of diagnosed benign pathology report from endometrial biopsy. In another word, additional investigations or operations including, transvaginal sonography, F&C, or flexible hysteroscopy, should be performed based on each individual's clinical risk factors. However, our specificity of endometrial biopsy was 100% for detecting both benign and malignant endometrial lesions. Consequently, the premalignant and malignant endometrial pathology from the endometrial biopsy can be assured for the correct diagnosis. For future study, the authors suggest a larger number of cases, diverse country region, and multi-level of hospital capacity setting to perform the prospective study. It should include PMB etiologies in Thailand and the diagnostic value of endometrial biopsy in surpassing data, as well as clinical risk factors for predicting the malignancy.

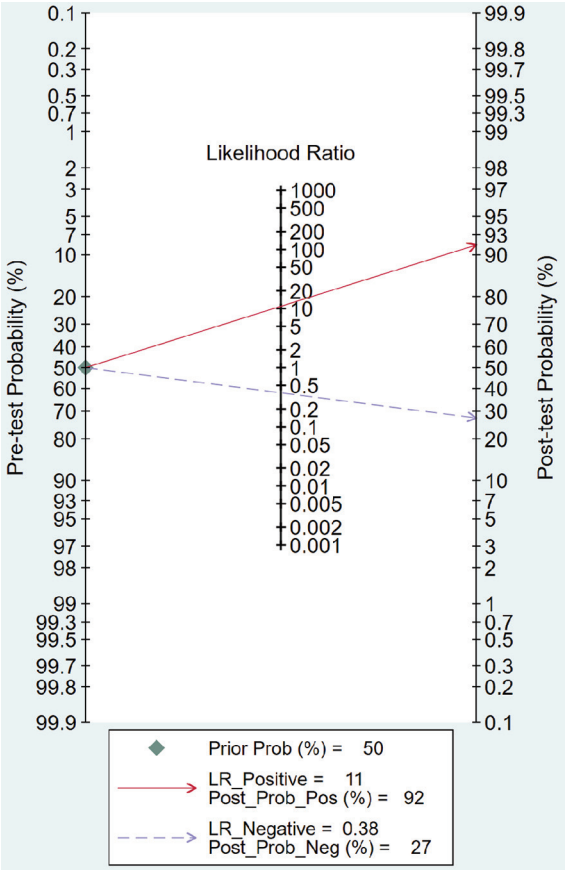

Figure 3. Fagan normogram demonstaed of diagnostic properties of endometrium biopsy in post-menopausal.

Conclusion

The most common causes of PMB were benign in nature, however, the endometrial hyperplasia and endometrial carcinoma should not be overlooked. The diagnostic performance of endometrial biopsy for PMB was relatively low, demonstrating by low sensitivity and some risks of undetected endometrial precancerous and cancerous lesion.

What is already known on this topic?

PMB is a common gynecological problem and one of cardinal symptoms of endometrial hyperplasia and endometrial cancer. The prompt and effective management will give a chance of cure the patient, due to a good prognosis in early radical treatment of the stage I endometrial cancer.

The endometrial biopsy is the first-line and recommended investigation in PMB women because of the comfort, less invasive, and convenient procedure at the out-patient department, comparing to F&C. The accuracy of endometrial biopsy for detecting endometrial hyperplasia and endometrial cancer is very high, more than 95% of sensitivity.

What this study adds?

In Thai PMB women, the sensitivity of endometrial biopsy for detecting both benign and malignant endometrial lesions have a relatively low sensitivity of only 62.5%, but a high specificity of 100%.

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Potential conflicts of interest

The authors declare no conflict of interest.

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