Original Research Article

Study of Post-Menopausal Bleeding in Women At ANMMCH, Gaya, Bihar

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Abstract:

Background: One of the most frequent reasons for referral to gynecological care is postmenopausal bleeding (PMB), mostly because of suspicions of an underlying endometrial cancer. The purpose of this study is to assess the relationship between patient characteristics and endometrial histological diagnosis, as well as the relationship between endometrial thickness (ET) and histopathological diagnosis in PMB-affected women.

Methods: The characteristics findings of 67 PMB patients' pelvic examinations were documented. Endometrial biopsy (EMB) and transvaginal sonography were used to evaluate all of the women.

Results: Endometrial adenocarcinoma (EAC) patients had a significantly longer PMB time than other patients, at 22.3 days on average. EAC sufferers have been observed to have greater body mass indices than other patients.

Conclusion: We suggest that all patients with PMB should be examined for EMB because nearly 4.5% of patients with PMB had EAC. Obese patients and those with persistent PMB should receive special attention.

Keywords: Transvaginal sonography; Endometrial biopsy; Postmenopausal bleeding; Endometrial carcinoma; Uterine diseases.

Introduction

Any uterine bleeding that takes place in a woman who is not on hormone replacement therapy (HRT) after one year of amenorrhea is known as postmenopausal bleeding (PMB).[1,2] In 5% of patients referred to gynecological clinics, PMB is a prevalent complaint. PMB patients need to be further examined since they have a 5–15% likelihood of having endometrial cancer (EC). The most frequent gynecologic malignancy is EC, and 95% of EC patients also have PMB.[1-3] Since EC frequently manifests early, unlike other cancers, where hysterectomy is a curative option, early and precise diagnosis is crucial.[1,2] As an initial step in the assessment of women with PMB, several guidelines advise measuring endometrial thickness (ET) using transvaginal ultrasonography (TVUS).[4–8] The purpose of the TVUS evaluation is to rule out the likelihood of EC.(4) When endometrial ultrasonography reveals an ET of ≤4 mm, the likelihood of endometrial disease is significantly decreased.[2,4]

In this study, we sought to determine the correlation between the ET cutoff value and the endometrial histopathologic diagnosis in order to rule out the possibility of EC in patients with PMB and to assess the relationship between patient presentation and endometrial histopathologic diagnosis. We also sought to diagnose endometrial pathology via TVUS and endometrial biopsy (EMB).

Material and Methods

From July 2019 to March 2020, this study was conducted at the Department of Obstetrics and Gynecology, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar. Each patient gave both verbal and written consent before any procedures began. We assessed 67 consecutive women who had been referred to the OB/GYN department of ANMMCH with PMB.

Following menopause, postmenopausal uterine bleeding, and serum follicle stimulating hormone (FSH) level ≥40 IU/L were the inclusion criteria for women with PMB. Women who had HRT and abnormal coagulation levels were not included in the study. All patients' age, BMI, menopause age, postmenopausal bleeding duration (PMBT), FSH, luteinizing hormone (LH) level, estradiol (E2) level, and coagulation test results (activated partial thromboplastin time [APTT], prothrombin time

[PT], and international normalized ratio [INR] levels) were also noted in addition to the results of the pelvic examination. An expert radiologist used TVUS to analyze all of the trial participants. All 67 women had EMB for histopathologic diagnosis. The same pathologist analyzed every biopsy, and a second pathologist looked at any materials that had been labeled as abnormal. Endometrial materials with the following histological diagnoses were categorized: atrophic, inactive, estrogen-affected, endometrial polyp, leiomyoma, endometrial hyperplasia, endometrial adenocarcinoma (EAC), or inadequate material. The information is displayed as mean standard deviation (SD).

Statistics were judged significant at p <0.05. The outcomes were examined using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA).

Results

A significant difference between the atrophied and inactive endometrium and the endometrium affected by estrogen, as well as between the endometrium with polyp inactive endometrium, and the endometrium affected by estrogen, was found when the histopathological findings were sorted according to patient age (p<0.05). Table 1 displays the patient characteristics and histological diagnosis.

Table 1: Histopathological diagnosis according to patient characteristics

Histopathologic Diagnosis (N)	Age (years)	Time after Menopause (Years)	BMI (Kg/m^2)	Estradiol (IU/L)	FSH (IU/L)	ET (mm)	PMBT (days)
	Mean ± Standard Deviation						
Atrophic Endometrium [17]	62.0 ± 8.4	14.5 ± 9.5	28.3 ± 2.0	14.2 ± 4.6	46.1 ± 13.0	2.6 ± 0.5	6.5 ± 4.3
Endometrium with Estrogen Effect [14]	53.2 ± 5.7	7.1 ± 5.0	26.9 ± 2.8	41.1 ± 21.6	52.2 ± 7.8	7.6 ± 3.1	7.5 ± 4.5
Inactive Endometrium [7]	52.7 ± 3.7	5.3 ± 3.0	27.3 ± 2.2	21.3 ± 7.0	53.7 ± 10.0	3.5 ± 3.8	7.4 ± 4.3
Endometrial Polyp [6]	61.3 ± 5.7	13.8 ± 5.8	25.9 ± 2.4	35.9 ± 23.2	54.4 ± 7.2	7.1 ± 5.0	6.8 ± 5.6
Endometrial Hyperplasia [5]	54.4 ± 2.5	10.6 ± 1.3	29.6 ± 5.2	39.5 ± 11.6	49.7 ± 7.3	9.2 ± 3.1	10.4 ± 2.9
Endometrial Adenocarcinoma [3]	60.7 ± 8.7	11.4 ± 8.1	33.0 ± 9.9	15.4 ± 2.7	43.1 ± 1.7	12.7±7.6	22.3 ± 2.5
Endometrial Leiomyoma [2]	58.5 ± 9.2	15.0 ± 7.1	25.3 ± 0.7	21.4 ± 1.0	48.3 ± 8.7	6.0 ± 5.7	4.0 ± 4.2
Insufficient Material [13]	58.8±10.2	11.0 ± 8.7	29.1 ± 7.3	21.4 ± 14.8	55.3 ± 33.3	5.6 ± 3.3	4.9 ± 2.8
Total	57.7 ± 8.0	10.8 ± 7.6	28.1 ± 4.5	26.0 ± 17.6	50.9 ± 17.0	5.3 ± 3.7	7.5 ± 5.3

A comparison of the histopathologic findings according to the duration of menopause showed a statistically significant difference between atrophy and endometrial sensitivity to estrogen and between inactive endometrium and atrophy and polyp (p<0.05). A statistically significant difference between EAC and endometrium influenced by estrogen and those with polyps can be found when comparing EMB results according to patient BMI (p <0.05).

A statistically significant difference could be noticed when comparing the EMB results based on the patient's E2 level between the endometrium impacted by estrogen and atrophy, insufficient material, inactive endometrium, and EAC (p<0.05), as well as between polyp and atrophy, insufficient material (p<0.05). No statistical significance was discovered when comparing the EMB results to the

serum FSH level. When we compared the histopathologic findings according to ET, we discovered a statistically significant difference between endometrial hyperplasia and insufficient material or inactive endometrium (p<0.05); between endometrial hyperplasia and atrophy; and between insufficient material and endometrium with estrogen effect or polyp.

We found a significant difference between EAC and all other histological diagnoses when comparing the EMB results in accordance with the patient PMBT (p <0.05). EAC was identified in three cases. While the ET of five patients with a histopathologic diagnosis of endometrial hyperplasia ranged from 6 mm to 13 mm, the ET of the third patient was measured to be 4 mm. When we looked into the patient PMBT, we discovered that patients with an EAC diagnosis had uterine

bleeding that lasted noticeably longer than those in other groups.Patients with an EAC diagnosis had the highest ET values, with a mean value of 12.7 mm; patients with endometrial hyperplasia had the next-highest mean values, 9.2 mm.

The Kruskal Wallis test has been applied to compare ET with the histopathologic diagnosis of endometrium (Table 2). Although there is a link between ET and endometrial hyperplasia, there is no evidence of a link between ET and EAC. Additionally, we discovered a positive association (Sherman's rho) between PMB, endometrial hyperplasia, and EAC.

Our study revealed that EMB should be carried out for patients with PMB, particularly those who have had long-term PMBT. However, more research involving bigger patient cohorts have to be carried out.

Table 2: Histopathological diagnosis based on a 4-mm cut-off for endometrial thickness

Histopathological Diagnosis	Endometrial thickness	
	<4 mm	≥4mm
Atrophic Endometrium	17 (100%)	0 (0%)
Insufficient Material	5 (38%)	8 (62%)
Inactive Endometrium	6 (86%)	1 (14%)
Endometrium with Estrogen Effect	2 (14%)	12 (86%)
Endometrial Polyp	2 (33%)	4 (67%)
Endometrial Leiomyoma	1 (50%)	1 (50%)
Endometrial Hyperplasia	0 (0%)	5 (100%)
Endometrial Adenocarcinoma	0 (0%)	3 (100%)

Discussion

In about 10% of cases, PMB can indicate EC, and in another 20%–40% of patients, it can indicate less dangerous problems like polyps.[1,9,10] Since postmenopausal uterine bleeding occurs in 95% of women with EAC, the most common gynecologic cancer, PMB should be further examined.[1,11]

The initial step when a patient has PMB is to refer them to a gynecological clinic for an exam and TVUS. Although there is ongoing discussion regarding the ET cut-off level, TVUS is an accurate method for excluding EC.[11] Only when ET is higher than the cut-off level is endometrial sample advised by guidelines [1,4,12,13]. The ET cut-offs used by various guidelines range from 3 to 5 mm.[1-13] In our investigation, a 4.0 mm ET cut-off had a 100% sensitivity and 68.1% specificity. According to Smith-Bindman et al. findings [7], the sensitivity for detecting EC is 96% and the specificity is 61% at a cut-off level of 5 mm.

For females with endometrial thickness ≤ 5 mm, conservative care is advised. TVUS can be used to rule out endometrial hyperplasia or EAC at an ET of ≤ 5 mm, according to a review by Gupta et al.[8] Timmermans et al.[6] recommended a cut-off level of ≤3 mm using a meta-analytic method that incorporated the individual patient data from a number of original investigations.

Three patients in our study had EC, according to the diagnosis. Endometrial sample was done because ET in 2 individuals evaluated by TVUS to be >4mm. TVUS determined the ET in the third patient to be 4 mm. We were able to identify the third patient with EAC based on these findings and the assumption that the cut-off point for endometrial thickness was ≥4mm. Between women, there is a large variation in both the ET and the likelihood of EC. Age, the length of time since menopause, obesity, hypertension, diabetes mellitus, metabolic syndromes, and reproductive variables have all been linked to this diversity in patient features.[2,14-17]

However, present recommendations are solely based on ET and do not systematically take other factors into account. The incorporation of these unique traits may enable a more accurate categorization of women with the ET.

In order to do this, we looked at the relationships between age, the number of years since menopause, BMI, the levels of the hormones E2 and FSH, ET, PMBT, and histopathologic diagnosis. The mean age of the patients in our study was 57.7, which is comparable to that reported in other studies[18,19], but in contrast to other studies, it was discovered that the malignancy group had a greater mean age than the other groups.[18]

We discovered an important difference between individuals with EAC and those with other histological diagnoses: the PMBT of patients with EAC was, on average, 22.3 days longer. In patients with endometrial hyperplasia, 10.4 days has been reported as the closest number. This makes us think that postmenopausal patients who report prolonged bleeding should receive greater attention.

According to studies, obesity raises the level of circulating estrogen, raising the risk of EC with higher ET.[20,21] BMI has been investigated in conjunction with ET with varying degrees of success and is believed to be a sensitive characteristic of obesity. While some studies have established a positive correlation between BMI and ET and have suggested that the risk of EC increases

in overweight women, Tsuda et al. [22], claim that there is no association between BMI and ET.[23,24] Although there was no correlation between BMI and ET in our investigation, EAC patients were found to have higher BMIs than other patients. According to Douchi et al.[20], there is no correlation between ET and the amount of time since menopause. According to Tsuda et al.[22], ET declines with an increase in time since menopause. The amount of time since menopause and ET were not linked in our study.

According to studies, the level of ET rises as E2 does.[20,23] But in response to patient E2 level, Andolf et al.[21] found no distinction between normal and thicker endometria. In our investigation, patients with estrogen-sensitive endometria and endometrial hyperplasia had the highest serum E2 levels.

In cases when a woman has PMB and an elevated ET, guidelines recommend endometrial sampling by TVUS to rule out EC. EMB, however, is an intrusive treatment that can result with problems such bleeding, infection, and perforation of the uterus. Additionally, the volume of tissue acquired during office sampling varies widely and is occasionally insufficient for accurate histological diagnosis. In 5.7% of cases, the diagnosis of endometrial hyperplasia and endometrial EC was missed by biopsy, according to Stovall et al.[25] comparison of the outcomes of EMB and hysterectomy for endometrial histopathologic diagnosis.

A sufficient tissue sample was not provided by EMB as frequently as 16% of the time in a large cohort study. Additionally, 90% of postmenopausal bleeding has a benign underlying etiology, which calls into doubt the need for a biopsy.[27] Clinical data analysis has led to inconsistent findings. According to Gull[28], as long as ET is ≤ 4 mm, the combination of TVUS and cervical cytologic examination is sufficient for women with PMB when the false negative rate of EMB methods is taken into account. According to Ferrazi et al.[29], managing postmenopausal atypical bleeding just requires the addition of individual risk factors to TVUS evaluation of ET.

Goldstein et al.[5] came to the conclusion that PMB needs additional assessment and that either TVUS or EMB might be used as a first-line diagnostic procedure, but more research is required to identify which method is more economically advantageous. In order to rule out endometrial pathology, Gupta et al.[8] recommendation is for all women with PMB to undergo both an outpatient endometrial sampling and an ultrasound. Fleischer et al.[30] recommended performing an EMB to rule out EC when the endometrial thickness was less than 4 mm and risk factors such obesity, late menopause, nulliparity, and HRT were present.

Conclusion

All instances of EAC were successfully identified at a cut-off value of 4 mm. We propose that EMB be conducted for all patients with PMB since in our study; about 4.5% of the individuals had EAC. The number of patients in our study, however, is insufficient to draw a firm conclusion. The recommendation of EMB will only be made to women who have a high chance of EC by aggregating and analyzing individual patient data, considering patient features from many studies with larger databases.

References

1. Van Hanegem N, Breijer MC, Khan KS, Clark TJ, Burger MP, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. Maturitas. 2011; 68: 155-164.
2. Breijer MC, Timmermans A, van Doorn HC, Mol BW, Opmeer BC. Diagnostic strategies for postmenopausal bleeding. Obstet Gynecol Int. 2010;850812.
3. Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. J Obste. Gynaecol. 2004; 24: 736-741.
4. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 440: The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. Obstet Gynecol.2009; 114: 409-411.
5. Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, et al. Evaluation of the woman with postmenopausal bleeding: society of radiologists in ultrasound-sponsored consensus conference statement. JUltrasound Med. 2001; 20: 1025-1036.
6. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010; 116: 160-167.
7. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998; 280: 1510-1517.
8. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-

analysis. Acta Obstet Gynecol Scand. 2002; 81:799-816.

9. Emanuel MH, Verdel MJC, Stas H, Wamsteker K, Lammes FB. An audit of true prevalence of intra-uterine pathology: the hysteroscopic findings controlled for patient selection in 1202 patients with abnormal uterine bleeding. Gynaecological Endoscopy. 1995; 4: 237-241.

10. Salman MC, Bozdag G, Dogan S, Yuce K. Role of postmenopausal bleeding pattern and women's age in the prediction of endometrial cancer. Aust NZJ Obstet Gynaecol. 2013; 53: 484-488.

11. Alcazar JL, Galvan R. Three-dimensional power doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium. Am J Obstet Gynecol. 2009;200: 44.e1-44. e6.

12. de Kroon CD, van Dongen H, Jansen FW. Gynaecological diagnosis of postmenopausal women with abnormal vaginal bleeding: a comparison with the guideline. Ned Tijdschr Geneeskd. 2006; 150: 586.

13. Epstein E. Management of postmenopausal bleeding in Sweden: a need for increased use of hydrosonography and hysteroscopy. Acta Obstet Gynecol Scand 83: 89-95.

14. van Doorn HC, Opmeer BC, Jitze Duk M, Kruitwagen RF, Dijkhuizen FP, et al. The relation between age, time since menopause, and endometrial cancer in women with postmenopausal bleeding. Int J Gynecol Cancer. 2007; 17: 1118-1123.

15. Chen HF, Liu MD, Chen P, Chen LH, Chang YH, et al. Risks of breast and endometrial cancer in women with diabetes: a population-based cohort study. PLoS One. 2013; 8: e67420.

16. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, et al. Metabolic syndrome and endometrial cancer: a meta-analysis. Endocrine. 2014; 45: 28-36.

17. Bornstein J, Auslender R, Goldstein S, Kohan R, Stolar Z, et al. Increased endometrial thickness in women with hypertension. Am J Obstet Gynecol. 2000; 183: 583-587.

18. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. Br J Obstet Gynaecol. 1995; 102: 133-136.

19. Lidor A, Ismajovich B, Confino E, David MP. Histopathological findings in 226 women with post-menopausal uterine bleeding. Acta Obstet Gynecol Scand. 1986 65: 41-43.

20. Douchi T, Yoshinaga M, Katanozaka M, Mitani M, Nagata Y. Relationship between body mass index and transvaginal ultrasonographic endometrial thickness in postmenopausal women. Acta Obstet Gynecol Scand.1998; 77: 905-908.

21. Andolf E, Dahlander K, Aspenberg P. Ultrasonic thickness of the endometrium correlated to body weight in asymptomatic postmenopausal women. Obstet Gynecol.1993; 82: 936-940.

22. Tsuda H, Kawabata M, Kawabata K, Yamamoto K, Umesaki N. Improvement of diagnostic accuracy of transvaginal ultrasound for identification of endometrial malignancies by using cutoff level of endometrial thickness based on length of time since menopause. Gynecol Oncol.1997 64: 35-37.

23. Byyny RL, Speroff L. A Clinical Guide for the Care of Older Women: primary and preventive care. (2nd Edtn), Williams & Wilkins, Baltimore, USA. 1996.

24. Rota M, Rumi F, Bagnardi V, Dal Maso L, Zucchetto A, et al. Modelling body mass index and endometrial cancer risk in a pooled-analysis of three case-control studies. BJOG. 2016; 123:285-92.

25. Stowall TG, Solomon SK, Ling FW Endometrial sampling prior to hysterectomy. Obstet Gynecol. 1989; 73: 405-409.

26. Machado F, Moreno J, Carazo M, León J, Fiol G, et al. Accuracy of endometrial biopsy with the Cornier pipelle for diagnosis of endometrial cancer and atypical hyperplasia. Eur J Gynaecol Oncol. 2003; 24: 279-281.

27. Dimitraki M, Tsikouras P, Bouchlariotou S, Dafopoulos A, Liberis V, et al. Clinical evaluation of women with PMB. Is it always necessary an endometrial biopsy to be performed? A review of the literature. Arch Gynecol Obstet. 2011; 283: 261-266.

28. Gull B, Carlsson S, Karlsson B, Ylöstalo P, Milsom I, 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: 509-515.

29. Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, et al. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding. An Italian multicenter study. Ultrasound Obstet Gynecol. 1996; 7: 315-321.

30. Fleisher AL, Manning FA, Jeanty P, Romeo R. Sonography in obstetrics and gynaecology principles and practice. 7th edition. Stanford Appleton & Lange, Connecticut, USA. 2010.