The significance of "Atrophic Endometrium" in Women with Postmenopausal Bleeding.

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Abstract

We evaluated the interpretation of atrophic endometrium (AE) histology as a common cause for postmenopausal bleeding (PMB). In our opinion, AE is physiologic and ubiquitous in postmenopausal women, but is not a cause of PMB. Referring to AE as a cause of PMB may result in misdiagnosis of cancer and delay in management. Endometrial sampling are notorious for missing focal lesions and transvaginal sonogram should be considered in cases of PMB and AE histology. If endometrial thickness is found, it is not compatible with AE and further workup is warranted to exclude focal lesions which are common cause for PMB.

Keywords:

Postmenopausal bleeding, endometrial sampling, atrophic endometrium, endometrial thickness, ultrasound.

tweetable abstract

Transvaginal sonogram should be considered in cases of postmenopausal bleeding and atrophic endometrium histology to exclude focal lesion etiology.

Manuscript

Postmenopausal bleeding (PMB) occurs in about 10% of postmenopausal women. The evaluation and management of PMB is a common and important part of many health care providers' daily practice [1, 2]. Approximately 10% of women with PMB will end up with cancer[3-5]. Consequently, 90% will be the result of benign etiologies. The challenge in the workup and management of PMB is therefore to detect all cancer cases without subjecting these women to unnecessary invasive procedures. Many benign conditions are associated with PMB: Endometrial and endo-cervical polyps, proliferative endometrium, cervicitis and endometritis. Atrophic endometrium (AE) has always been considered a dominant cause of PMB, with ranges between 30 to 50% [6-8]. In fact in 2018, the ACOG committee opinion stated that "Postmenopausal vaginal bleeding usually is caused by atrophic changes of the vagina or endometrium." [3]. While bleeding from atrophic vaginitis is quite common and easily diagnosed on routine speculum examination, we questioned the atrophic endometrium part of the statement as a cause of PMB. As there was no reference to the statement, we reviewed the literature and made an effort to verify the source of this important assumption and the histo-pathological data to support the statement. Atrophic endometrium is defined as an endometrial lining deprived of the functionalis layer and consisting exclusively of a thin endometrial basalis layer with a few narrow tubular glands lined by cuboidal epithelium. On pathology it does not show proliferative endometrium, secretory endometrium or mixed activity[9].

The suggestion of AE as a cause for PMB can be traced back to the article of Te Linde in 1940 [10]. This was a pivotal paper which first proclaimed that "malignancy is responsible for the PMB until unequivocally

proved otherwise". In this article Te Linde also wrote: "Endometritis occurring after the menopause may be responsible for bleeding from the atrophic uterine mucosa". To support his theory, Te Linde reported that a combination of pus and adhesions can cause PMB. There is no pathological confirmation or references to support the statements in the article. The publication was written in a different era and this was prior to newer technology including hysteroscopy, ultrasound and immuno-histochemistry. It was also a time in which "expert opinion" was sufficient for a theory to thrive and become a fact. The notion that cancer and AE cause PMB persists to this day. While cancer being a cause for PMB is well documented and proven, the proof for AE being a cause of PMB is lacking and in our opinion potentially misleading.

Review of the literature shows that cancer as a cause for PMB has decreased over the years from as high as 50% to 10% with a reciprocal increase in the percentage of benign causes for the PMB[7-12]. Postmenopausal women have not changed much over the years although there has been an increase in obesity[13], patient longevity [14] and probably a lower threshold for the workup of PMB. The shift in PMB etiology is probably secondary to the introduction of new technologies which have improved our ability to make an accurate diagnosis in women with PMB. For example, polyps were rarely documented in the older literature and now are being diagnosed frequently [7, 15]. The fact that many patients with PMB had a histological diagnosis of AE was a potential source for the different theories[16-19]: Chronic congestion of the uterus, blood dyscrasias, atherosclerosis and vitamin deficiency. In 1971, Meyer et al' [20] suggested three pathways for AE as a cause of PMB: Uterine prolapse, myometrial atherosclerosis, and rupture of atrophic endometrial cysts. While the association of uterine prolapse and vaginal atrophy are clinically recognized [21], the other two hypotheses did not hold true over the years. The most recent pathophysiology of "atrophy-related endometritis" causing PMB was published in a review article by Ferenczy in 2003[22]. In this manuscript, Ferenczy hypothesized that the hypo-estrogenic milieu causes endometrial atrophy and the absence of endometrial fluid causes friction. This results in micro-erosions of the surface epithelium and chronic inflammation which are prone to light bleeding. The manuscript is an excellent review article, but we failed to find any original article to support the hypothesis of "atrophy-related endometritis" causing PMB.

We examined many prominent medical textbooks and physician guidelines (including Novak gynecology and ACOG Committee Opinion) and they all affirm that AE is an important cause of PMB[3, 23-28]. In fact, in Novac Gynecology, AE is suggested as the cause of PMB in 60-80% of PMB. Up-to-date, a popular internet medical information provider, was the only source that presented a reference, the Ferenczy article, to support the proposal that AE is a cause PMB[24]. The above examples affirm how the notion of AE as a cause of PMB which was suggested by Te Linde, continues to persist in the literature and became a medical "fact". We didn't find any original article with scientific evidence for AE being a cause of PMB. In fact we believe that AE is simply an incidental finding in the workup of women with PMB. AE is associated with PMB simply because the endometrial cavity of most postmenopausal women is atrophic. However, that does not necessarily mean that AE is the cause of the PMB. We are making a case against AE as a cause for PMB in general and specifically against AE as the cause of endometritis.

Our supporting evidence:

1) Endometritis is not necessarily associated with uterine bleeding.

Intrauterine contraceptive device (IUCD) is known to cause an inflammatory reaction of the endometrium [29]. However, postmenopausal women with an IUD are mostly asymptomatic[30-31].

2) Endometritis or active bleeding is rarely seen during hysteroscopy for PMB.

Endometritis is a condition that can be diagnosed on hysteroscopy (characterized by the visualization of edema, hyperemia, inflammation and exudate formation).[32-33]. Multiple studies were published on hysteroscopy in PMB, but endometritis is rarely present visually or histologically.

3) AE is a common pathological finding in PMB, but it is rarely seen with endometritis [7, 11, 12, 19, 20, 33, 34].

Meyer et al' [20], who studied AE in PMB, specifically stated "No atrophic endometritis was noted" in any histological specimens. In our recent study of women 50 years and older (75% had PMB) [34], there was only

one case of endometritis out of 560 biopsies. It will be fair to ask: How come we diagnose AE so frequently, but we fail to see the endometritis, which is the "etiology" for the bleeding. Finally, in the Blaustein's classical pathology text, AE is not considered as a cause of endometrits[8].

4) The incidence of PMB actually decreases with increasing age.

As a woman ages, the residual function of the ovary and the estrogen milieu is decreasing. We would expect the endometrium to become more and more atrophic as she gets older. If AE is really a cause of PMB, we would expect to see an increase in the incidence of PMB as women get older. However, the literature conclusively shows that the incidence of PMB decreases with increasing age [(35-37)].

5) AE is ubiquitous in postmenopausal women, still over 90% of these women will not have PMB.

There are about half a billion postmenopausal women worldwide[(38)]. All those postmenopausal women are estrogen deprived and harbor AE, but they rarely have PMB. Importantly, in the 10% of women who do have PMB, we often find pathology to explain it.

6) Pathological studies show that AE is actually associated with amenorrhea and not with bleeding.

Magos [(39)] studied different regimens of hormonal replacement therapy. Absolute amenorrhea of the women was always associated with AE on histological examination.

7) Focal endometrial lesions are a common cause of PMB.

Endometrial pathology can be diffuse or focal. "Blind" endometrial biopsies or dilatation and curettage are notorious for missing many focal lesions such as polyps [(40-41)]. When the aspiration catheter is blindly sampling the endometrium, we might miss the focal cavitary lesions and sample the AE which covers the entire endometrial cavity (illustrated in Figure 1 and Video S1). When we perform an endometrial aspiration, and get a pathology report of "normal endocervical tissue" - we interpret the result as failure to sample the endometrial cavity. We do not attribute the endocervical tissue to be the cause of the PMB. We believe that we should use the same logic when we get a histological report of AE.

In our opinion, the above data support our assumption that AE is not a cause of PMB. Defining AE as a cause of PMB may be potentially harmful for the following reasons:

1) Accepting the AE result might give false reassurance to the patient and her provider, while missing the real cause for the bleeding, such as a polyp [(40-41, 43]

2) The stakes are much higher in cases of the mis-diagnosis of cancer which starts as a focal lesions surrounded by AE[(42)]. Type 2 endometrial carcinoma is not related to unopposed estrogenic stimulation and often arises in AE[(42)]. Uterine sarcoma is another cancer which is often missed on endometrial biopsy and is likely to show AE [(44)].

3) The notion that AE is the cause of PMB has allowed some health care providers to "treat" the AE with estrogens. The concept of treating AE is present in textbooks and guidelines for physicians and patients[(45-49)]. We could not find any study that examined the safety or outcome of this management.

We suggest the following as explanations for the high prevalence of AE in PMB:

1) Missed focal lesions cause PMB more often than previously known. With the development of newer diagnostic technologies, the recent literature suggests that the incidence of missed focal lesions is higher than previously reported: Nan Hanegem et al' assessed 98 women who underwent hysteroscopy and found that 59.3% had an endometrial polyp. 51% identified in the initial workup and additional 8.3% were found during follow up evaluation [(43)].

2) The source of the PMB might not be uterine. Rectal, vulvo-vaginal and urological bleeding might be misinterpreted by the elderly woman as PMB.

3) A surge of estrogen followed by a withdrawal bleeding. The presence of estrogen activity in the endometrium of older woman has been documented by us and others [7, 34].

To avoid the misdiagnosis of cancer in cases of PMB with AE histology, we propose a simple management: Evaluate the endometrium with transvaginal sonogram. If the endometrial echo is thin, it is very unlikely to miss any significant pathology. However, if endometrial thickening is found (as seen in image 1), AE is unlikely to be the diagnosis and further workup is needed. This simple management may avoid unnecessary invasive procedures with their associated morbidity, cost and discomfort.

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Contribution to authorship

Ohad D. Rotenberg MD - Development of the concept idea, writing, literature research.

Gary L. Goldberg, MD - Guidelines of clinical perspective, editing.

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References

1) Astrup K, Olivarius NDF. Frequency of spontaneously occurring postmenopausal bleeding in the general population. Acta ObstetGynaecolScand2004;83:203–7.

2) Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. J ObstetGynaecol 2004; 24:736.

3) The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. ACOG Committee Opinion No. 734. American College of Obstetricians and Gynecologists. ObstetGynecol May 2018 - Volume 131 - Issue 5 - p e124–e129.

4) Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, et al. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound-Sponsored Consensus Conference statement. J Ultrasound Med 2001;20:1025–36.

5) Smith-Bindman R1, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, Brand R, Grady D. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities JAMA. 1998 Nov 4;280(17):1510-7.

6) Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. Br J ObstetGynaecol 1995 Feb;102(2):133-6.

7) Van den Bosch T, Ameye L, Van Schoubroeck D, et al. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts Views Vis Obgyn 2015; 7:17.

8) Robert J. Kurman, Lora Hedrick Ellenson and Brigitte M. Ronnett (Eds.) Blaustein's Pathology of the Female Genital Tract Sixth Edition 2011 page 382.

9) Buckley C.H. and Fox H. (2002). The normal endometrium, as seen in biopsy material. In: Biopsy pathology of the endometrium. Second edition. Buckley C.H. and Fox H. (eds). Arnold. London. pp 27-42. ey CH, Fox H, eds. Biopsy pathology of the endometrium. 2nd ed. London: Arnold, 20.

10) Te Linde, R. W. (1940) Causes of postmenopausal bleeding. The American Journal of Surgery, 48, 289.

11) Novak, Edmund B Postmenopausal bleeding. June 1964 - Volume 7 - Issue 2 - ppg 464-475.

12) Dreisler E1, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol. 2009 Jan;33(1):102-8.

13) Katherine M. Flegal, PhD1; Deanna Kruszon-Moran, MS1; Margaret D. Carroll, MSPH1; Cheryl D. Fryar, MSPH1; Cynthia L. Ogden, PhD1 Trends in Obesity Among Adults in the United States, 2005 to 2014 JAMA. 2016;315(21):2284-2291.

14) Laura Marczak, PhD; Kevin O'Rourke, MFA; Dawn Shepard, BA When and Why People Die in the United States, 1990-2013 JAMA. 2016; 315(3):241.

15) Frank P. Paloucek, MD; John B. Graham, MD; Clyde L. Randall, MD Benign Postmenopausal Vaginal Bleeding JAMA. 1967;199(10):701-703.

16) Schumamm E, Hyatt R Postmenopausal vaginal bleeding. Obstetrical & Gynecological Survey: August 1952 - Volume 7 - Issue 4 - ppg 544-546.

17) Kanter AE, Klawand AH. Postmenopausal bleeding. Urg Clin North Am. 1950 Feb;30(1):287-97.

18) Brzezinsky A, Bromberg YM Significance of postmenopausal genital bleeding in Jewish women. Obstet Gynecol. 1953 Mar;1(3):359-63.

19) Evans TN. Postmenopausal bleeding. Clin Obstet Gynecol. 1958 Sep;1(3):809-18.

20) Meyer WC, Malkasian GD, Dockerty MB, Decker DG. Postmenopausal bleeding from atrophic endometrium. Obstet Gynecol. 1971 Nov;38(5):731-8.

21) Rahn DD1, Carberry C, Sanses TV, Mamik MM, Ward RM, Meriwether KV, Olivera CK, Abed H, Balk EM, Murphy M. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014 Dec;124(6):1147-56.

22) Ferenczy Pathophysiology of endometrial bleeding Maturitas 2003 May 30;45(1):1-14.

23) Berek & Novak's gynecology (14th ed. Berek, Jonathan S. Lippincott Williams & Wilkins, 2007. page 1349. Table 33.3: Causes of Postmenopausal Bleeding.

24) http://www.uptodate.com/contents/postmenopausal-uterine-bleeding#H19.

25) http://www.aafp.org/afp/1999/1001/p1371.

26) http://www.webmd.com/menopause/guide/postmenopausal-bleeding.

27) Jeffrey B. Halter, Joseph G. Ouslander et al' Hazzard's Geriatric Medicine and Gerontology, 7e Gynecologic Disorders Table 42-4: Differential diagnosis of vaginal bleeding in older women.

28) https://www.health.harvard.edu/womens-health/abnormal-uterine-bleeding-in-peri-and-postmenopausal-womenPublished: January, 2011.

29) Ortiz ME1, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception. 2007 Jun;75(6 Suppl):S16-30. Epub 2007 Mar 29.

30) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 121: Long-acting reversible contraception: Implants and intrauterine devices. Obstet Gynecol. 2011 Jul;118(1):184-96.

31) Maruti Sinha, 1 Rekha Rani,2 Ridhima Gupta,3 Kishan Chand,4 and Gurcharan Kaur5 Lippes Loop Inserted 45 Years Back: The Dilemma to Remove It or Leave It in situ. A Case Report with Review of Literature Clin Diagn Res. 2015 Apr; 9(430).

32) Cicinelli E, De Ziegler D, Nicoletti R, Colafiglio G, Saliani N, Resta L, Rizzi D, De Vito D. Chronic endometritis: correlation among hysteroscopic, histologic, and bacteriologic findings in a prospective trial with 2190 consecutive office hysteroscopies. Fertil Steril 2008;89:677 – 684.

33) Garuti G1, Sambruni I, Colonnelli M, Luerti M. Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women. J Am Assoc GynecolLaparosc. 2001 May;8(2):207-13.

34) Ohad Rotenberg, MD, Malte Renz, MD, PhD, Laura Reimers, MPH, Georgios Doulaveris, MD, Juliana Gebb, MD, Gary L. Goldberg, MD, and Pe'er Dar, MD . Simultaneous endometrial aspiration and sonohysterography for the evaluation of endometrial pathology in women aged 50 years and older. ObstetGynecol 2015 Feb; 125:414.

35) Astrup K1, OlivariusNde F, Møller S, Gottschau A, Karlslund W. Menstrual bleeding patterns in pre- and perimenopausal women: a population-based prospective diary study. Acta ObstetGynecol Scand. 2004 Feb;83(2):197-202.

36) Astrup K1, OlivariusNde F. Frequency of spontaneously occurring postmenopausal bleeding in the general population. Acta ObstetGynecol Scand. 2004 Feb;83(2):203-7.

37) Burbos N1, Musonda P, Giarenis I, Shiner AM, Giamougiannis P, Morris E, Nieto JJ Age related differential diagnosis of vaginal bleeding in postmenopausal women: a series of 3047symptomatic postmenopausal women. Menopause Int. 2010 Mar;16(1):5-8.

38) JoAnn E. Manson, MD, DrPH Overview on menopause. Chapter 1 page 4. http://www.menopause.org/docs/2012/cg_a.pdf Chapter 1 page 4.

39) Magos AL, Brincat M, Studd JW, Wardle P, Schlesinger P, O'Dowd T. Amenorrhea and endometrial atrophy with continuous oral estrogen and progestogen therapy in postmenopausal women. Obstet Gynecol. 1985 Apr;65(4):496-9.

40) Epstein E1, Ramirez A, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. Acta ObstetGynecol Scand. 2001 Dec;80(12):1131-6.

41) Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, Dordoni D. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding. An Italian multicenter study. Ultrasound ObstetGynecol1996;7:315–21.

42) Geels YP1, Pijnenborg JM, van den Berg-van Erp SH, Bulten J, Visscher DW, Dowdy SC, Massuger LF. Endometrioid endometrial carcinoma with atrophic endometrium and poor prognosis. Obstet Gynecol. 2012 Nov;120(5):1124-31.

43) N. van Hanegem, M.C. Breijer, S.A. Slockers, M.H. Zafarmand, P.M.A.J. Geomini, R. Catshoek, J.M.A. Pijnenborg, L.F. van der Voet, F.P.H.L.J. Dijkhuizen, G.C.R. van Hoecke, N. Reesink-Peters, S. Veersema, M.H.A. van Hooff, P.J.M. van Kesteren, J.A. Huirne, B.C. Opmeer, M.Y. Bongers, B.W.J. Mol, A. TimmermansDiagnostic workup for postmenopausal bleeding: a randomised controlled trial. BJOG. 2017 Jan;124(2):231-240. doi: 10.1111/1471-0528.14126. Epub 2016 May 26.

44) Bansal N1, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas Gynecol Oncol. 2008 Jul;110(1):43-8.

45) Obstetrics and Gynaecology: an evidence-based guide 2nd Edition Chapter 19 page 257.

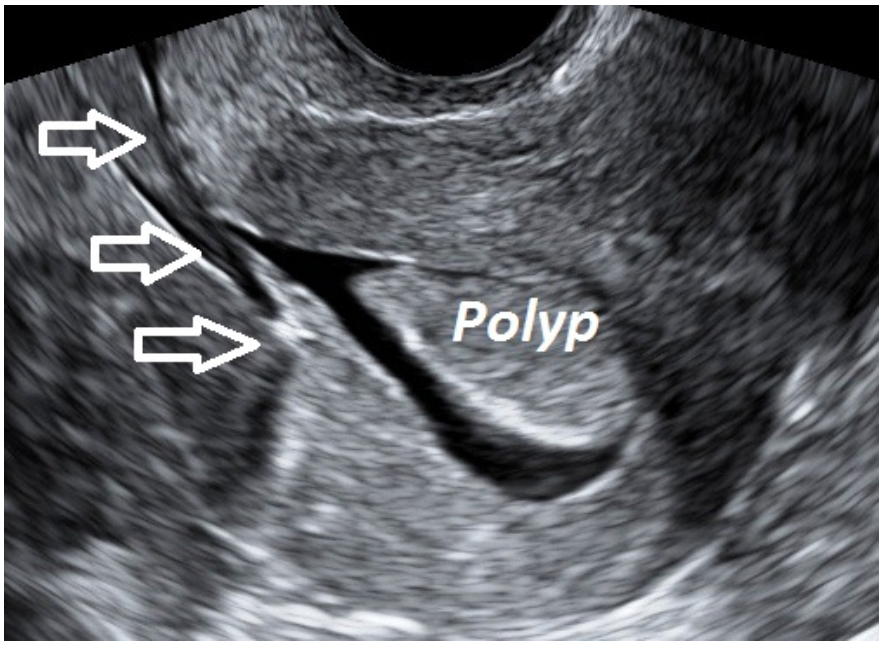
46) ACOG: Frequently asked questions. Perimenopausal bleeding and bleeding after Menopause. https://www.acog.org/~/media/For%20Patients/faq162.pdf. November 2018.

47) http://www.webmd.com/menopause/guide/postmenopausal-bleeding.

48) RACGP: The women with postmenopausal women bleeding. Reprinted from Australian Family Physician Vol. 36, No. 3, March 2007

49) Otify M, Fuller J, Ross J, Shaikh H, Johns J. Endometrial pathology in the postmenopausal woman – an evidence based approach to management. The Obstetrician & Gynaecologist 2015;17:29–38.

Figure 1-Depicts a reroverteduterus with a fundal endometrial polyp. The catheter tip (marked by arrows) is sampling the anterior endometrium and missing the polyp.



Video S1:Aretroverted uterus with endometrial polyp. The catheter tip is seen digging within the anterior endometrium missing the fundal polyp.