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Invited Editorial

Postmenopausal bleeding: Which endometrial thickness is safe in menopausal hormone therapy users?

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Postmenopausal bleeding and unscheduled bleeding in women using menopausal hormone therapy (MHT) leads to concerns in both patients and healthcare professionals. Vaginal bleeding may be the first warning of endometrial cancer and should lead to further evaluation without delay.

Ultrasonography has been demonstrated to be an excellent first-line investigation [1], and the measurement of endometrial thickness (ET) can be used for triage of women before more invasive procedures (e.g., blind endometrial biopsy or hysteroscopy). Endometrial atrophy is the histological finding in most cases of postmenopausal bleeding and a thin endometrium. The finding of a thin, well-defined endometrium is reassuring, with no need for biopsy.

The ideal cut-off for endometrial thickness for an invasive test is a trade-off between sensitivity and specificity. A low threshold for ET may lead to unnecessary procedures. However, raising the ET limit will lead to underdiagnosing of pathology. The ideal cut-off needs to have a high negative predictive value for endometrial cancer.

The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 734 on evaluation of postmenopausal bleeding states that 'an endometrial thickness of 4 mm or less has a greater than 99% negative predictive value for endometrial cancer' [2]. This threshold is widely recommended internationally.

However, in MHT users the ideal cut-off for invasive procedures has not been investigated thoroughly, and the evidence base for another endometrial thickness cut-off threshold is lacking.

Levine in 1995 described changes in endometrial thickness in postmenopausal MHT users [3]. The paper included a flowchart suggesting different cut-off levels of ET for intervention based on data for 62 asymptomatic women, using three different hormonal regimens. A conservative threshold of <8 mm was chosen as a guideline for ET that does not require follow-up in *asymptomatic* women. A threshold of 8 mm was also suggested by Mossa and co-workers. They found that a higher incidence of signs (abnormal bleeding or endometrial thickness $\geq$ 5 mm) did not coincide with a higher incidence of malignant pathology in MHT users. Furthermore, the authors stated that a cut-off of 8 mm should be used for hysteroscopy. The impact of symptomatic benign findings was not discussed [4].

The Smith-Bindman meta-analysis of 35 studies included 5892 women with vaginal bleeding. A threshold of 5 mm to define abnormal endometrial thickening identified 96% of women with endometrial cancer and 92% of women with endometrial disease, with false-positive rates of 39% and 19% respectively. There was no significant difference in the sensitivity between MHT users and non-users, but the proportion of false-positive results was 23% for MHT users compared with 8% in MHT non-users [5].

Changing the threshold to obtain greater specificity would lead to a decline in sensitivity and more cancers missed. As transvaginal ultrasound is an inexpensive and non-invasive modality, it is ideal for the initial evaluation of abnormal bleeding, while the more invasive office endometrial biopsy has a high false-negative rate in case of focal endometrial lesions.

A study by Omodei in 2000 demonstrated that there is no substantial difference in endometrial thickness in women taking sequential versus continuous combined MHT (mean 3.6 mm vs 3.2 mm), if the ET measurement is taken approximately on the fifth day following the last progestin pill [6]. In Omodei's study, 52 patients underwent hysteroscopic biopsies either due to (1) ET > 4 mm (n = 28; of these, 11 had unexpected bleeding) revealing no cases of endometrial cancer or atypia, or due to (2) unexpected bleeding and ET $\leq$ 4 mm (n = 24), all with endometrial atrophy on final histology. ET measured soon after withdrawal bleeding is the lowest during sequential therapy cycles. It is therefore the best time for measurement of ET to reduce false-positive findings.

Recent publications, unfortunately, refer to an 8 mm cut-off [7,8]. This is of concern in view of the paucity of evidence, especially relating to current MHT regimens which were not in use when the studies were undertaken.

Suggestions for another cut-off for ET in symptomatic MHT users should be evidence-based. However, the data are not available. Thus, with the currently available evidence, endometrial thickness criteria

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should be the same in both MHT users and non-users experiencing abnormal bleeding after the menopause.

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