Introduction

Postmenopausal bleeding (PMB) is the most common symptom of the endometrium. Cervical cancer must also not be forgotten, especially in women with a thin endometrium. Therefore, all women presenting with PMB should undergo evaluation with transvaginal ultrasound to estimate the risk of endometrial cancer, and speculum examination/cervical cytology to rule out cervical pathology. Management strategies using ultrasound as the primary investigation tool have been shown to be more cost effective than those using endometrial biopsy for the investigation of PMB. In women with PMB, the primary aim is to estimate the risk of endometrial cancer, since women at low risk of cancer can be managed expectantly, whereas women at high risk must undergo endometrial biopsy.

The secondary goal is to rule out the presence of focal lesions since this is of major importance to determine the most appropriate biopsy procedure. Finally, in women with an established diagnosis of endometrial cancer ultrasound can be used to assess the extension of the tumour. The focus of this short opinion piece is to discuss the clinical role of both established and novel ultrasound techniques in the assessment of women with PMB.

Established techniques

Measurement of the endometrial thickness (ET) has so far been the most simple and accurate ultrasound technique to estimate the risk of endometrial cancer, and speculum examination/cervical cytology to rule out cervical pathology. There is solid scientific evidence that transvaginal ultrasound (TVS) examination can reliably distinguish women who are at low risk (ET < 5 mm) from those who are at high risk of endometrial pathology (ET \(\geq 5\) mm). The odds of endometrial cancer is reduced 10-fold after a negative scan, that is if the ET measures < 5 mm. The 5 mm cut-off can be used in all women irrespective of HRT use. A simplified version of the guidelines suggested by the reference group of Ultrasound in Obstetrics and Gynaecology in Sweden is presented in Fig. 1.'
It is justifiable to refrain from endometrial sampling in women with PMB and an ET < 5 mm, because the risk of endometrial cancer in these women is very low (0.1–1.0%)⁴. In women with PMB and a thin endometrium, we must not forget to rule out cervical pathology such as cervical cancer as this is twice as common as endometrial cancer in these women⁶. During long term follow-up women with PMB and a thin ET (< 5 mm) at the initial TVS have a persistently increased risk of cervical pathology⁶, whereas the risk of endometrial pathology is the same as for women with no bleeding⁷. In women with repeated bleeding there is an increased risk of both cervical and endometrial pathology⁸,⁹, indicating that there is a need for both endometrial and cervical sampling.

Women with an ET ≥ 5 mm have a high risk of endometrial pathology and should therefore undergo endometrial biopsy. A large proportion of these women have focally growing pathological lesions in the uterine cavity⁹. Dilatation and curettage (DC) will fail to diagnose and remove half of the benign and 10% of the malignant focally growing lesions¹⁰–¹². Therefore, women with focal lesions should undergo operative hysteroscopy, whereas simple endometrial biopsy devices can be used in women without focal lesions. In women with a strong suspicion of malignancy, endometrial biopsy should be performed at the time of TVS examination so that women with confirmed cancer can proceed rapidly to hysterectomy.

Saline infusion sonography (SIS) can quickly and accurately¹³–¹⁷ detect focal lesions and can therefore help to choose the most appropriate biopsy procedure. The sensitivity of SIS for the detection of focal lesions is 93–100% and the specificity is 85–96%¹³–¹⁷. It is better tolerated, less painful and cheaper than diagnostic hysteroscopy¹⁶,¹⁸,¹⁹. In women with unmeasurable or ill defined endometrium, one should not draw the conclusion that the endometrium is thin. According to our own unpublished data, 5% of these women have cancer (Epstein, unpublished). The use of SIS is helpful in this situation as it will help us to see the true appearance of the endometrium and the endometrial cavity.

**Novel techniques for risk-estimation of endometrial malignancy in women with PMB**

We know that all women with an ET ≥ 5 mm are at an increased risk of cancer. It also is important among these women to quantify the risk, since this will enable us to potentially refrain from invasive procedures in women at high risk of surgery. In addition, it makes it possible to optimise the timing and the type of surgery and we can ask for prompt histological evaluation in those deemed to be high-risk cases.

It is often difficult to differentiate between benign and malignant endometrium based on endometrial grayscale morphology assessment especially in women with an ET < 15 mm²⁰. There are, however, several studies showing that endometrial morphology assessment can be useful in the prediction of endometrial cancer²⁰–²⁵. Endometrial echogenicity and border in combination with ET has been shown to be a better predictor of endometrial cancer than ET measurement alone²⁰–²². The best predictor of cancer at SIS is the finding of an irregular surface focal lesion (sensitivity 89% specificity 67%), Fig. 2. Assessment of vascular morphology of endometrial vessels can also be used to estimate the risk of endometrial cancer²⁰–²³. The presence of multiple vessels has a sensitivity of around 80% for the detection of cancer at a specificity of 54–100%, Fig. 3²¹. Irregular vascular branching and areas of densely packed vessels might also be useful in the prediction of malignancy since these phenomena are very uncommon in benign cases²¹.

Vascular indices of areas or volumes make it possible to objectively quantify power Doppler signals. 2D vascularity index (VI) has been reported to be useful in the risk estimation of cancer in women with PMB²⁶. In a selected study population comprising 84 women with known hyperplasia or endometrial cancer, 3D power Doppler vascular indices was found to be significantly higher in malignant than in benign lesions. In addition, the VI was significantly higher in > Stage I endometrial tumours²⁶. More studies are needed to determine the clinical value of power Doppler indices for the prediction of endometrial cancer.

It is still uncertain if endometrial 3D volume measurements have an advantage over ET measurements, for the prediction of endometrial cancer, since studies have shown conflicting results²⁷–²⁹. Volume measurements clearly need to be superior to thickness measurements to have a clinical role since volume measurements are more complicated and require sophisticated equipment. With the present knowledge...
there seems to be no reason to abandon ET measurements.

Can mathematical models improve the risk assessment? We found that a logistic regression model comprising ET, VI and a woman’s history of hormone therapy use had an area under the curve (AUC) of 0.88 for the prediction of endometrial cancer\(^2\). Oposkine and co-workers show a slightly better AUC of 0.91 using a logistic regression model comprising only ET and endometrial morphology\(^2\). Adding Doppler variables did not significantly improve their model’s performance. The clinical value of mathematical models needs to be further evaluated in prospective multi-centre studies.

What about reproducibility of ET measurement as compared to endometrial morphology assessment? The inter-observer agreement between two experienced examiners was excellent for ET measurement in our own study with a Kappa value of 0.89. Oposkine and co-workers found that the inter-observer agreement between two experienced examiner for endometrial morphology assessment was generally moderate to good, with a kappa value of 0.49–0.78\(^3\). Assessment of vascular morphology showed a similar reproducibility as previously reported for endometrial thickness measurement\(^4\).

Novel techniques for the evaluation of the endometrial cavity in women with PMBAs mentioned previously, the secondary goal in the assessment of PMB is to rule out focal lesions. The established ultrasound technique for the assessment of the endometrial cavity is SIS.

Timmerman and co-workers showed that “feeding vessels” are predictive of polyps and focally growing lesions, Fig. 4\(^1\). The question is can this method replace SIS? The feeding vessel has been reported to have an excellent accuracy for the prediction of polyps\(^5,10\). The method however seems to be less good for the over all prediction of focally growing lesions. In our own unpublished material comprising 224 women with PMB, we found a high detection rate (90%), but a lower specificity (48%) indicating that the absence of a feeding vessel will not exclude a focal lesion (Epstein, unpublished). One should be aware that top of the line Doppler equipment is needed for adequate assessment of endometrial vascularity.

Summary

TVS can accurately discriminate women at high or low risk of endometrial cancer using a cut-off 5 mm. Women with an ET <5 mm can be managed expectantly but do not forget to rule out cervical cancer. SIS should be performed in all women with PMB with an ET ≥ 5 mm to rule out focal lesions. All women with focal lesions should undergo operative hysteroscopy, since these lesions will not be adequately removed or diagnosed with blind sampling procedures. One should suspect endometrial cancer in lesions with multiple vessels, irregular echogenicity, or an irregular surface at SIS.

**References**

1. Medverd JR, Dubinsky TJ. Cost analysis model: US versus endometrial biopsy in evaluation of peri- and postmenopausal abnormal vaginal bleeding. *Radiology* 2002; 222 (3): 619–27.
2. 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 (10): 1025–36.
3. 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 (9): 799–816.
4. Smith Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities [see comments]. *JAMA* 1998; 280 (17): 1510–7.
5. Epstein E. Management of postmenopausal bleeding in Sweden: a need for increased use of hydrosonography and hysteroscopy. *Acta Obstet Gynecol Scand* 2004; 83 (1): 89–95.
6. Epstein E, Jamei B, Lindqvist PG. High risk of cervical pathology among women with postmenopausal bleeding and endometrium ≤ 4.4 mm: long-term follow-up results. *Acta Obstet Gynecol Scand* 2006; 85 (11): 1368–74.
7. 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 predictors of endometrial cancer. *Am J Obstet Gynecol* 2003; 188 (2): 401–8.
8. Van Doorn HC, Timmermans A, Opmeer BC, Kruitwagen RF, Dijkstraen FP, Kooi GS, 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 (1): 89–3.
9. Epstein E, 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 Obstet Gynecol Scand* 2001; 80 (12): 1131–6.
10. Gebauer G, Hafner A, Siebzehnrubl E, Lang N. Role of hysteroscopy in detection and extraction of endometrial polyps: results of a prospective study. *Am J Obstet Gynecol* 2001; 184 (2): 59–63.
11. Goldfarh HA. D&C results improved by hysteroscopy. *N J Med* 1989; 86 (4): 277–9.
12. Stovall TG, Solomon SK, Ling FW. Endometrial sampling prior to hysterectomy. *Obstet Gynecol* 1989; 73 (3 Pt 1): 405–9.
13. Bernard JP, Lecuru F, Darles C, Robin F, de Bievre P, Taurelle R. Saline contrast sonohysterography as first-line investigation for...
women with uterine bleeding. *Ultras Obstet Gynecol* 1997; 10 (2): 121–5.

14 Epstein E, Ramirez A, Skoog L, Valentin L. Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with postmenopausal bleeding and endometrium > 5 mm. *Ultras Obstet Gynecol* 2001; 18 (2): 157–62.

15 Kamel HS, Darwish AM, Mohamed SA. Comparison of transvaginal ultrasonography and vaginal sonohysterography in the detection of endometrial polyps. *Acta Obstet Gynecol Scand* 2000; 79 (1): 60–4.

16 Widrich T, Bradley LD, Mitchinson AR, Collins RL. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. *Am J Obstet Gynecol* 1996; 174 (4): 1327–34.

17 Williams CD, Marshburn PB. A prospective study of transvaginal hydrosonography in the evaluation of abnormal uterine bleeding. *Am J Obstet Gynecol* 1998; 179 (2): 292–8.

18 Rogerson L, Bates J, Weston M, Duffy S. A comparison of outpatient hysteroscopy with saline infusion hysterosonography. *Br J Obstet Gynecol* 2002; 109: 800–4.

19 Timmerman D, Deprest J, Bourne T, Van den Berghe I, Collins WP, Vergote I. A randomized trial on the use of ultrasonography or office hysteroscopy for endometrial assessment in postmenopausal patients with breast cancer who were treated with tamoxifen. *Am J Obstet Gynecol* 1998; 179 (1): 62–70.

20 Epstein E, Valentin L. Gray-scale ultrasound morphology in the presence or absence of intrauterine fluid and vascularity as assessed by color Doppler for discrimination between benign and malignant endometrium in women with postmenopausal bleeding. *Ultrasound Obstet Gynecol* 2006; 28 (1): 89–95.

21 Opolskiene G, Sladkevicius P, Valentin L. Ultrasound assessment of endometrial morphology and vascularity to predict endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm. *Ultrasound Obstet Gynecol* 2007; 30 (3): 332–40.

22 Randelzhofer B, Prompeler HJ, Sauerbrei W, Madjar H, Emons G. Value of sonomorphological criteria of the endometrium in women with postmenopausal bleeding: a multivariate analysis. *Ultrasound Obstet Gynecol* 2002; 19 (1): 62–8.

23 Sheikh M, Sawhney S, Khurana A, Al-Yatama M. Alteration of sonographic texture of the endometrium in post-menopausal bleeding. A guide to further management. *Acta Obstet Gynecol Scand* 2000; 79 (1): 1006–10.

24 Alcazar JL, Castillo G, Minguiz JA, Galan MJ. Endometrial blood flow mapping using transvaginal power Doppler sonography in women with postmenopausal bleeding and thickened endometrium. *Ultrasound Obstet Gynecol* 2003; 21 (6): 583–8.

25 Epstein E, Skoog L, Isberg PE, De Smet F, De Moor B, Olofsson PA, *et al.* An algorithm including results of gray-scale and power Doppler ultrasound examination to predict endometrial malignancy in women with postmenopausal bleeding. *Ultrasound Obstet Gynecol* 2002; 20 (4): 370–6.

26 Merce LT, Alcazar JL, Lopez C, Iglesias E, Bau S, Alvarez de los Heros J, *et al.* Clinical usefulness of 3-dimensional sonography and power Doppler angiography for diagnosis of endometrial carcinoma. *J Ultrasound Med* 2007; 26 (10): 1279–87.

27 Gruboeck K, Jurkovic D, Lawton F, Savvas M, Tailor A, Campbell S. The diagnostic value of endometrial thickness and volume measurements by three-dimensional ultrasound in patients with postmenopausal bleeding. *Ultrasound Obstet Gynecol* 1996; 8 (4): 272–6.

28 Odeh M, Vainerovsky I, Grinin V, Kais M, Ophir E, Bornstein J. Three-dimensional endometrial volume and 3-dimensional power Doppler analysis in predicting endometrial carcinoma and hyperplasia. *Gynecol Oncol* 2007; 106 (2): 348–53.

29 Yaman C, Habelsberger A, Tews G, Polz W, Ebner T. The role of three-dimensional volume measurement in diagnosing endometrial cancer in patients with postmenopausal bleeding, *Gynecol Oncol* 2006; 110 (3): 390–5.

30 Epstein E, Valentin L. Intraobserver and interobserver reproducibility of ultrasound measurements of endometrial thickness in postmenopausal women. *Ultrasound Obstet Gynecol* 2002; 20 (5): 486–91.

31 Timmerman D, Verguts J, Konstantinovic ML, Moerman P, Van Schoubroeck D, Deprest J, *et al.* The pedicle artery sign based on sonography with color Doppler imaging can replace second-stage tests in women with abnormal vaginal bleeding. *Ultrasound Obstet Gynecol* 2003; 22 (2): 166–71.

32 Alcazar JL, Galan MJ, Minguiz JA, Garcia-Manero M. Transvaginal color Doppler sonography versus sonohysterography in the diagnosis of endometrial polyps. *J Ultrasound Med* 2004; 23 (6): 743–8.