Chelsea and Westminster Hospital NHS
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All women with abnormal bleeding on HRT should have a hysteroscopy and biopsy- the case FOR it!

National Association for Premenstrual Syndromes (NAPS) Study Day on Women's Health

Friday 17th November 2023

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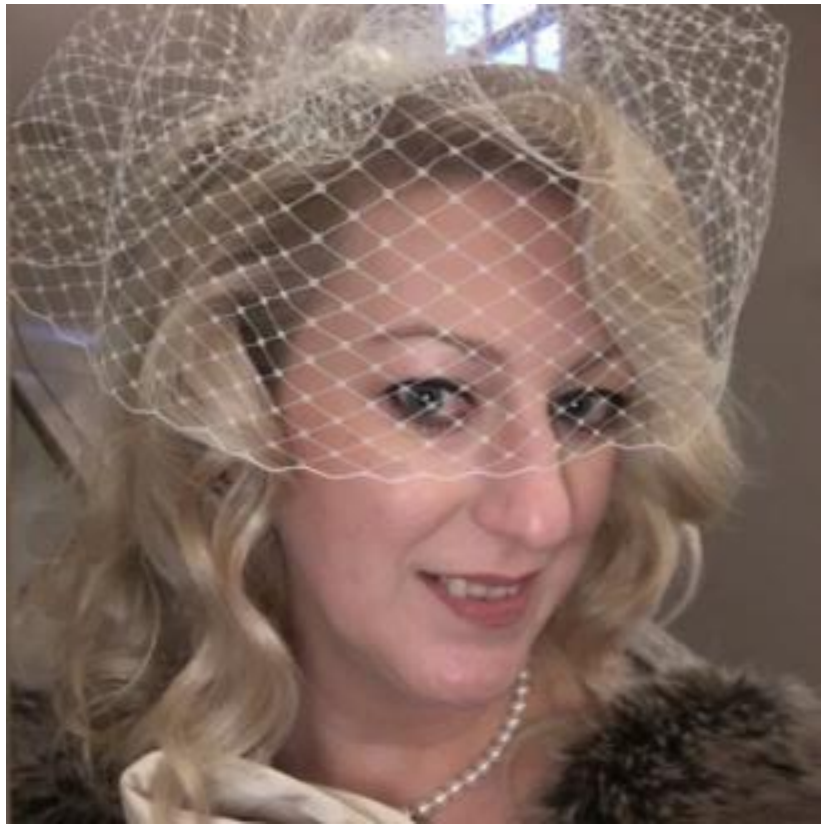
Declarations

NONE



Expert panel

NICK PANAY
BSC MRCOG MFSRH
NAPS CHAIRMAN

MS A. P. HAWKINS
BSC MROCG DFSRH
NAPS TRUSTEE

MS C. L. DOMONEY
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DANI SINGER
PSYCHOTHERAPIST/COUNSELLOR; MBACP [SNR ACCRED]/UKCP REG
Expert panel

AMANDA MOORE
BSC (HONS), MSC NUTRITION, UKVRN

MICHAEL CRAIG
MB BS PHD FRCOG FRCPSYCH
NAPS TRUSTEE

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Emotional and practical support with specialist information from experts

THE DEBATE ‘FOR’!

POINT 1
Surely, we need to prove it's not cancer!

- No evidence that general **screening of asymptomatic** postmenopausal women by transvaginal ultrasound scanning (TVS) or **endometrial sampling** improves outcomes from endometrial cancer (EC)[1] .

- **Endometrial sampling** is indicated for **symptomatic** postmenopausal women with a thickened endometrium on TVS[2,3] .

- The probability of EC with postmenopausal bleeding (PMB) is 5-10%[4,5] .

- Age-related risk; EC diagnosis in 2015-17 was 50% in women > 70 years old but 6.5% of uterine cancers in the UK were diagnosed in <50 years[3] . **Symptomatic women**: PMB, persistent intermenstrual/ irregular bleeding or infrequent heavy bleeding and RF: obesity, PCOS, etc.

1. Dijkhuis BC, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2012;40(6):621-9.
2. van Hanegem N, et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2016;197:147-55.
3. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice (2021)
4. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018;178(9):1210-22
5. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. Br J Obstet Gynaecol. 1995;102(2):133-6

POINT 1

Surely, we need to prove it's not cancer!

- Hysteroscopy should be recommended for all pre-menopausal patient at high risk of EC with TVUS abnormalities in whom **outpatient biopsy has failed or was non-diagnostic[1] .**

- Do not offer 'blind' endometrial biopsy to women with Heavy Menstrual Bleeding (HMB). **Obtain an endometrial sample only in the context of diagnostic hysteroscopy in pre- and perimenopausal women[2] .**

- **"Women who decline hysteroscopy, then consider pelvic ultrasound but detecting uterine cavity causes for HMB is limited"[1] .**

1. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice (2021)
2. National Institute for Health and Care Excellence. NICE guidelines (NG88) Heavy menstrual bleeding: assessment and management; 14 March 2018; https://www.nice.org.uk/guidance/ng88. 2018.

POINT 1

Surely, we need to prove it's not cancer!

- **Transvaginal ultrasound (TVS)** with double thickness measurement of endometrium (ET) should be employed as **initial screening investigation** for women presenting with **PMB**[1] .

- TVS can reliably exclude women with **PMB who do not require endometrial biopsies: ET of < 4 mm** (high negative predictive value >99%)[2] . Sensitivities of 98%, 95% and 90% at cut-off levels of 3 mm, 4 mm and 5 mm of ET respectively to exclude EC[3] .

- **Accuracy of TVS is lower in black women**[1] **:** ?fibroids or more non-endometrioid cancers, compared to white women.

- Surveillance, Epidemiology and End Results (SEER) data: sensitivity of 47.5% (95% CI 46.0 to 49%) using a cut off of ≥4 mm in black women, compared to a sensitivity of 87.9% (95% CI 87.6 to 88.3%) in white women[4] .

- **PMB/ unscheduled bleeding on HRT should have an endometrial biopsy, if ET > 5mm**[1,5]

1. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice (2021)
2. Wong AS, et al. Reappraisal of endometrial thickness for the detection of endometrial cancer in postmenopausal bleeding: a retrospective cohort study. BJOG. 2016;123(3):439-46.
3. Timmermans A, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(1):160-7
4. Doll KM, et al. Estimated Performance of Transvaginal Ultrasonography for Evaluation of Postmenopausal Bleeding in a Simulated Cohort of Black and White Women in the US. JAMA oncology. 2021;7(8):1158-65.
5. Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998;280(17):1510-7.

Point 2
Early cancer detection saves lives

- **"In patients with PMB, not on HRT, a TVS endometrial thickness screening measurement of ≥ 4 mm, an outpatient endometrial biopsy should be carried out"[1] .**

- Pipelle® biopsy has a high diagnostic accuracy when an adequate specimen is obtained (positive likelihood ratio (LR) 66, post-test probability of endometrial cancer of 81.7% for a positive test and 0.9% for a negative test (LR 0.14).

- Endometrial biopsy is also accurate in excluding endometrial cancer, even if an insufficient sample is obtained, provided the sampling device was inserted more than 4 cm through the cervical canal[2] .

- However, **hysteroscopy is still needed** if <4cm sampling depth, persistent abnormal vaginal bleeding, despite a negative endometrial biopsy[1] or polyp found on histology.

1. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice (2021)
2. Clark TJ, et.al. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA. 2002;288(13):1610-21

Point 3
Addressing patient concerns and ensuring well-being

- "Women on HRT with unscheduled bleeding should have their HRT discontinued for six weeks"[1,2] ;

- Those with persistent bleeding should be referred to a rapid access gynaecology clinic, **without re-starting HRT** as "may interfere with TVS assessment"[1,2] ?4mm or 5mm ET

- **? QoL and anxiety: waiting up to 8wks for secondary care appointment and up to 10wks for diagnosis (if opted for GA hysteroscopy)**

- **Cut to the chase: get a diagnostic hysteroscopy and EBx! Allows visualization of abnormal areas and targeted biopsies/ excision- polyps/ fibroids. TVUS is not treatment**

- **Patient acceptability and diagnostic accuracy with outpatient hysteroscopy are comparable to hysteroscopy under anaesthesia[2]**

1. National Institute for Health and Care Excellence. NICE guidelines (NG12) Suspected cancer: recognition and referral. June 2015, update Sep 2020; Available at: https://www.nice.org.uk/guidance/ng12. 2020.
2. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations to Practice (2021)

Point 3

Addressing patient concerns and ensuring well-being

- Lynch syndrome (LS) autosomal dominant cancer predisposition condition and up to 1: 280 people with this gene have cancer (most are unaware)[1,2] .

- LS Carriers are at increased risk of early-onset colorectal, endometrial, ovarian and other cancers. Lifetime risk for endometrial cancer are 40-60% and justifies screening[3,4] .

- Use of ultrasound alone is debated among pre-menopausal women – often more investigations and eventual hysteroscopy & endometrial biopsy for final reassurance with red flag/ ongoing symptoms[5,6] .

Cut to the chase: get a diagnostic hysteroscopy and EBx! Allows visualization of abnormal areas and targeted biopsies/ excision- polyps/ fibroids. TVUS is not treatment

1. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? Cancer Prev Res (Phila). 2011;4(1):1-5.
2. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-12.
3. Dominguez-Valentin M, Sampson JR, Seppala TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25.
4. Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. JAMA oncology. 2017;3(12):1702-6.
5. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Correction to: Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther. 2018;35(4):590.
6. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther. 2018;35(4):577-89.

Point 4
Tailored treatment plans/ personalised lifelong care plans

- 3% of all endometrial cancers (EC) are due to Lynch syndrome (LS)[1,2]. Early diagnosis of EC enable universal LS screening- NICE-endorsed and cost-effective!

- Allows targeted testing of relatives (on average 3 more found), healthy carriers identified and offered: symptom education, family planning, bowel cancer screening and proactive risk-reducing surgery where requested[3].

- Fertility-sparing management is possible with all low-grade EC confined to the endometrium and close monitoring.

- Strict surveillance during treatment (high dose oral progestogens/ IUS) includes **endometrial biopsy and repeat imaging at 3 monthly intervals** to exclude disease progression[4] . **Could Hysteroscopy and biopsy will give greatest reassurance?**

1. Ryan NAJ, et al. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet Med. 2019;21(10):2167-80
2. National Institute for Health and Care Excellence. NICE Diagnostics Guidance [DG42]. Testing strategies for Lynch syndrome in people with endometrial cancer; 28 October 2020; https://www.nice.org.uk/guidance/dg42/resources/testing-strategies-for-lynch-syndrome-in-people-with-endometrial-cancer-pdf-10538078291892020 .
3. Crosbie EJ, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21(10):2390-400.

Point 5
Economic healthcare system benefits

- TVS followed by endometrial biopsy, if needed, is the most cost-effective strategy for the UK population in which the prevalence of endometrial carcinoma is lower than 15%[1] .

- An RCT has shown a prevalence rate of **6% premalignancy** in endometrial polyps diagnosed **by hysteroscopy** in PMB with **previous normal endometrial biopsy**[2] .

- "More studies required before routine recommendation of hysteroscopy for all PMB"[3] ….**is access preventing roll-out because TVUS is more widely performed (sonographers/ doctors)?**

- Greater accuracy using hysteroscopy to diagnose EC and hyperplasia with abnormal uterine bleeding (a systematic review of data on 26,346 women)[4] . A positive hysteroscopy result: increased probability of cancer to 71.8% from a pre-test probability of 3.9% and a negative hysteroscopy result reduced the probability of cancer to 0.6%.

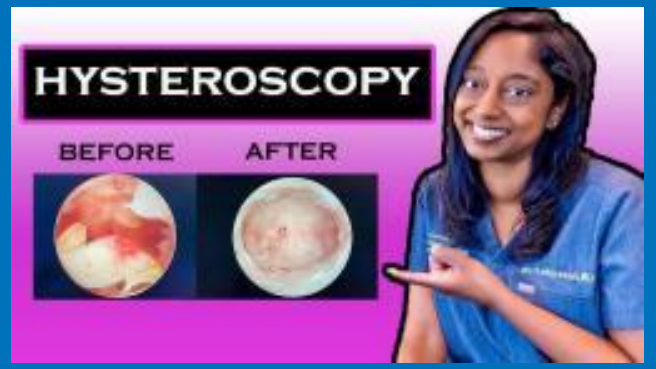
1. Dijkhuizen FP, et al. Cost-effectiveness of the use of transvaginal sonography in the evaluation of postmenopausal bleeding. Maturitas. 2003;45(4):273-82.
2. van Hanegem N, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. BJOG. 2017;124(2):231-40
3. British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice (2021)
4. Clark TJ, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG. 2002;109(3):313-21.

Conclusion

- Routine hysteroscopy and biopsy for all bleeding on HRT is a proactive and sensible
- It facilitates early cancer detection and prevention of complications, definitive earlier reassurance of cancer exclusion, personalized treatment plans, with potential long-term emotional and cost benefits to both patients and the NHS.
- Also, empowers women to take charge of their health and well-being.

Hysteroscopy is necessary for all women with abnormal bleeding on HRT

National Association for Premenstrual Syndromes (NAPS)
https://www.pms.org.uk/



THANK YOU