

Diagnosis of Endometrial Cancer in Women with Abnormal Vaginal Bleeding

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INTRODUCTION

Endometrial cancer is the most common gynaecological malignancy, with an annual incidence of 19.5 cases per 100,000 women in Canada in 1993. The age-standardized death rate is 3.6 per 100,000 women.¹ The median age at diagnosis is the sixth decade, although 20 to 25 percent of cases will be diagnosed premenopausally. There are multiple risk factors including obesity, nulliparity, anovulation and menopause.²

The diagnosis of endometrial cancer is usually made during the evaluation of abnormal vaginal bleeding. Because of this symptom, 75 percent of endometrial cancers are diagnosed at an early stage. Abnormal perimenopausal or post-menopausal bleeding is associated with endometrial cancer in approximately 10 percent of cases.³ Atypical endometrial hyperplasia (AEH) is felt to be a precursor of endometrial cancer, and may progress, over time, to endometrial cancer in five to 25 percent of patients. In addition, AEH is associated with a co-existing endometrial cancer in approximately 20 percent of patients.⁴

The use of combined estrogen and progesterone hormone replacement therapy (HRT) can reduce, although not eliminate, the risk of endometrial cancer in women taking HRT. Those patients reported in the literature who developed endometrial cancer while taking HRT had abnormal or unexpected vaginal bleeding as a presenting symptom.⁵⁻⁶

Diagnostic approaches to the assessment of abnormal uterine bleeding are divided into invasive and non-invasive methods. Invasive methods include:

1. dilatation and curettage (D&C);
2. endometrial biopsy;
3. hysteroscopy and directed biopsy.

Non-invasive methods include:

1. ultrasonography;
2. endometrial cytology. This is not felt to be useful in diagnosis due to low accuracy and will not be discussed further.

INVASIVE METHODS OF DIAGNOSIS

DILATATION AND CURETTAGE

Dilatation and fractional curettage (D&C) has traditionally been the standard for investigation of abnormal uterine bleeding. The diagnostic accuracy of D&C has not been well studied, but in one study 60 percent of patients had less than half the uterine cavity curetted and 16 percent had less than a quarter.⁷ A critical review of 33 reports of 13,598 D&Cs and 5,851 office biopsies showed that D&C had a higher complication rate than office biopsy but that the adequacy of the specimens was comparable.⁸

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ENDOMETRIAL BIOPSY

A variety of instruments has been developed over the last decade for use in the office as alternatives to the expense, risk and inconvenience of fractional D&C. The Pipelle (Unimar, Connecticut) and similar instruments, for example the Pipette (Milex Products Inc., Chicago), the Tis-U-Trap (Milex Products Inc., Chicago) and the Z-sampler (BMI Medical Systems, California) are commonly used in Canada. With the use of these devices, the sensitivity for detecting endometrial cancer ranges from 67 to 96 percent.⁹⁻¹¹ Adequate specimens were obtained in 87 to 96 percent of women in studies with large numbers of premenopausal patients.^{9,10} Inadequate specimens were obtained in 22 percent of patients who were post-menopausal.^{10,12} Severe pain occurred in 6.7 percent of patients.¹⁰ Samples were impossible to obtain in 1.5 percent due to cervical stenosis.¹³

A dilemma exists if there is a negative initial biopsy and the bleeding persists. One study followed 263 patients with a negative initial biopsy (either benign diagnosis or insufficient tissue). One-third (86 patients) underwent further sampling, presumably due to continued symptoms. Four (5%) were found to have a uterine malignancy in the ensuing two years and five (6%) had complex hyperplasia. The authors, therefore, recommended further evaluation in the form of repeat biopsy or transvaginal ultrasound in patients with persistent symptoms after a negative initial biopsy, due to the high risk (11%) of an existing lesion having been overlooked.¹²

HYSTEROSCOPY AND DIRECTED BIOPSY

Some advocate this method as the standard for the diagnosis of abnormal uterine bleeding. However, a recent study of 373 patients which retrospectively compared hysteroscopy and D&C, concluded that hysteroscopy did not improve upon the sensitivity of D&C in the detection of endometrial hyperplasia or carcinoma.¹⁴ However, hysteroscopy is known to be a superior method for the detection of endometrial polyps and submucosal myomas.¹⁵ Caution is advised in the indiscriminate use of hysteroscopy in patients suspected of having endometrial cancer, as there have been at least three case reports suggesting that retrograde dissemination of endometrial cancer during hysteroscopy may occur.¹⁶⁻¹⁸ A recent retrospective case-controlled study which followed for two years 27 patients with endometrial cancer who had had hysteroscopy prior to their definitive therapy, concluded that preceding diagnostic fluid hysteroscopy did not seem to increase the risk of early recurrence in patients with endometrial cancer confined to the uterus.¹⁹ The incidence of positive cytological findings in the study group (10%) was comparable to that reported in patients who had not had hysteroscopy.

NON-INVASIVE METHODS

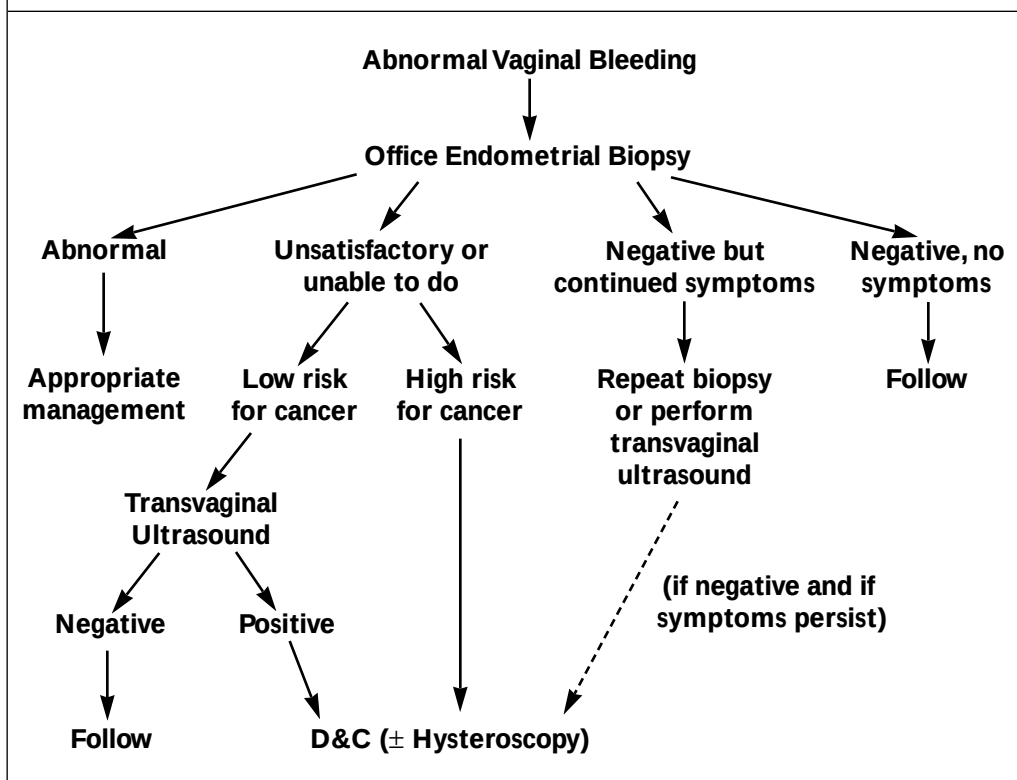
TRANSVAGINAL ULTRASOUND

Two large studies of 930 women²⁰ and 1,138 women²¹ reported experiences with transvaginal ultrasound in women with post-

menopausal bleeding. Both used a bi-endometrial (double layer) thickness of four millimetres as a cut-off point. The sensitivity was 96 to 98 percent and the specificity was 36 to 68 percent. The false positive rate was 44 to 56 percent. Thickness could not be measured in three to 4.7 percent but the reason for this was not stated. One of the studies reported two cancers in patients with a thickness less than 3.5mm, giving a false negative rate of two per 930 (0.2%).²⁰

The use of hormonal replacement therapy (HRT) does have the effect of increasing endometrial thickness but there are insufficient data, at present, to suggest a different cut-off of endometrial thickness for HRT users.²¹ Similarly, post-menopausal patients taking tamoxifen for breast cancer have a clearly

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increased endometrial thickness when compared to post-menopausal breast cancer patients not taking tamoxifen.²² Tamoxifen is known to induce changes in the endometrium which lead to polyps, hyperplasia and even carcinoma in some patients. The acceptability of transvaginal ultrasound in the older woman has not been extensively studied.

RECOMMENDATIONS

1. Office endometrial biopsy should be the initial diagnostic procedure of choice due to its convenience, accuracy, availability, safety and low cost **(Grade B)**.
2. If an office endometrial biopsy cannot be performed or the sample is insufficient, then patients should be triaged according to their risk for endometrial cancer. Those felt to be at low risk for endometrial cancer or in whom atrophy is suspected or who are medically unfit, should proceed to transvaginal ultrasound. Those at high risk (i.e. obese, nulliparous, post-menopausal, diabetic women, or those taking tamoxifen) should proceed to D&C, with or without hysteroscopy, as a negative ultrasound would not necessarily be completely reassuring and a positive ultrasound would require tissue sampling regardless **(Grade B)**.
3. There is no consensus in the literature as to what the cut-off value for normal endometrial thickness should be. It has been reported as anywhere from four mm to eight mm. Obviously, the lower the cut-off, the higher the sensitivity for detection of such abnormalities as endometrial cancer or its precursors, but at a cost of lower specificity **(Grade B)**.
4. Persistent bleeding after negative initial evaluation should not be ignored, and should be investigated further, as at least 10 per cent of patients will harbour disease **(Grade C)**.
5. Patients taking continuous combined HRT who experience vaginal bleeding after the first six months of therapy should be investigated with an endometrial biopsy, as should patients on sequential HRT who experience bleeding outside the expected time, i.e. after completing their progesterone **(Grade B)**.
6. Patients taking tamoxifen who experience vaginal bleeding should be investigated with endometrial biopsy **(Grade B)**.

Individual recommendations have been graded according to the level of evidence on which they are based:

Grade A: Randomized trials.

Grade B: Other robust experimental or observational studies.

Grade C: More limited evidence, but the advice relies on expert opinion and has the endorsement of respected authorities.

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REFERENCES

1. National Cancer Institute of Canada: Canadian Cancer Statistics 1998. Toronto, Canada 1998.
2. Feldman S, Cook EF, Harlow BL, Berkowitz RS. Predicting endometrial cancer among older women who present with abnormal vaginal bleeding. *Gynecol Oncol* 1995;56:376-81.
3. Creasman WT. Endometrial cancer: incidence, prognostic factors, diagnosis, and treatment. *Semin Oncol* 1997;24:140-50.
4. DiSaia PJ, Creasman WT. Endometrial Hyperplasia/Estrogen Therapy. In: *Clinical Gynecologic Oncology*. Baltimore: Mosby-Year Book, Inc. 1997;p111.
5. Stock RJ, Kanbour A. Prehysterectomy curettage. *Obstet Gynecol* 1975;45:537-41.
6. Gambrell RD. Strategies to reduce the incidence of endometrial cancer in postmenopausal women. *Am J Obstet Gynecol* 1997;177:1196-204.
7. Leather AT, Savvas M, Studd WW. Endometrial histology and bleeding patterns after 8 years of continuous combined estrogen and progesterone therapy in postmenopausal women. *Obstet Gynecol* 1991;78:1008-10.
8. Chambers JT, Chambers SK. Endometrial sampling: When? Where? Why? With what? *Clin Obstet Gynecol* 1992;35:28-39.
9. Guido RS, Kanbour-Shakir A, Rulin MC, Christopherson WA. Pipelle endometrial sampling: sensitivity in the detection of endometrial cancer. *J Reprod Med* 1995;40:553-5.
10. Stovall TG, Ling FW, Morgan PL. A prospective, randomized comparison of the Pipelle endometrial sampling device with the Novak curette. *Am J Obstet Gynecol* 1991;165:1287-90.
11. Ferry J, Farnsworth A, Webster M, Wren B. The efficacy of pipelle endometrial biopsy in detecting endometrial cancer. *Aust N Z J Obstet Gynaecol* 1993;33:76-8.
12. Feldman S, Chapter A, Welch W, Berkowitz RS. Two year follow-up of 263 patients with post/perimenopausal women vaginal bleeding and negative initial biopsy. *Gynecol Oncol* 1994;55:56-9.
13. Van den Bosch T, Vandendael A, Van Schoubroeck D, Wranz PAB, Lombard CJ. Combining vaginal ultrasonography and office endometrial sampling in the diagnosis of endometrial disease in postmenopausal women. *Obstet Gynecol* 1995;85:349-52.
14. Ben-Yehuda OM, Kim YB, Leuchter RS. Does hysteroscopy improve on the sensitivity of dilatation and curettage in the diagnosis of endometrial hyperplasia or carcinoma? *Gynecol Oncol* 1998;68:4-7.
15. Townsend DE, Fields G, McCausland A, Lauffman K. Diagnostic and operative hysteroscopy in the management of persistent postmenopausal bleeding. *Obstet Gynecol* 1993;82:419-24.
16. Romano S, Chimoni Y, Muralee D, Shalev E. Retrograde seeding of endometrial cancer during hysteroscopy. *Gynecol Oncol* 1992;44:116-8.
17. Schmitz MJ, Nahas WA. Hysteroscopy may transport malignant cells into the peritoneal cavity. *Eur J Gynaecol Oncol* 1994;15:121-4.
18. Egarter C, Krestan C, Kurz C. Abdominal dissemination of malignant cells with hysteroscopy. *Gynecol Oncol* 1996;63:143-4.
19. Gucer F, Tamussino K, Moser F, Arian G, Winter R. Two-year follow-up of patients with endometrial carcinoma after preoperative fluid hysteroscopy. *Int J Gynecol Cancer* 1998;8:476-80.
20. 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. *Ultrasound Obstet Gynecol* 1996;7:315-21.
21. Karlsson B, Granberg S, Wikland M, Ylostalo P, Torvid K, Marsal K, Valentin L. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding - A Nordic multicenter study. *Am J Obstet Gynecol* 1995;172:1488-94.
22. Cheng W, Lin H, Tong P, Huang S. Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated perimenopausal and postmenopausal breast cancer patients. *Gynecol Oncol* 1997;66:233-7.