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Endometrial cancer: Diagnostic methods in postmenopausal vaginal bleeding

Aljoša MANDIĆ
Tamara VUJKOV

DEPARTMENT OF GYNECOLOGIC ONCOLOGY, INSTITUTE OF ONCOLOGY SREMSKA KAMENICA, SREMSKA KAMENICA, SERBIA AND MONTENEGRO

Postmenopausal vaginal bleeding (PMB) is the leading symptom of endometrial cancer. More than 70% of patients with endometrial cancer are postmenopausal.
Despite PMB as a leading symptom in diagnosis of endometrial cancer, PMB could be caused by some benign processes in endometrium such as hyperplasia and focal endometrial disease, such as a polyp. The golden standard for histological evaluation of the endometrium is curettage. Transvaginal ultrasound (TVS) and measurement of endometrium thickness is also one of the favored methods in the last decade. Sonographic imaging of the endometrium can be extremely helpful, because endometrial cancer is nearly always associated with thickening and heterogeneity of the endometrium except in case of atrophy-associated adenocarcinoma of the endometrium, which is not associated with thickening. Hysteroscopy found place as a favored method in diagnosis of focal endometrial lesions. Saline infusion sonohysterography (SIS) is a relatively new imaging procedure. The SIS will show whether the endometrium is diffusely thickened, in which case curettage would be the next step, or focally thickened, in which case hysteroscopy with biopsy would be the next step. Combination of some diagnostic procedures, such as TVS, SIS, hysteroscopy, endometrial biopsy, and curettage, should decrease false positive and false negative results, which may affect the correct diagnosis and treatment.

KEY WORDS: *Endometrial Neoplasms; Postmenopause; Uterine Hemorrhage, Ultrasonography; Curettage; Biopsy*

INTRODUCTION

In United States, Canada and West Europe endomentrial cancer is diagnosed in 8% to12% of all female malignant tumors, and in countries of East Europe in 2% to 4% (1). According to the Register of Cancer the standard incidence rate of endometrial cancer in central part of Serbia is 9.1 in 1996, and 12.3 in 1999 per 100 000 (2). Endometrial cancer is still the most curable among 10 most common cancers in women because PMB as a leading clinical symptom occur mostly when disease is still limited to the uterine corpus (International Federation of Gynecology and Obstetrics [FIGO] stage I and II), in which the probability of long-term disease-free survival is high.

Approximately 50 percent of endometrial carcinomas occur in women with particular risk factors for the disease (3). Seventy-five percent of women with endometrial carcinoma are postmenopausal (4). In the mid of 1970s two articles made a global alert, suggesting that estrogen hormone replacement therapy may influence the development of endometrial cancer (5,6).

Any characteristic that increases exposure to unopposed estrogen, such as unopposed estrogen therapy, obesity, anovulatory cycles, and estrogen-secreting neoplasms, increases the amount of unopposed estrogen and thereby increases the risk for endometrial cancer (7-11). Ninety percent of patients with endometrial cancer have abnormal vaginal bleeding usually presented as menometrorrhagia in perimenopausal woman or menstrual-like bleeding in postmenopausal (12).

The term postmenopausal bleeding (PMB) refers to any vaginal bleeding in a postmenopausal woman other than expected cyclic bleeding that occurs with sequential hormone replacement therapy (HRT) (13). The likelihood that endometrial cancer is the cause of postmenopausal bleeding depends on the woman's age; the probability is 9 % for women in their 50s, 16% for those in their 60s, 28% for those in their 70s, and 60% for those in their 80s (14). Any postmenopausal bleeding or spotting is suspicious and should be evaluated. However, PMB could be caused by some

Address correspondence to:
Dr. Aljoša Mandić, Department of Gynecologic Oncology, Institute of Oncology Sremska Kamenica, Institutski put 4, 21204 Sremska Kamenica, Serbia and Montenegro

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benign processes in endometrium such as hyperplasia, and focal endometrial disease such as a polyp. The close relationship between PMB and endometrial carcinoma points to the importance of diagnostic evaluation that should be undertaken in any women with PMB. This is a main reason why endometrial carcinoma is usually diagnosed in its early stages because most women quickly report postmenopausal vaginal bleeding to their physicians.

The range of available tests has expanded over the last decade therefore the decision concerning the optimal testing algorithm has become considerably more complex.

Available tests include: transvaginal sonography (TVS), saline infusion sonohysterography (SIS), office biopsy, hysteroscopy, dilation and curettage.

DIAGNOSTIC PROCEDURES AND THEIR SIGNIFICANCE

The gold standard for histological evaluation of the endometrium has been dilatation and curettage (D&C). However, in two studies comprising both pre- and post-menopausal women with abnormal uterine bleeding, 40-90% of polyps and 43-66% of hyperplasias were missed by D&C (15,16). It is very important to diagnose these benign pathological lesions for several reasons:

- They might be a cause of PMB,
- They continue to give the patient symptoms,
- They are resulting in repeated diagnostic procedures and
- Finally but most important is that both polyps and hyperplasia are risk factors for developing endometrial cancer.

Epstein E et al. showed that in women with focally growing lesions at hysteroscopy, agreement between the D&C diagnosis and the final diagnosis was unacceptably poor (59%), whereas in women without focal lesions, the agreement was excellent (94%). Rehysteroscopy after D&C revealed focally growing lesions to remain totally or partly in situ in 87% of the women (17). These findings were in agreement with the findings of Englund et al., who reported that the uterine cavity was satisfactorily emptied in only 35% of women undergoing D&C (18). The results of the study showed that most pathological lesions in the uterine cavity manifest a focal growth pattern, and that hysteroscopic resection was superior to D&C as a diagnostic tool in women with focally growing lesions.

Office hysteroscopy or SIS can be used as the first step of investigation to disclose the presence of focal lesions in the uterine cavity (19). Before 1982, diagnostic evaluation was routinely accomplished by surgical dilation and curettage (D&C) of the endometrium. More recently, a suction catheter technique for endometrial tissue sampling, performed in an office setting, has been shown to be more than 85% sensitive for the detection of endometrial carcinoma (20,21). Endometrial biopsy (EMB) can easily be performed in the office with minimal or no analgesia. In some patients, office EMB cannot be adequately performed because of cervical stenosis or patient intolerance or, as occurs in 5% to 15% of patients, because the specimen may not provide sufficient information to exclude endometrial cancer (22,23).

Use of transvaginal ultrasonography (TVS) to evaluate patients with postmenopausal bleeding has become increasingly popular in the past decade (24,25,26). In comparison with EMB, TVS is better tolerated and has a higher rate (>95%) of diagnostic results (22,27). Transvaginal ultrasound transducers allow better resolution and more accurate measurement of the thickness of the endometrium than abdominal transducers.

To determine how thin an endometrium should be to reasonably exclude cancer, many large studies have been performed. Standardization of sonographic technique for evaluating the endometrium is the most important. The endometrium is measured at its maximum thickness in the longitudinal axis of the uterine body. This measurement included both endometrial layers (corresponding to the distance between the two basal layers of the anterior and posterior uterine walls at the echogenic interface between endometrium and myometrium). Fluid that may be present in the endometrial cavity must be excluded (28-32). These studies have shown that when an endometrial thickness threshold of 4 or 5 mm is used, the sensitivity for detecting endometrial carcinoma approaches 95% (27,33). Karlsson and associates evaluated endometrium of 1168 postmenopausal patients with bleeding by TVS and curettage. They confirmed the cut-off value of 5 mm, below which the risk of endometrial abnormality is low (5.5%) (33).

Measurement of 4 mm in a patient at high risk for a pathologic process or with repeated bleeding episodes should stimulate further investigation (as if the ET were 5 mm or more) (26).

On the basis of an endometrial thickness of 5 mm or more, biopsies should be indicated after more than half ultrasonography examinations, but less than 10 percent of these examinations will reveal serious endometrial disease. Because of the high false positive rate, ultrasonography is not a practical screening procedure in asymptomatic women, regardless of whether they are receiving estrogen replacement therapy (25).

Archer et al., diagnosed only one well-differentiated endometrial carcinoma in women receiving hormone-replacement therapy, in which endometrial biopsy was performed before treatment among 801 asymptomatic perimenopausal and postmenopausal women (34).

Screening in high-risk group of 597 women, 45 to 69 years of age who had hypertension, diabetes or both, found no endometrial cancers and 6 women with atypical hyperplasia (35).

Tamoxifen, as estrogen antagonist, has estrogenic (agonist) effects on endometrium and stimulates hyperplasia of endometrium increasing risk of endometrial carcinoma.

In one randomized study with transvaginal ultrasonography endometrium was significantly thicker in tamoxifen-treated women (mean, 10.4 +/- 5.0 mm, as compared with 4.2 +/- 2.7 mm for the controls; P <0.001) (36).
Recent retrospective review in tamoxifen-treated women who underwent dilation and curettage found that only those with the symptom of vaginal bleeding had uterine cancer (37).
Focal endometrial lesions occur in about 40% of women with PMB, which could increase false-positive results using TVS only (38). Tissue sampling, SIS, or hysteroscopy with D&C should be performed. One advantage of hysteroscopy is that it permits biopsy of a focal mass.
Saline infusion sonohysterography is a relatively new imaging procedure during which TVS is performed while sterile saline is infused into the endometrial cavity via a transcervically placed catheter. Saline infusion sonohysterography can be performed safely and easily as an outpatient procedure. SIS is favored when a focal endometrial abnormality is suspected on the transvaginal sonogram to confirm that a focal abnormality is indeed present and to define the nature of the focal abnormality better (polyp versus fibroid). Subsequent hysteroscopy could be used then to remove the focal abnormality, if appropriate. Recent studies showed that SIS is more sensitive for detecting focal endometrial abnormalities than either TVS or EMB (38,39). Also the SIS will show whether the endometrium is diffusely thickened, in which case EMB or D&C would be the next step.

HYPERPLASIA AND ATROPHY-ASSOCIATED ADENOCARCINOMA OF ENDOMETRIUM

Despite knowing that hyperplasia, endometrium thickness of 5 mm and more, and PMB increases risk of endometrial cancer and increased the sensitivity of the TVS, Deligdisch and Holinka pointed out that there are two types of endometrial cancer (40):
1. Hyperplasia-associated cancer
2. Atrophy-associated adenocarcinoma of endometrium
There is a difference in pathological features, degree of progress and hormone receptors between these two types of carcinomas (41,42). This atrophy-associated adenocarcinoma could increase false negative results with TVS and in these patients with PMB and very thin endometrium we must perform other tests, which are available in that moment.
It is very important to distinguish these two types because previous studies indicate that atrophy-associated adenocarcinoma and hyperplasia-associated endometrial cancer have different prognoses. Atrophy-associated adenocarcinoma of the endometrium is more likely to be poorly differentiated, to invade the underlying myometrium, and to be of ominous histological types. These characteristics are associated with a worse prognosis. Hyperplasia-associated cancers tend to be a better differentiated, less invasive, and only of the usual endometrioid histological type (42,43). Type accompanied with endometrial hyperplasia may be an estrogen-dependent cancer.
Westhoff C et al. showed that the younger age, higher weight, absence of cigarette smoking, and earlier age at menarche recorded for subjects with hyperplasia- related cancers support the belief that this type of endometrial cancer is estrogen-related (44).
Ohkawara S et al. showed that in the group with hyperplasia-associated endometrial carcinoma frequency of this disease was high in young patients, myometrial invasion was shallow in depth and many patients were in an early stage. The frequency of endometrioid adenocarcinoma and adenocarcinoma was high. Many patients showed positive estrogen (ER) and progesterone receptors (PR) with high PR value. Prognosis of this group was favorable (45).
Whether these two types of endometrial carcinoma with or without hyperplasia are subsets of the same disease that have a different set of component causes or we have to consider it separately should be proven in large epidemiological studies.
It is plausible that hyperplasia-associated adenocarcinoma of the endometrium may be caused by estrogen exposure and estrogen-mediated risk factors, whereas the atrophy-associated cancers may have a different set of causes.

CONCLUSION

There are numerous reports and studies about treating PMB as a leading symptom of endometrial cancer with different conclusions and recommendations.
In 2001, the Society of Radiologists in Ultrasound Consensus Statement on Postmenopausal Bleeding published guidelines that should be applied in patients with PMB (46):
1. Any woman with PMB (bleeding other than that occurring at the expected time in the cycle of sequential HRT) should undergo diagnostic evaluation to determine the cause of bleeding.
2. Either office biopsy or TVS is an acceptable initial test. If TVS is used, the critical feature is the maximal double-thickness width of the endometrium, measured on a sagittal image and excluding any fluid that may be present in endometrial cavity. Until there is definitive information concerning the choice between 4 mm and 5 mm as the appropriate positivity criterion for endometrial thickness, Doubilet would recommend using 4 mm, because that will miss fewer cancers (i.e., has higher sensitivity) than 5 mm.
3. Unless the initial test provides a definitive diagnosis, further testing must be carried out. In particular, following guidelines should be considered:
- If the initial test is TVS, it is generally agreed that an endometrial thickness of 4 mm or less virtually excludes significant disease (especially cancer), so that no further testing need be performed unless the patient's clinical condition changes. If the endometrial

thickness is greater than 4 mm or the endometrium is inadequately visualized, office biopsy or saline infusion sonohysterography SIS should be performed and followed, if needed, by further testing to achieve a diagnosis (e.g., hysteroscopy if SIS shows a focal endometrial lesion).

- If the initial test is office biopsy, unless the biopsy provides a specific pathologic diagnosis, TVS should be performed. Subsequent testing, if any, will depend on the result of the TVS (as outlined above).

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