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Endometrial Hyperplasia: A Review

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Endometrial hyperplasia is a precursor to the most common gynecologic cancer diagnosed in women: endometrial cancer of endometrioid histology. It is most often diagnosed in postmenopausal women, but women at any age with unopposed estrogen from any source are at an increased risk for developing endometrial hyperplasia. Hyperplasia with cytologic atypia represents the greatest risk for progression to endometrial carcinoma and the presence of concomitant carcinoma in women with endometrial hyperplasia. Abnormal uterine bleeding is the most common presenting symptom of endometrial hyperplasia. Specific Pap smear findings and endometrial thickness per ultrasound could also suggest the diagnosis. Unopposed estrogen in women taking hormone replacement therapy increases the risk of endometrial hyperplasia. Tamoxifen has demonstrated its efficacy in treating women at risk for breast cancer, but it increases the risk of endometrial hyperplasia. The choice of treatment for endometrial hyperplasia is dependent on patient age, the presence of cytologic atypia, the desire for future childbearing, and surgical risk. Endometrial hyperplasia without atypia responds well to progestins. However, women with atypical hyperplasia should be treated with hysterectomy unless other factors preclude surgery.

Target Audience: Obstetricians & Gynecologists, Family Physicians.

Learning Objectives: After completion of this article, the reader should be able to describe the definition and classification of endometrial hyperplasia, to outline the clinical features of a patient with endometrial hyperplasia, to point out the natural history of endometrial hyperplasia, and to summarize the diagnostic options for patients with endometrial hyperplasia.

Endometrial hyperplasia is a precursor to the most common female genital malignancy: endometrial carcinoma of endometrioid histology. The American Cancer Society (ACS) predicts that 40,100 new cases of uterine cancer will be diagnosed in 2003, of which 95% are expected to be endometrial in origin. The ACS also estimates that approximately 6800 U.S. women will die from uterine cancers in 2003 (1). Unopposed estrogens from anovulatory cycles and exogenous use in postmenopausal women have been shown to increase the likelihood of endometrial hyperplasia and endometrial carcinoma (2–5). A classification system for endometrial hyperplasia has been developed based on the complexity of endometrial glands and cytologic atypia. Atypical hyperplasia has been most strongly associated with progression to endometrial carcinoma and the presence of concomitant endometrial carcinoma in association with endometrial hyperplasia.

Progression of endometrial hyperplasia to more aggressive pathology is related to the initial endometrial diagnosis. Simple hyperplasia often regresses if the source of exogenous estrogen is removed. However, atypical hyperplasia often progresses to adenocarcinoma unless medical intervention occurs (6).

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Hormone replacement therapy has undergone multiple research trials to determine the appropriate dose and type of progestin to counteract estrogenic overstimulation of the endometrium.

Endometrial hyperplasia is typically diagnosed by endometrial biopsy or endometrial curettage after a woman presents to her gynecologist with abnormal uterine bleeding. The modality of treatment is dependent on the patient's age, desire for future childbearing, and the presence of cytologic atypia in the endometrial specimen. Progestins have been successfully used in women with endometrial hyperplasia that are appropriate for nonsurgical management.

DEFINITIONS AND CLASSIFICATIONS

Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an increase in the glands/stroma ratio. Endometrial hyperplasia is further classified into simple and complex hyperplasia based on the complexity and crowding of the glandular framework (Table 1). *Simple hyperplasia* (formerly *cystic* or *mild hyperplasia*) is a proliferative lesion with minimal glandular complexity and crowding with abundant stroma between glands. *Complex hyperplasia* (formerly *moderate hyperplasia*) represents a proliferative lesion with severe glandular complexity and crowding (Fig. 1A). In complex hyperplasia, the glands can vary in size, and minimal stroma is seen between glands.

Endometrial hyperplasia is further classified based on the presence of cytologic atypia. Cytologic atypia refers to enlarged epithelial cells that are hyperchromatic with prominent nucleoli and an increased nuclear-to-cytoplasmic ratio (Fig. 1B). Cytologic atypia is the most important prognostic factor for progression to carcinoma. A simpler classification for endometrial hyperplasia has been recommended based on the importance of cytologic atypia: *hyperplasia without atypia* and *atypical hyperplasia* (formerly *severe hyperplasia* or *adenomatous hyperplasia*) (7). Less than 2% of hyperplasias without atypia progress to carcinoma, and the mean duration of progression to carcinoma takes almost 10 years. Atypical hyperplasia progresses to carcinoma in 23% of cases over a mean duration of 4 years (Table 2) (8).

TABLE 1 **Classification of endometrial hyperplasia**

1. Simple hyperplasia
2. Complex hyperplasia (adenomatous)
3. Simple atypical hyperplasia
4. Complex atypical hyperplasia (adenomatous with atypia)

* From World Health Organization, Kurman RJ, ed. Blaustein's Pathology of the Female Genital Tract 5th ed. New York Springer-Verlag. 2002: 467–500. Reprinted by permission of Springer-Verlag.

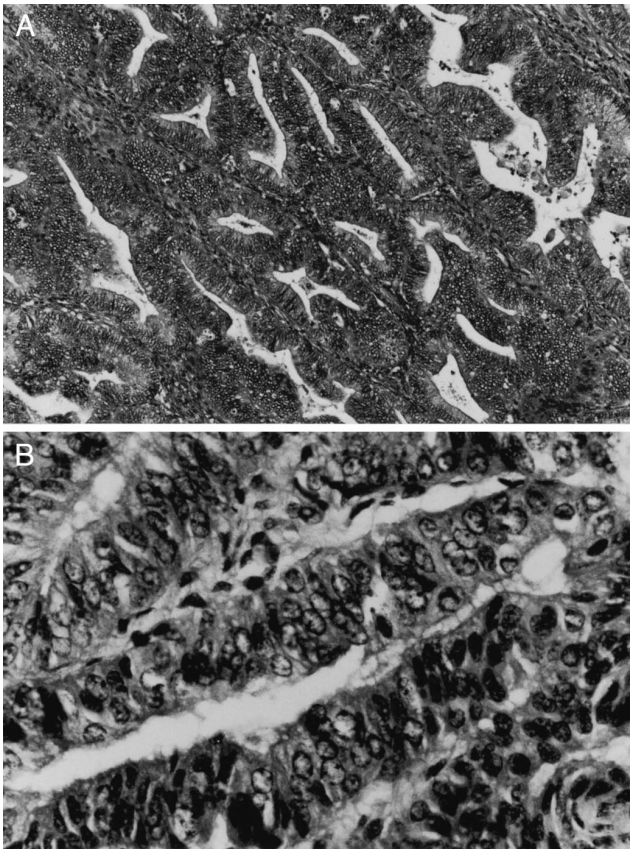

Fig. 1 (**A**) Complex adenomatous hyperplasia without atypia. Note the prominent glandular crowding with minimal stromal separation (hematoxylin & eosin [H&E], 40×). (**B**) Complex adenomatous hyperplasia with atypia. Atypical cellular features include nuclear stratification with rounding of nuclei, nuclear hyperchromasia, and prominent nucleoli in some cells (H&E, 400×).

PATHOGENESIS

The normal menstrual cycle is characterized by increasing expression of the oncogene bcl-2 throughout the proliferative phase of the cycle. bcl-2 is an oncogene located on chromosome 18 that was first recognized in follicular lymphoma (9–11) but has since been reported in many other human neoplasms (12–17). Cellular apoptosis is partially inhibited by the expression of bcl-2 leading to prolonged cell survival (18). Expression of bcl-2 appears to be partly regulated through hormonal control, and its expression is markedly decreased at the onset of the secretory phase of the menstrual cycle (19, 20). The declining expression of bcl-2 correlates with the ap-

TABLE 2 **Comparison of follow up of patients with simple and complex hyperplasia and simple and complex atypical hyperplasia (170 patients)**

Pathology	No. of patients (%)	No. regressed (%)	No. persisted (%)	No. progressed to carcinoma (%)
Simple hyperplasia	93	74 (80)	18 (19)	1 (1)
Complex hyperplasia	29	23 (80)	5 (17)	1 (3)
Simple atypical hyperplasia	13	9 (69)	3 (23)	1 (8)
Complex atypical hyperplasia	35	20 (57)	5 (14)	10 (29)

* From Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of 'untreated' hyperplasia in 170 patients. Cancer (Phila) 1985;56:403– 412. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

pearance of apoptotic cells within the endometrium noted on electron microscopy during the secretory phase of the menstrual cycle (21).

The identification of bcl-2 expression in normal proliferative endometrium prompted investigators to study the potential role of bcl-2 in endometrial hyperplasia. bcl-2 expression has been demonstrated to be increased in endometrial hyperplasia (19,22). However, this increase in bcl-2 expression seems to be limited to complex hyperplasia. Surprisingly, its expression is decreased in atypical hyperplasia and endometrial carcinoma relative to proliferative endometrium (22).

The role of the Fas/FasL gene also has been investigated recently in the development of endometrial hyperplasia (27). Fas is a member of the tumor necrosis factor/nerve growth factor family that binds to FasL (Fas ligand) and initiates apoptosis. Fas and FasL expression are increased in endometrial samples after progestational treatment (27). An interaction between Fas and bcl-2 expression could contribute to the development of endometrial hyperplasia. bcl-2 expression has been demonstrated to decrease in the presence of intrauterine progesterone, whereas Fas expression was noted to increase (28).

The aforementioned studies have begun to give us some insight into the molecular changes that lead to the clinical development of endometrial hyperplasia and carcinoma. However, our understanding is incomplete and further studies are necessary to better clarify the influence of bcl-2 and Fas/FasL on the molecular pathogenesis of endometrial hyperplasia and endometrial carcinoma.

CLINICAL FEATURES

Presentation

Abnormal uterine bleeding is the most common presenting symptom of endometrial hyperplasia. Unopposed estrogen from exogenous use or anovulatory cycles results in a hyperplastic endometrium with subsequent breakthrough bleeding. Younger patients in their reproductive years typically present with endometrial hyperplasia secondary to polycystic ovarian syndrome (PCOS). PCOS results in unopposed estrogen stimulation secondary to anovulatory cycles. Younger patients can also present with increased levels of estrogen secondary to peripheral conversion of androstenedione in adipose tissue (obese patients) or estrogen-secreting ovarian tumors (eg, granulosa cell tumors and ovarian thecomas). The peripheral conversion of androgens to estrogens in androgen-secreting tumors of the adrenal cortex is a rare etiology of endometrial hyperplasia.

Postmenopausal patients with endometrial hyperplasia almost invariably present with vaginal bleeding. Although carcinoma must be considered in this age group, endometrial atrophy represents the most common cause of postmenopausal bleeding. In a study of 226 women with postmenopausal bleeding, 7% were found to have carcinoma, 56% were noted to have atrophy, and 15% were diagnosed with some form of hyperplasia (29). Hyperplasia and carcinoma typically present with heavy vaginal bleeding, whereas patients with atrophy usually present with light spotting (7).

Specific Pap smear findings increase the chances of detecting endometrial pathology. The risk of endometrial carcinoma in postmenopausal women with abnormal uterine bleeding is increased 3- to 4-fold when the Pap smear includes histiocytes containing phagocytosed acute inflammatory cells or normal endometrial cells. However, the incidental finding of histiocytes in an asymptomatic postmenopausal woman has not been found to be associated with an increased risk of endometrial hyperplasia or carcinoma (30). The incidence of underlying uterine pathology is increased in women with Pap smears with atypical glandular cells (AGC). In 45 patients with Pap smears designated as AGUS/favor endometrial

origin, 14 patients (31%) had clinically significant uterine lesions demonstrated by endometrial biopsy (EMB). These lesions included 6 endometrial adenocarcinomas (13%), 5 endometrial hyperplasias (11%), and 3 squamous lesions (7%). Fifty-five percent of the total patient group was postmenopausal, and 10 of the 11 significant endometrial pathologies were noted in these women (31).

Age has a significant impact on follow-up pathologies for AGC Pap smears. In a retrospective study of 281 women with AGC Pap smears, 90 women (32%) had a significant abnormality requiring intervention. In patients less than 50 years of age, only 7 patients (5%) had nonsquamous lesions, whereas 19 patients (15%) over the age of 50 years had nonsquamous lesions. Patients over the age of 50 years with AGC Pap smears were almost 13 times more likely than women less than 50 years of age to have uterine cancer (32).

The terminology for AGUS Pap smears has recently been revised. The 2001 Bethesda System classifies atypical glandular cells (AGC) based on origin (endocervical vs. endometrial) and "not otherwise specified" (AGC NOS). Colposcopy with endocervical sampling is recommended for women with all classifications of atypical glandular cells (AGC), with the exception that women with *atypical* endometrial cells on Pap smear should initially undergo endometrial sampling. Endometrial sampling should also be included in the initial workup with colposcopy and endocervical sampling in women over 35 years of age and in younger women with unexplained vaginal bleeding (33).

Natural History of Endometrial Hyperplasia

In a retrospective review, Kurman described the natural history of endometrial hyperplasia (8). In this historical study, 170 women with endometrial hyperplasia were followed for 1 year without hysterectomy. Only 2 patients (2%) originally diagnosed with hyperplasia without atypia progressed to carcinoma. In both of these patients, the original diagnosis of hyperplasia without atypia progressed through atypical hyperplasia before the diagnosis of endometrial carcinoma. However, in patients diagnosed with atypical hyperplasia (simple and complex), 11 progressed to endometrial carcinoma (23%), and 29% of patients with *complex* atypical hyperplasia went on to develop endometrial carcinoma (Table 2).

Hyperplasia without atypia tends to spontaneously regress, whereas atypical hyperplasias are more likely to progress (6). Endometrial carcinoma with concomitant hyperplasia is associated with less aggressive disease. In a study of 214 women with endometrial carcinoma, 43% of patients were diagnosed with concomitant endometrial hyperplasia. In this group of women, carcinomas were better differentiated and of lower surgical stage. The risk of recurrence was also significantly lower in women with concomitant hyperplasia at the time of original diagnosis (4% vs. 17%), and 5-year survival (96% vs. 85%) was significantly higher in the group of women with concomitant hyperplasia (34).

The frequent association of atypical hyperplasia and cancer means that when a diagnosis of atypical hyperplasia is made, the clinician must be concerned that endometrial carcinoma concomitantly exists within the uterus. When an endometrial biopsy or curettage specimen is diagnosed as atypical hyperplasia, the risk of concomitant carcinoma in the same uterus has been reported as 17% to 25% (35–37). However, 2 recent studies have concluded that the concomitant presence of carcinoma in uteri sampled for endometrial hyperplasia is considerably higher. In a retrospective analysis of 44 women who underwent hysterectomy within 10 weeks of uterine sampling exhibiting atypical hyperplasia, 19 demonstrated coexistent endometrial carcinoma (43%). Seventeen had myometrial invasion (89%), including 7 patients (37%) with deep invasion (FIGO stage IC or higher) (38). Another study reviewed the endometrial sampling results of 45 patients who underwent hysterectomy for a preoperative diagnosis of endometrial hyperplasia. No case of concomitant carcinoma was found in the group of women ($n = 21$) with endometrial hyperplasia without atypia. However, in women diagnosed with atypical hyperplasia, 12 of 24 hysterectomy specimens (50%) had concomitant endometrial carcinoma, and 75% of these patients were stage IB or greater (39). A current prospective study of atypical hyperplasia is being performed by the Gynecologic Oncology Group (GOG).

Development and Progression of Endometrial Hyperplasia in Patients Taking Hormone Replacement Therapy

Postmenopausal women treated with supplemental estrogens are at an increased risk of endometrial hyperplasia and carcinoma if a progestin is not used to oppose the proliferative actions of estrogens on uterine endometrium. Studies have sought to identify the minimal concentration and dosing interval of progestins to counteract the risk of endometrial hy-

perplasia and carcinoma. In a double-blind, randomized, multicenter study of 1176 healthy postmenopausal women, patients received 1 of 3 continuous hormone replacement therapy (HRT) regimens: 17 beta-estradiol 1 mg, 17 beta-estradiol 1 mg/0.1 mg norethindrone acetate, or 17 beta-estradiol 1 mg/0.25 mg norethindrone acetate (40). Of the women who took unopposed estrogen, 14.6% developed endometrial hyperplasia (2 cases of atypical hyperplasia). Although less than 1% of patients in the continuous-combined groups developed endometrial hyperplasia, there were 2 cases of atypical hyperplasia in these 2 groups combined. Continuous norethindrone acetate effectively negated the risk of endometrial hyperplasia associated with estrogen therapy during the first 12 months of treatment. A randomized, double-blind, placebo-controlled, multicenter trial assessed the effect of various combinations of norethindrone acetate and ethinyl estradiol on the uterine endometrium of 945 postmenopausal women. Twenty-six cases of endometrial hyperplasia were identified after 12 months of follow up. Of these 26 cases, 24 cases of endometrial hyperplasia occurred in women taking unopposed estrogen (10% of unopposed estrogen patients). The 2 remaining cases of endometrial hyperplasia occurred in 1 patient taking placebo and in 1 woman receiving 0.2 mg norethindrone acetate/5 mg ethinyl estradiol (41).

Development and Progression of Endometrial Hyperplasia in Patients Taking Selective Estrogen Receptor Modulators

Tamoxifen

Tamoxifen has been used successfully for over 25 years as an adjuvant treatment for breast cancer (42). A randomized, double-blind trial was conducted in 1994 to assess the impact of 20 mg tamoxifen per day on the uterus and ovaries of 111 postmenopausal women at high risk for developing breast cancer (43). During a follow-up period of 3 to 75 months, 16% of tamoxifen-treated patients developed atypical hyperplasia, whereas no patients in the placebo group developed hyperplasia. A total of 39% of tamoxifen-treated patients developed abnormal endometrial histology, including atypical hyperplasia, endometrial proliferation, polyps, or mitotic cells. The National Surgical Adjuvant Breast and Bowel Project (NSABP) ran a randomized, prospective trial to assess the efficacy of 20 mg tamoxifen per day in preventing breast cancer in 13,388 women at high risk for breast cancer (44). The study concluded that the incidence of invasive breast cancer was reduced 49% versus placebo during 69 months of follow up. However, in the same population of women, the relative risk (RR) of endometrial cancer in the tamoxifen-treated group versus the placebo-treated group was 2.53 (95% confidence interval, 1.35–4.97). The absolute risk for endometrial cancer in the tamoxifen-treated group was 13.0 per 1000 women versus 5.4 per 1000 women taking placebo. The increased risk was most pronounced in women 50 years of age or older (RR, 4.01 in women 50 years of age or older and 1.21 in women 49 years or younger). All invasive endometrial cancers (n = 36) were FIGO stage I.

Tamoxifen-treated patients demonstrate thick, cystic, and irregular endometrial linings that mimic findings associated with endometrial neoplasia (45). A prospective trial of premenopausal and postmenopausal women with breast cancer taking tamoxifen was conducted to evaluate endometrial change using ultrasound and endometrial sampling. In 33 postmenopausal women taking tamoxifen, 3 cases of atypical hyperplasia and 1 case of endometrial carcinoma (12%) were noted. No cases of atypical hyperplasia or carcinoma were noted in the nontreated group. Among premenopausal patients, endometrial thickness did not differ significantly between tamoxifen-treated patients and control subjects; however, in postmenopausal women, endometrial thickness in tamoxifen-treated patients was significantly thicker (12.11 mm vs. 5.41 mm) (46).

The increased incidence of endometrial hyperplasia and endometrial carcinoma in tamoxifen-treated women has prompted investigators to perform multiple studies to identify women at risk for developing these uterine pathologies (47–51). Ultrasound has been used to evaluate the endometrium of tamoxifen-treated postmenopausal patients with breast cancer, but its use alone has not proven effective in following these women (51). A prospective study using routine endometrial biopsy (EMB) to follow patients treated with tamoxifen was performed in 111 women with breast cancer at 6-month intervals for 2 years and then yearly for 3 years. A total of 635 EMBs were performed, and 12.6% (n = 14) of patients underwent dilation and curettage (D&C) for an abnormal EMB. Only 3 cases of endometrial hyperplasia (without atypia) were diagnosed. The authors concluded that the use of routine EMB in tamoxifen-treated patients is of limited value (47). In another prospective study of 67 tamoxifen-treated women, 4 cases of endometrial hyperplasia were discovered (1 atypical hyperplasia and 1 adenocarcinoma). Abnormal vag-

inal bleeding was noted in each patient before endometrial sampling, which would have prompted endometrial evaluation regardless of tamoxifen treatment (52). Routine screening with either ultrasound or EMB has not proven effective in following tamoxifen-treated patients (47,51). The American College of Obstetricians and Gynecologists (ACOG) provides a Committee Opinion regarding following tamoxifen-treated patients (53). They recommend yearly gynecologic examination with investigation of any abnormal bleeding or spotting. They do not recommend any type of screening tests for these women.

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen agonist activity on bone and serum lipid metabolism, and its activity is antagonistic in the uterus and breast. The MORE trial (Multiple Outcomes of Raloxifene Evaluation) was a multicenter, randomized, double-blind trial of 7705 postmenopausal women with osteoporosis designed to assess the efficacy and safety of raloxifene. The risk of breast cancer was reduced 76% in women treated with raloxifene for 3 years. Women treated with raloxifene versus placebo were significantly more likely to have documented endometrial thickness greater than 5 mm on at least 1 follow-up ultrasound. In 1781 women with baseline and follow-up ultrasounds, 14.2% of raloxifene-treated women and 10.1% of patients in the placebo group developed endometrial thickness greater than 5 mm. However, the incidence of endometrial hyperplasia and endometrial carcinoma was the same in 196 women undergoing EMB. In both groups, there were 3 cases of endometrial hyperplasia and 2 cases of endometrial carcinoma (54). Subsequent studies comparing raloxifene with unopposed estrogen and combined HRT have confirmed the safety of raloxifene on the uterine endometrium (55,56).

DIAGNOSIS

Abnormal uterine bleeding is the most common presenting complaint in women in which a workup of endometrial hyperplasia is initiated. Women with postmenopausal bleeding will be found to have endometrial hyperplasia in 15% of cases and cancer in 10% of cases (57). Incidental ultrasound findings of thickened endometrium necessitate diagnostic studies for endometrial hyperplasia. Women under 40 years of age presenting with abnormal uterine bleeding typically have hormonal disturbances that resolve without having to pursue other diagnostic modalities, including ultrasound, EMB with Pipelle, or endometrial curettage. In a study of 460 women 40 years of age or younger with abnormal uterine bleeding, 6 women (1.3%) were noted to have simple hyperplasia. No cases of atypical hyperplasia were noted in this group of women (58). However, women under the age of 40 years with predisposing risk factors for endometrial carcinoma such as obesity and PCOS should have a more comprehensive evaluation, usually including ultrasound and occasionally endometrial biopsy. In a study of 36 patients with PCOS, an endometrial thickness less than 7 mm and an intermenstrual interval less than 3 months was only associated with a proliferative endometrium; there were no patients with endometrial hyperplasia (59).

Numerous diagnostic modalities have been investigated to optimally diagnose the etiology of abnormal uterine bleeding and to identify those patients at greatest risk for endometrial hyperplasia or carcinoma.

Ultrasonography

Transvaginal ultrasonography is a noninvasive and relatively inexpensive diagnostic procedure to detect endometrial pathology. However, in postmenopausal women, its efficacy as a screening modality to detect endometrial hyperplasia or carcinoma is not known. In the PEPI trial (Postmenopausal Estrogen/Progestin Interventions), a threshold endometrial thickness of 5 mm produced a positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for endometrial hyperplasia or carcinoma of 9%, 99%, 90%, and 48%, respectively. As a screening modality in asymptomatic postmenopausal women taking estrogen or estrogen–progesterone replacement, this threshold endometrial thickness (5 mm) would require more than 50% of the subjects to undergo endometrial biopsy (60).

Ultrasound could serve as a guide to determine if women with postmenopausal bleeding (PMB) require further diagnostic tests (eg, Pipelle EMB or curettage) to determine the presence of endometrial hyperplasia or endometrial carcinoma. In 339 women with PMB, no women with endometrial thickness less than or equal to 4 mm developed endometrial carcinoma over a 10-year follow-up period (61).

Pipelle Endometrial Biopsy

Endometrial sampling with Pipelle is an effective and relatively inexpensive means to collect tissue for histologic diagnosis in women with abnormal uterine bleeding. In a prospective, randomized comparison of Pipelle (n = 149) versus curette (n = 126) in women with abnormal uterine bleeding, insufficient tissue was noted in only 12.8% and 9.5% of patients, respectively. The difference was not significant ($P > 0.05$). In both groups of patients, pathology at the time of hysterectomy agreed with the original diagnosis in 96% of cases (62). The previous study describes women with numerous etiologies for abnormal uterine bleeding; however, of great importance is the ability of Pipelle to correctly diagnose women with endometrial hyperplasia and carcinoma. In a metaanalysis of 7914 patients, Pipelle had a sensitivity of 99% for detecting endometrial cancer in postmenopausal women, but in women with endometrial hyperplasia, sensitivities decreased to approximately 75% (63).

Hysteroscopy and/or Dilatation and Curettage

Hysteroscopy has generally been accepted as the gold standard for evaluating the endometrial cavity. Endometrial polyps and submucosal fibroids are detected by hysteroscopy with sensitivities as high as 92% and 82%, respectively (64,65). However, hysteroscopy alone for detecting hyperplasia and/or carcinoma results in a high false-positive rate necessitating the use of dilation and curettage for tissue diagnosis (66). Office hysteroscopy has recently been evaluated as a modality to diagnose intrauterine pathology. In conjunction with targeted biopsies, office hysteroscopy had a sensitivity, specificity, PPV, and NPV of 98%, 95%, 96%, and 98%, respectively, when compared with the histologic findings at the time of hysterectomy (67).

Sonohysterography

Sonohysterography is a relatively novel approach to diagnose the etiology of abnormal uterine bleeding. The benefits of sonohysterography over standard transvaginal sonography include the ability to better evaluate intrauterine pathology such as polyps or submucosal fibroids. However, sonohysterography alone has limited value in diagnosing endometrial hyperplasia and carcinoma. EMB with Pipelle is a proven and effective means to diagnose endometrial hyperplasia and carcinoma but lacks sensitivity in diagnosing benign intrauterine lesions. Several investigators have combined transvaginal sonohysterography and EMB with Pipelle to identify the etiology of abnormal uterine bleeding and, specifically, postmenopausal bleeding. When compared with the gold standard, D&C with hysteroscopy, transvaginal sonohysterography, and EMB with Pipelle produced sensitivities greater than 94% (68, 69).

Women with postmenopausal bleeding should undergo a thorough physical examination to determine the source of bleeding. If physical examination does not provide an explanation for the vaginal bleeding, transvaginal ultrasound should guide further management (Fig. 2). Postmenopausal women with a thickened endometrial lining (>5 mm) or women with persistent unexplained vaginal bleeding should undergo endometrial biopsy. The diagnosis of hyperplasia or atypical hyperplasia on endometrial biopsy should be evaluated by dilatation and curettage to obtain a more extensive specimen (7).

Although many studies have proposed alternative management schemes for women with abnormal bleeding, these studies should be considered investigational until further studies are performed. Patient age and risk factors for endometrial carcinoma should influence the physician's choice of diagnostic modality for abnormal bleeding. In premenopausal women with abnormal bleeding, bleeding is often hormonally mediated and self-limited (7). Ultrasound could be useful in diagnosis if an abnormality is noted on the pelvic examination. However, women with risk factors for endometrial carcinoma (PCOS,

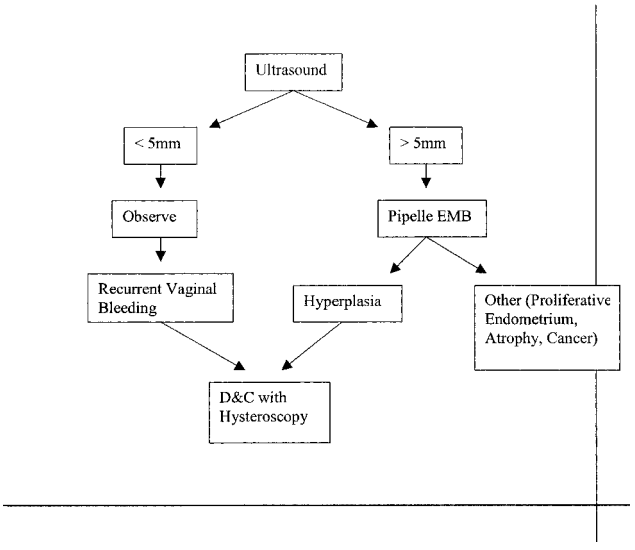

Fig. 2 Diagnostic algorithm for women with postmenopausal bleeding.

obesity, or persistent bleeding) should undergo tissue sampling by EMB with a thickened endometrial stripe (>5 mm). Perimenopausal and postmenopausal women with abnormal bleeding should initially undergo ultrasound with subsequent EMB when a thickened endometrium (>5 mm) has been demonstrated. Women with PMB and a thin endometrial lining on ultrasound (<5 mm) are likely to have atrophy (61). Women with persistent PMB should undergo D&C with hysteroscopy to determine the etiology of the bleeding.

TREATMENT

Multiple studies have demonstrated the efficacy of conservative management with progestins and gonadotropin-releasing hormone-agonists (GnRH-agonists) in treating women with endometrial hyperplasia. Opting for conservative management in women with endometrial hyperplasia depends on several factors, including the patient's age, desire for future childbearing, surgical risk, and the presence of cytologic atypia in the endometrial specimen.

Progestins have been used to treat endometrial hyperplasia for over 40 years (23). In a group of 52 postmenopausal women diagnosed with atypical hyperplasia or hyperplasia without atypia, 90% of patients were noted to have complete remission after treatment with 40 mg megestrol acetate per day over a mean duration of 42 months (70). Megestrol acetate has a low side effect profile and has been shown to be safe at higher doses. At doses of 160 to 320 mg per day for 3 months, no significant changes in blood glucose levels or serum lipid profiles were noted, although women did demonstrate a small increase in weight gain (71).

In a study of premenopausal women with atypical hyperplasia and well-differentiated carcinoma, Randall and Kurman suggested initiating treatment with 20 mg megestrol acetate twice per day and titrating accordingly pending the results of endometrial sampling performed every 3 to 6 months (72). The authors identified 17 women under the age of 40 treated with megestrol acetate or medroxyprogesterone. Sixteen of these patients demonstrated regression to benign endometrial findings. The median length of treatment required to regress to a benign endometrium was 9 months (range, 3–18 months). The single patient that did not respond to progestin treatment received 4 months of continuous 120 mg megestrol acetate per day. A hysterectomy 3 years later demonstrated moderately differentiated carcinoma with no myometrial invasion. In patients treated with medroxyprogesterone, the dose was initiated at 10 mg per day and increased accordingly based on results of endometrial sampling every 3 to 6 months (72).

Cyclic medroxyprogesterone acetate has been used effectively to treat menopausal women with endometrial hyperplasia without atypia. In 65 patients with hyperplasia without atypia, 10 mg medroxyprogesterone acetate per day for 14 days was initially given to patients. Regression of hyperplasia was noted in 80% of patients, and 92% of these patients had reverted to a normal endometrium by 12 months of therapy. No endometrial carcinomas were noted in this group after a mean 7-year follow up (73). In the same study, continuous medroxyprogesterone acetate was used to treat women with atypical hyperplasia. Women received 20 mg medroxyprogesterone acetate per day for at least 6 months, only 5 patients (25%) reverted to a normal endometrium, and 5 patients were diagnosed with stage I endometrial carcinoma over a mean of 5.5 years. The authors suggested that in patients who revert to a normal endometrium, 10 mg medroxyprogesterone acetate per day for 14 days per month would provide adequate suppression (73). This study emphasizes 2 important conclusions regarding cytologic atypia treated with progestins: there is a significantly increased risk of progression to carcinoma, and there is a higher incidence of resistance to regression to benign endometrium.

Atypical hyperplasia can be treated successfully with progestins, but postmenopausal women with cytologic atypia should be strongly encouraged to undergo hysterectomy secondary to the high risk of coexistent endometrial cancer and progression to cancer. Premenopausal women with atypical hyperplasia who choose to proceed with progestin treatment must be followed closely with endometrial biopsy every 3 to 6 months. Progestin concentration should be adjusted based on endometrial histology.

Gonadotropin-releasing hormone agonists have also been used successfully in treating women with endometrial hyperplasia. In a study of 42 women with either simple hyperplasia (n = 30) or atypical hyperplasia (n = 12), 6 months of treatment with either leuprolide acetate or triptorelin resulted in regression of hyperplasia in all but 7 patients. These 7 patients were originally diagnosed with hyperplasia without atypia (74). Progestins have been added to GnRH-agonist regimens with favorable results in treating women with atypical hyperplasia. Norethisterone acetate at a dosage of 500 mg weekly for 3 months with 3.75 mg triptorelin depot every month for 6 months resulted in regression in 16 of 19

patients after 5-year follow up. Of the 3 patients who were considered treatment failures, 1 recurred, 1 persisted, and 1 progressed (75).

CONCLUSION

Endometrial hyperplasia is a relatively common gynecologic condition that affects women in their teenage years to postmenopausal years. Younger women typically develop endometrial hyperplasia secondary to unopposed estrogen from anovulatory cycles. Postmenopausal women with endometrial hyperplasia can develop disease after HRT with unopposed estrogen.

Routine screening for women at high risk for endometrial hyperplasia has not proven efficacious or cost effective. Ultrasound measurement of endometrial thickness is a useful noninvasive technique for preliminary evaluation of women with irregular or postmenopausal bleeding. Endometrial biopsy is indicated in women with a thickened endometrium or persistent bleeding, and dilatation and curettage should be done in patients with a biopsy diagnosis of endometrial hyperplasia or symptoms of persistent bleeding.

Close follow up is recommended in women who opt for progestins for treatment of endometrial hyperplasia. Endometrial biopsy has demonstrated its usefulness in following women on hormonal treatment. The necessity of treating women with complex atypical hyperplasia cannot be overemphasized secondary to the high risk of progression to endometrial carcinoma. Titrating the progestin dose could be necessary to avoid undesirable side effects and provide optimal opportunity for hyperplasia regression. Hysterectomy is recommended in postmenopausal women with atypical hyperplasia who do not have contraindications to surgery.

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