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Endometrial Intraepithelial Neoplasia

ABSTRACT: Endometrial hyperplasia is of clinical significance because it is often a precursor lesion to adenocarcinoma of the endometrium. Making the distinction between hyperplasia and true precancerous lesions or true neoplasia has significant clinical effect because their differing cancer risks must be matched with an appropriate intervention to avoid undertreatment or overtreatment. Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. At present, the endometrial intraepithelial neoplasia schema is tailored most closely to this objective, incorporating modified pathologic criteria based upon evidence that has become available since the creation of the more widely used 1994 four-class World Health Organization schema (in which atypical hyperplasia is equated with precancerous behavior). The accuracy of dilation and curettage compared with endometrial suction curette in diagnosing precancer and excluding concurrent carcinoma is unclear. Hysteroscopy with directed biopsy is more sensitive than dilation and curettage in the diagnosis of uterine lesions. When clinically appropriate, total hysterectomy for endometrial intraepithelial neoplasia provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions. Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy that may be appropriate for women who are poor surgical candidates or who desire to retain fertility.

Conclusions and Recommendations

Sensitive and accurate diagnosis of true premalignant endometrial lesions can reduce the likelihood of developing invasive endometrial cancer. Based on available data and expert opinion, the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology make the following consensus recommendations:

- The endometrial intraepithelial neoplasia schema seems to be preferable to the 1994 four-class World Health Organization (WHO94) schema. Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. At present, the endometrial intraepithelial neoplasia schema is tailored most closely to this objective, incorporating modified pathologic criteria based upon evidence that has become available since the creation of the more widely used WHO94 schema (in which atypical hyperplasia is equated with precancerous behavior). The preferred terminology is "endometrial intraepithelial neoplasia" (rather than "atypical endometrial hyperplasia").
- Regarding tissue sampling, hysteroscopy, while not required, is recommended with directed dilation and curettage (D&C) to include any discrete lesions as well as the background endometrium. This will provide the best opportunity to confirm the diagnosis of a true premalignant endometrial lesion and exclude an associated endometrial carcinoma. When clinically appropriate, total hysterectomy for endometrial intraepithelial neoplasia provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions.

- Supracervical hysterectomy, morcellation, and endometrial ablation are unacceptable for treatment of endometrial intraepithelial neoplasia.
- Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy that may be appropriate for women who are poor surgical candidates or who desire to retain fertility.
- Posthormonal treatment surveillance after nonsurgical management of endometrial intraepithelial neoplasia may include serial endometrial sampling every 3–6 months, but the appropriate frequency has not yet been determined.

Background

Endometrial hyperplasia is of clinical significance because it is often a precursor lesion to adenocarcinoma of the endometrium (1, 2). The precursor lesion of type I endometrioid adenocarcinoma is endometrial intraepithelial neoplasia. Estrogenic stimulation of the endometrium, unopposed by progestins, causes proliferative glandular epithelial changes. This finding, due to prolonged hormonal exposure, is biologically distinct from true precancerous lesions and true neoplasia. Making the distinction between hyperplasia and true precancerous lesions or true neoplasia has significant clinical effect because their differing cancer risks must be matched with an appropriate intervention to avoid undertreatment or overtreatment. The focus of this Committee Opinion is the classification of endometrial hyperplasia and treatment options. Gynecologists should be aware of the two nomenclature schemas and that the endometrial intraepithelial neoplasia schema seems to be preferable to the WHO94 schema. Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. At present, the endometrial intraepithelial neoplasia schema is tailored most closely to this objective, incorporating modified pathologic criteria based upon evidence that has become available since the creation of the more widely used WHO94 schema (in which atypical hyperplasia is equated with precancerous behavior). "Endometrial intraepithelial neoplasia" (rather than "atypical endometrial hyperplasia") is the preferred terminology that will be used throughout this document.

Endometrial Hyperplasia Classification Systems

There are currently two systems of endometrial precancer nomenclature in common usage: 1) the WHO94 schema and 2) the endometrial intraepithelial neoplasia diagnostic schema developed by the International Endometrial Collaborative Group (2). The WHO94 schema classifies histology based on glandular complexity and nuclear atypia and is comprised of four categories of risk classification: 1) simple hyperplasia, 2) complex hyperplasia, 3) simple hyperplasia with atypia, and 4) complex hyperplasia with atypia. These categories are descriptive in nature, and interpretation is subjective; accordingly, studies indicate poor reproducibility of the individual case classification (3, 4). Moreover, the individual categories do not suggest specific management algorithms. This older schema is the one most commonly used by pathologists, but transitioning to the endometrial intraepithelial neoplasia nomenclature would provide greater benefit to clinical management.

In the endometrial intraepithelial neoplasia schema, endometrial precancer is termed "endometrial intraepithelial neoplasia" (5, 6). Pathologic criteria were used to develop three disease categories: 1) benign (benign endometrial hyperplasia), 2) premalignant (endometrial intraepithelial neoplasia), and 3) malignant (endometrial adenocarcinoma, endometrioid type, well differentiated) (Table 1 and Table 2). By applying the endometrial intraepithelial neoplasia schema to routinely obtained endometrial tissues, pathologists present the clinician with a disease-specific classification that informs treatment decisions. Diagnosis using the endometrial intraepithelial neoplasia schema has been confirmed as prognostic in several retrospective studies and one prospective study (7–9). Two of these studies also suggest that interobserver reproducibility using the endometrial intraepithelial neoplasia schema can be greater than with the WHO94

Table 1. Diagnostic Criteria for Endometrial Intraepithelial Neoplasia* ⇦

Nomenclature	Topography	Functional Category	Treatment
Benign endometrial hyperplasia	Diffuse	Prolonged estrogen effect	Hormonal therapy, symptomatic
Endometrial intraepithelial neoplasia	Focal progressing to diffuse	Precancerous	Hormonal therapy or surgery
Endometrial adenocarcinoma, endometrioid type, well differentiated	Focal progressing to diffuse	Malignant	Surgery, stage based

*Previously known as atypical endometrial hyperplasia.

Data from Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer 2005; 103:2304–12 *and* Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 2000;76:287–90.

Table 2. Definitions of Endometrial Intraepithelial Neoplasia* Criteria ⇦

Endometrial Intraepithelial Neoplasia* Criteria	Comments
Architecture	Area of glands greater than stroma (volume percentage stroma less than 55%)
Cytology	Cytology differs between architecturally crowded focus and background
Size greater than 1 mm	Maximum linear dimension exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria (ie, basalis, secretory, polyps, repair)
Exclude cancer	Carcinoma if maze-like glands, solid areas, or appreciable cribriforming

*Previously known as atypical endometrial hyperplasia.

Data from Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer 2005;103:2304–12 *and* Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 2000;76:287–90.

schema (7, 9), which is why gynecologic oncologists prefer the endometrial intraepithelial neoplasia schema.

Precancer Diagnosis: Endometrial Sampling and Imaging

Sensitive and specific detection of endometrial precancer and exclusion of coexisting carcinoma are prerequisites for management of patients with premalignant endometrial lesions. Excluding concurrent carcinoma by endometrial suction curette is especially problematic: approximately 40% of patients who receive a premalignant endometrial intraepithelial neoplasia diagnosis by endometrial suction curette receive a carcinoma diagnosis by using a hysterectomy specimen (8, 10).

The accuracy of D&C compared with endometrial suction curette in diagnosing precancer and excluding concurrent carcinoma is unclear. Both have sampling limitations: approximately 60% of D&C specimens sample less than one half of the uterine cavity (11). The method of sampling is less important if management includes definitive treatment with a hysterectomy, which eliminates the risk of failure to diagnose an endometrial cancer. Dilation and curettage and endometrial suction curette sampling devices have been reported to yield equal rates of cancer detection in patients with abnormal uterine bleeding (12). A single-institution retrospective series found that D&C used to diagnose endometrial intraepithelial neoplasia was less likely to miss cancer (which was evident on subsequent hysterectomy) than the use of endometrial suction curette (27% compared with 46%, respectively) (13). Mass lesions that impinge upon the uterine cavity may deflect flexible endometrial suction curette devices, which prevents adequate assessment of the endometrial cavity. Hysteroscopy with directed biopsy is more sensitive than D&C in the diagnosis of uterine lesions (14). Regarding tissue sampling, hysteroscopy, while not required, is recommended with directed D&C to include any discrete lesions as well as the background endometrium. This will provide the best opportunity to confirm the diagnosis of a true premalignant endometrial lesion and exclude an associated endometrial carcinoma. The small volume of tissue obtained by currently available technologies for sampling the endometrium may limit an accurate assessment of cancer risk. Current diagnostic schema should include an assessment of sample adequacy, as is recommended for evaluation of cervical cytology specimens (15).

Diagnosis of Endometrial Cancer Among Women With Postmenopausal Bleeding

Transvaginal ultrasonography has excellent negative predictive value for endometrial cancer in women with postmenopausal bleeding. When transvaginal ultrasonography is performed for patients with postmenopausal bleeding and an endometrial thickness of 4 mm or less is found, endometrial sampling is not required because of the very low risk of uterine malignancy in these patients (16). An endometrial thickness greater than 4 mm in a patient with postmenopausal bleeding should trigger alternative evaluation (such as sonohysterography, office hysteroscopy, or endometrial biopsy), as should an inability to adequately visualize endometrial thickness. The significance of an endometrial thickness greater than 4 mm in an asymptomatic, postmenopausal patient has not been established, and this finding need not routinely trigger evaluation (16). The utility of ultrasonographic depiction of endometrial thickness for ruling out malignancy is limited to the postmenopausal patient who has bleeding.

Management of Endometrial Intraepithelial Neoplasia

The primary objectives in a patient in whom endometrial intraepithelial neoplasia has been newly diagnosed are the following: ruling out a concurrent adenocarcinoma, designing a treatment plan that can accommodate delayed discovery of an occult carcinoma, and preventing the progression to endometrial cancer. Total hysterectomy

is an effective means of treating a biopsy diagnosis of endometrial intraepithelial neoplasia; parameters guiding nonsurgical management are not as well defined.

Surgical Assessment and Management Options

When clinically appropriate, total hysterectomy for endometrial intraepithelial neoplasia provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions (10). Current surgical options include abdominal, vaginal, and minimally invasive procedures. These methods are acceptable to perform a hysterectomy with or without bilateral salpingo-oophorectomy in patients with a biopsy diagnosis of endometrial intraepithelial neoplasia.

Supracervical hysterectomy, morcellation, and endometrial ablation are unacceptable for treatment of endometrial intraepithelial neoplasia. Because of concerns about underlying carcinoma, a supracervical hysterectomy should not be performed (17). Removal of the cervix and lower uterine segment along with the uterine corpus permits staging of any incidentally discovered cancer and reduces the risk of leaving behind residual disease. Uterine morcellation is contraindicated in patients with a suspected or proven uterine malignancy. Regardless, with this type of surgical approach, patients should be clearly informed of the possibility of having to undergo additional surgery to complete surgical staging if a carcinoma is identified.

The scope of the operation may be changed based on intraoperative assessment and pathologic review. Evaluation could include opening the specimen to assess for gross evidence of a tumor or myoinvasion. If invasive cancer is suspected, the pathologist should exercise judgment in deciding if frozen section analysis is indicated, and the surgeon needs to be aware that there is a small risk of discordance between the frozen and the final pathologic interpretations.

Frozen section may help guide decisions about the need for comprehensive surgical staging. The correlation between frozen section and final pathology for histology, grade, and depth of myometrial invasion is approximately 97.5%, 88%, and 98.2%, respectively (18). Furthermore, high-risk disease is identified more efficiently in frozen section compared with low-risk disease (19). If a gynecologic oncologist is not available, one reasonable strategy is to await final pathologic assessment of the uterus in order to better select patients who would benefit from comprehensive surgical staging.

Comprehensive surgical staging with pelvic and para-aortic lymph node dissection at the time of hysterectomy for endometrial intraepithelial neoplasia would result in overtreatment and increased surgical risk for the vast majority of patients. The risk of a concurrent high-risk uterine carcinoma (high grade, deep invasion) in women with a biopsy diagnosis of endometrial intraepithelial neoplasia is approximately 10% (10, 20). Pelvic and para-aortic lymph node dissection as a routine part of treatment for endometrial intraepithelial neoplasia would result in a large majority of patients being subjected unnecessarily to the risks associated with comprehensive surgical staging. Total hysterectomy, with or without oophorectomy, along with peritoneal washings, may be the most appropriate surgical treatment for endometrial intraepithelial neoplasia, with additional staging involving a gynecologic oncologist.

One potential disadvantage of vaginal hysterectomy is the technical difficulty, in some instances, of removing the ovaries. Comprehensive surgical staging, if indicated, is not feasible with a vaginal approach. Bilateral salpingo-oophorectomy is not absolutely required, especially in premenopausal women and, in fact, removal of both ovaries in premenopausal or perimenopausal women without a confirmed gynecologic malignancy may result in increased overall morbidity and mortality (21). The risks of surgical menopause should be weighed against the risk of an underlying carcinoma that would require subsequent surgery to remove the ovaries.

Nonsurgical Management Options

Nonsurgical management is acceptable for patients who desire future fertility or patients with sufficient medical comorbidities precluding surgical management. The therapeutic goals for patients who desire future fertility are complete clearance of disease, reversion to normal endometrial function, and prevention of invasive adenocarcinoma. The therapeutic goals for patients who are poor surgical candidates include disease stabilization, reduction of the risk of developing endometrial cancer, and conversion to chronic medical management. Current nonsurgical management options are limited to hormonal therapy.

Several studies have evaluated the use of hormonal treatment to induce regression of hyperplasia. The use of progestins is of great interest and has an acceptable toxicity profile. Treatment with progestins may be an option for any patient who wants to retain fertility; any patient with a hyperplastic or precancerous lesion who desires uterine retention; and most elderly patients with medical comorbidities who carry a diagnosis of endometrial intraepithelial neoplasia, a low-grade malignancy, or both.

Progesterone counterbalances the mitogenic effects of estrogens and induces secretory differentiation (22). To date, neither the dose nor the schedule for progestin agents has been well standardized in published studies, but several studies have suggested the clinical effectiveness of progestins for the treatment of endometrial hyperplasia (23–30).

Medroxyprogesterone acetate and megestrol acetate, with different doses and schedules, are the most common progestin therapies used in the clinical setting (Table 3). Regression of hyperplasia (simple, complex, and atypical) has been observed in 80–90% of individuals receiving medroxyprogesterone acetate (10 mg daily for 12–14 days

Table 3. Hormonal Treatment for Endometrial Intraepithelial Neoplasia* ⇦

Hormonal Agent	Dosage and Length
Medroxyprogesterone acetate	10–20 mg/d, or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every 3 months
Micronized vaginal progesterone	100–200 mg/d or cyclic 12–14 days per month
Megestrol acetate	40–200 mg/d
Levonorgestrel intrauterine system	52 mg in a steroid reservoir over 5 years

*Previously known as atypical endometrial hyperplasia.

Modified from Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Society of Gynecologic Oncology Clinical Practice Committee. Obstet Gynecol 2012;120:1160–75.

per month) or micronized progesterone in vaginal cream (100 mg for 12–14 days per month) when treated for 3 months (31–34). However, if endometrial intraepithelial neoplasia is present, there is a higher incidence of failure of medical management and subsequent development of cancer (33).

Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy that may be appropriate for women who are poor surgical candidates or who desire to retain fertility. In addition to systemic administration of hormonal agents, some studies have investigated the use of intrauterine devices (IUDs) for the delivery of progestins. The 5-year levonorgestrel-releasing intrauterine system (levonorgestrel IUD) provides a potential alternative to oral progestogen. Local-acting progesterone has an effect on the endometrium that is several times stronger than that exerted by systemic products and has a decreased systemic effect. Most studies have a relatively small sample size, but in a study of 105 women with simple, complex, or atypical hyperplasia, regression of hyperplasia with use of a levonorgestrel IUD was up to 90%, although only approximately 67% in the presence of atypia (28). A systematic review and meta-analysis found a pooled regression rate of 69% (95% confidence interval, 58–83) in 14 studies (n=189) of women with atypical hyperplasia treated with oral progestins. Pooling the seven studies (n=36) of women with atypical hyperplasia treated with the levonorgestrel IUD found a regression rate of 90% (95% confidence interval, 62–100) (35).

There are still several unresolved issues regarding hormonal treatment of endometrial intraepithelial neoplasia. The optimal treatment dose and duration has not been determined, nor has it been determined whether treatment should be cyclic or continuous. The appropriate length of follow-up after treatment also has not been defined clearly. Appropriate measures of the clinical and histologic response to progestogen treatment also are lacking. Full examination of the endometrium is required to measure regression, persistence, or progression of endometrial intraepithelial neoplasia. Examination of the entire uterus after hysterectomy is considered ideal but is not an option for patients who receive nonsurgical management. Posthormonal treatment surveillance after nonsurgical management of endometrial intraepithelial neoplasia may include serial endometrial sampling every 3–6 months, but the appropriate frequency has not yet been determined.

There is no consensus on the preferred nonsurgical treatment of endometrial intraepithelial neoplasia; therefore, it is difficult to recommend a standard regimen. Several proposed treatment strategies are shown in Table 3. Treatment with an oral progestin or a 5-year levonorgestrel IUD is a reasonable first option and, based on the patient's clinical situation (eg, no longer desires fertility, has completed childbearing, or has become an acceptable-risk surgical candidate), should be continued for 12 months or more unless progression is identified. For many women, the underlying hormonal cause of endometrial intraepithelial neoplasia remains after therapy is completed. Sloughing of the target lesion may be followed by recurrence if treatment is not continued indefinitely. Obesity is associated with an increased incidence of endometrial cancer. Because endometrial intraepithelial neoplasia is often an antecedent of endometrial cancer, clinicians may counsel patients about weight loss or bariatric surgery to reduce the risk of recurrence. Long-term systemic medical treatment to prevent reappearance of endometrial intraepithelial neoplasia requires awareness of potential adverse effects. Edema, gastrointestinal disturbances, and thromboembolic events are infrequent with these treatments, thereby making medical management a reasonable therapeutic option for patients for whom surgical management is not optimal (36).

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