Management of Endometrial Precancers

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In the United States, endometrial cancer is the most commonly diagnosed cancer of the female reproductive system. Strategies to sensitively and accurately diagnose premalignant endometrial lesions are sorely needed. We reviewed studies pertaining to the diagnostic challenges of endometrial precancers, their predictive value, and evidence to support management strategies. Currently, two diagnostic schemas are in use: the four-class 1994 World Health Organization hyperplasia system, based on morphologic features of architectural complexity and nuclear atypia and, more recently, the two-class endometrial intraepithelial neoplasia system, which is quantitative. Diagnosis should use criteria and terminology that distinguish between clinicopathologic entities that can be managed differently. In some instances, such as for women with hereditary nonpolyposis colon cancer, biomarkers may aid in diagnosis, but the clinical utility of biomarkers has yet to be determined. Total hysterectomy is curative for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, and provides a definitive standard for assessment of a concurrent carcinoma, when clinically appropriate. If hysterectomy is performed for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, then intraoperative assessment of the uterine specimen for occult carcinoma is desirable, but optional. Nonsurgical management may be appropriate for patients who wish to preserve fertility or those for whom surgery is not a viable option. Treatment with progestin therapy may provide a safe alternative to hysterectomy; however, clinical trials of hormonal therapies for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia have not yet established a standard regimen. Future studies will need to determine the optimal nonsurgical management of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, standardizing agent, dose, schedule, clinical outcomes, and appropriate follow-up.

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Adenocarcinoma of the endometrium is the most common pelvic cancer among American women, with an estimated incidence of 43,470 and 7,950 deaths attributable to the disease in 2010.[1] The endometrioid subtype of endometrial adenocarcinoma comprises approximately 80–85% of the cancers arising from the lining of the endometrium and is frequently preceded by a precursor lesion.[2,3] Here, we review and discuss the identification and management of precursor lesions to the more common histologic subtype, endometrioid endometrial cancer, in which prolonged estrogenic stimulation plays a causal role. This review does not address the diagnosis or management of uterine papillary serous carcinomas, which comprise approximately 5–10% of newly diagnosed uterine carcinomas.

Endometrioid endometrial carcinoma and its precursor lesions are associated with excess estrogenic stimulation of the endometrium, resulting in

proliferative glandular epithelial changes. Risk factors for the development of endometrial carcinoma include obesity, unopposed estrogen, diabetes, and nulliparity.[4,5] Adiposity is consistently associated with increased risk for endometrial cancer; case-control studies report a 200–400% linear increase in risk in individuals with body mass indexes (BMIs, calculated as weight (kg)/[height (m)]^2) higher than 25.[9] Current data from the National Health and Examination Survey (NHANES) indicate that one third of U.S. adults are obese (BMI higher than 30), and that the prevalence of overweight and obesity continues to increase. The increased risk of endometrial cancer in overweight (BMI higher than 25) and obese persons appears to be greater in postmenopausal women than in younger women.[10] Accordingly, the growing epidemic of obesity in this country, in conjunction with an aging cohort, has the potential to result in a significant increase in endometrial carcinoma and its precursors.

Clinicians have long recognized the indolent nature of the lesion considered to be the precursor to endometrial carcinoma; in 1900, T. S. Cullen described histologic features of this lesion.[11] Subsequently, generations of gynecologic pathologists have attempted to identify histologic parameters that could predict disease[12] (Table 1). The classification system most widely used currently is based on the schema of Kurman et al,[13] which uses architectural features and cytologic atypia to identify precursor lesions, termed atypical endometrial hyperplasia. A classification schema introduced more recently is based on a constellation of quantitative morphologic measures associated with clonality and uses the terminology endometrial intraepithelial neoplasia.[14,15]

Despite a growing understanding of the biology of endometrial carcinoma, the ability to accurately distinguish precursor lesions from invasive cancer based on tissue biopsy results has been difficult. Many attempts to reclassify retrospectively collected data have resulted in an extensive lexicon for endometrial cancer precursors.[13,16–21] A profusion of nonstandard terminology combined with ill-defined or poorly reproducible diagnostic criteria makes it difficult to retrospectively interpret and compare much of the published literature regarding endometrial precancers.[22,23] We present consensus recommendations for the diagnosis and management of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia based on the current available literature and clinical experience (Table 2).

BIOLOGY OF PRECANCEROUS LESIONS OF THE ENDOMETRIUM

Unopposed estrogenic stimulation of the endometrium causes proliferative glandular epithelial changes, including glandular remodeling relative to the stroma, resulting in variably shaped, irregularly distributed glands. Glandular epithelium may undergo metaplastic changes, most commonly to a ciliated tubal type epithelium. The response to

Table 1. Comparison of Some Proposed Classifications of Endometrial Hyperplasia

Beutler et al (1963)[16]	Campbell and Barter (1961)[74]	Gusberg and Kaplan (1963)[19]	Gore and Hertig (1966)[18]	Vellios (1972)[21]	Hendrickson and Kempson (1979)[75]	Tavassoli and Kraus (1978)[20]	Kurman et al (1985)[13]
Cystic proliferation	Benign hyperplasia	Mild adenomatous hyperplasia	Cystic hyperplasia	Cystic hyperplasia	Hyperplasia without atypia	Cystic hyperplasia	Simple, nonatypical
Glandular hyperplasia	Atypical hyperplasia type I	Moderate adenomatous hyperplasia	Adenomatous hyperplasia	Adenomatous hyperplasia	Hyperplasia with mild atypia		
					Hyperplasia with mild atypia	Adenomatous hyperplasia	Complex, nonatypical
	Atypical hyperplasia type II		Anaplasia	Atypical hyperplasia			Simple atypical
Glandular hyperplasia with atypical epithelial proliferation	Atypical hyperplasia type III	Marked adenomatous hyperplasia	Carcinoma in situ	Carcinoma in situ	Hyperplasia with severe atypia	Atypical hyperplasia	Complex atypical

Table 2. Rating the Recommendations

Strength of recommendation	Description
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
Quality of evidence	
I	Evidence from at least one randomized, controlled trial
II	Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Terminology used for recommendations*	
Recommended	Good data to support use when only one option is available
Preferred	Option is the best (or one of the best) when there are multiple other options
Acceptable	One of multiple options when there are either data indicating that another approach is superior or when there are no data to favor any single option
Unacceptable	Good data against use

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*The assignment of these terms represents an opinion ratified by vote by the Consensus Committee.

estrogenic stimulation in the normal epithelium reflects a field effect, which is relatively uniform. Prolonged hormonal exposures may act as positive (estrogens) or negative (progestins) selection factors for sporadically mutated endometrial glands. In these cases, the background hormonal effects appear to be punctuated by localized proliferation of a positively selected clone having a more crowded density and altered cytology.[15] These two biologically distinct types of lesions, those that represent hormonal field effects and those that are true precancerous lesions (endometrial intraepithelial neoplasia), thus represent different processes that may either present independently or coexist in the same patient. Making the distinction between hyperplasia and true neoplasia has significant clinical effect, because their differing cancer risks must be matched with an appropriate intervention to avoid undertreatment or overtreatment.

Consensus Recommendation. Sensitive and accurate diagnosis of true premalignant endometrial lesions can reduce likelihood of development of invasive endometrial cancer (classification AII, Table 2).

ENDOMETRIAL HYPERPLASIA CLASSIFICATION SYSTEMS

There are currently two systems of endometrial precancer nomenclature in common usage: the 1994 four-class World Health Organization schema (WHO94) and the endometrial intraepithelial neoplasia diagnostic schema.[3] The WHO94 is based on a seminal, albeit small and retrospective, study in 1985 by Kurman et al[13] that correlated cytologic atypia with increased risk for cancer. The WHO94 classifies histology based on glandular complexity and nuclear atypia, and comprises four categories of risk classification: simple hyperplasia; complex hyperplasia; simple hyperplasia with atypia; and complex hyperplasia with atypia.[13] These categories are descriptive in nature and interpretation is subjective; accordingly, studies indicate poor reproducibility of the individual case classification.[24,25] Moreover, the individual categories do not suggest specific management algorithms.

In the schema developed by International Endometrial Collaborative Group, endometrial precancers

are termed endometrial intraepithelial neoplasia, reflecting their clonal origin, noninvasive growth, and risk of concurrent or incipient carcinoma.[14,22] Histomorphologic, genetic, clinical, and biological data were used to develop quantitative pathologic criteria for three disease categories of benign, premalignant, and malignant disease. (Table 3) A diagnosis of endometrial intraepithelial neoplasia is rendered when a lesion has a minimum dimension of 1 mm, the area of glands exceeds the area of stroma, the cytology is changed relative to background, and both benign mimics, including polyps, secretory endometrium, and effects of exogenous estrogen and cancer, can be excluded (Table 4). By applying the endometrial intraepithelial neoplasia schema to routinely obtained and stained endometrial tissues, pathologists present the clinician with disease-specific classification suited to treatment decisions. Endometrial intraepithelial neoplasia diagnosis has been confirmed as prognostic in several retrospective studies and in one prospective study.[26–28] Recent studies suggest that clinical outcome prediction and interobserver reproducibility using the endometrial intraepithelial neoplasia system can be greater than for the WHO94 schema.[26,28] Case-control studies reviewing histopathology of either atypical hyperplasia[29] or endometrial intraepithelial neoplasia[30] demonstrate positive predictive value of both of these diagnoses.[31] Although a diagnosis of either atypical hyperplasia or endometrial intraepithelial neoplasia has predictive value in terms of identifying risk for carcinoma, because both diagnostic schema are limited by the quality of the diagnostic tissue specimen, absent more accurate means of identifying negative predictive value, it would not be unreasonable to include a statement of specimen adequacy.

Consensus Recommendation. Pathologic diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently. These include true premalignant lesions, diffuse hormonal effects, and their mimics. At present, the endometrial intraepithelial neoplasia schema is most closely tailored to this objective, incorporating modified pathologic criteria based on new evidence since creation of the more widely used WHO94 endometrial hyperplasia schema (in which atypical hyperplasias are equated with precancerous behavior) (classification AII, Table 2).

PRECANCER DIAGNOSIS: SAMPLING AND ADJUNCTIVE TESTING

Sensitive and specific detection of endometrial precancers and exclusion of coexisting carcinoma are prerequisites for management of patients with premalignant endometrial lesions. Imperfect sampling methods, coupled with subjective diagnostic criteria, make detection and classification difficult. Excluding concurrent carcinoma by curettage or biopsy is especially problematic; approximately 40% of patients with a biopsy diagnosis of endometrial intraepithelial neoplasia or atypical hyperplasia in fact have carcinoma diagnosed in a hysterectomy specimen.[27,32] The Gynecologic Oncology Group's GOG-167, the largest prospective study to date, was designed to assess the rate of concurrent carcinoma in hysterectomies performed immediately after a tissue diagnosis of atypical endometrial hyperplasia. Concurrent carcinoma was diagnosed in 123 of 289 (42.6%) evaluable cases, 43 of which had features of risk, including myoinvasion or grade 2 or grade 3 carcinomas.

The accuracy of dilation and curettage compared with Pipelle endometrial biopsy in diagnosing a precancer, and excluding concurrent carcinoma, is unclear. Both have sampling limitations: approximately 60% of curettage specimens sample less than half of the uterine cavity.[33] The method of sampling is less important if management includes a hysterectomy. Both curettage and Pipelle sampling devices have been reported to yield equal rates of cancer detection in patients with abnormal uterine bleeding.[34] A single-

Table 3. Functional, Diagnostic, and Therapeutic Aspects of the Endometrial Intraepithelial Neoplasia Classification

EIN Nomenclature	Topography	Functional Category	Treatment
Benign architectural changes of unopposed estrogens (endometrial hyperoplasia)	Diffuse	Estrogen effect	Hormonal treatment
EIN	Focal, later diffuse	Precancer	Hormonal or surgical
Carcinoma	Focal, later diffuse	Cancer	Surgical, stage based

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Table 4. Subjective Histological Endometrial Intraepithelial Neoplasia Criteria. All criteria must be fulfilled for a diagnosis of endometrial intraepithelial neoplasia to be made

EIN Criterion	Comments
Architecture	Area of glands exceeds that of stroma
Cytology	Cytology differs between architecturally crowded focus and background
Diameter [mt] 1 mm	Maximum linear dimension of the lesion exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria: basalis, secretory, polyps, repair, and others
Exclude cancer	Carcinoma if maze-like meandering glands, solid areas, or appreciable cribriforming

institution retrospective series found that atypical endometrial hyperplasia diagnosed by dilation and curettage compared with Pipelle was less likely to miss cancer evident only on subsequent hysterectomy (27% compared with 46%, respectively).[35] Mass lesions that impinge on the uterine cavity, such as polyps or uterine leiomyomas, may deflect Pipelle devices, which are flexible, preventing adequate assessment of the endometrial cavity. Endometrial sampling may be better-accessed by a rigid curet.[36] Hysteroscopy does not significantly increase detection of otherwise occult cancers.[37] Moreover, not all precancerous lesions can be visualized by hysteroscopy.[38] In sum, the very small volume of tissue obtained by currently available technologies for sampling the endometrium is rate-limiting in terms of providing an accurate assessment of risk. Current diagnostic schema should include some sort of assessment of sample adequacy, as is recommended for assessing cervical cytology specimens.[39] For example, the endometrial intraepithelial neoplasia diagnostic criteria are predicated on a minimal lesion diameter of 1 mm.

Transvaginal ultrasonography may have predictive value for endometrial carcinoma among postmenopausal women. Meta-analysis of 5,892 symptomatic women (ie, with postmenopausal bleeding) in 35 published studies showed that an endometrial thickness of 5 mm or more identified 95% of all endometrial cancers. Conversely, in this population, women with an endometrial thickness of less than 4 mm only had a 1% probability of cancer. This cutoff did not vary significantly between women with or without hormone replacement therapy.[40] Among postmenopausal women, endometrium thickness more than 1 cm as assessed by transvaginal ultrasonography is correlated with an increased risk of endometrial carcinoma.[41–46] Overall, the value of uterine ultrasonography may be limited to the postmenopausal patient, because there are no effective interpretive criteria for the premenopausal woman, in whom normal endometrial stripe thickness overlaps substantially with that of women with cancer.[47–49]

Although clonality assays and computerized tissue morphometry have been informative research tools in histopathologic and clinical outcome studies, neither is suited to routine use in most diagnostic laboratories. Diagnosis of endometrial precancers, whether as atypical hyperplasia or endometrial intraepithelial neoplasia, for now, is best accomplished by an experienced pathologist using routinely stained (hematoxylin and eosin) sections and a standard light microscope.

Consensus Recommendation. Diagnostic tissue sampling may be successfully accomplished in a number of preferred tissue formats, including curettage and biopsy (Pipelle) (classification AII, Table 2). Devices that yield crushed (jawed devices), cauterized (hot loops), or very small (jawed devices) samples are unacceptable (classification DIII, Table 2). Direct hysteroscopic visualization is not a requirement, and when performed for purposes of excluding a precancerous lesion the surgeon should always attempt to include any discrete lesions as well as random background endometrium in the pathology sample (classification CIII, Table 2)

Consensus Recommendation. Exclusion of concurrent carcinoma is a necessary diagnostic goal of the patient with newly diagnosed atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (classification AII, Table 2).

PRECANCER DIAGNOSIS: BIOMARKERS

Several biomarkers for the detection and cancer risk assessment of precancerous endometrial lesions have been proposed; however, these individual markers have not yet shown sufficiently high independent predictive value to warrant clinical use.

MANAGEMENT OF ATYPICAL ENDOMETRIAL HYPERPLASIA OR ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA

The primary objectives in the patient with newly diagnosed endometrial intraepithelial neoplasia or atypical endometrial hyperplasia are ruling out a concurrent adenocarcinoma and designing a treatment plan that can accommodate delayed discovery of an occult carcinoma. Ideally, identification of quantifiable parameters associated with risk of carcinoma would allow a third objective, namely, prevention of progression to endometrial cancer. At present, management of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia can be divided into surgical and nonsurgical options. Although total hysterectomy is an effective means of treating a biopsy diagnosis of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, parameters guiding nonsurgical management are not as well-defined.

SURGICAL ASSESSMENT AND MANAGEMENT OPTIONS

Currently, surgical options include abdominal, vaginal, and minimally invasive procedures (such as laparoscopic or robotic approach). These methods are acceptable to perform a hysterectomy with or without bilateral salpingo-oophorectomy in patients with a biopsy diagnosis of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia. Total hysterectomy is the current standard of care for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, providing definitive assessment of a possible concurrent carcinoma, and effectively treating premalignant lesions.[32]

The American College of Obstetrics and Gynecology has commented that "women with known or suspected gynecologic cancer…or endometrial hyperplasia are not candidates for a supracervical procedure."[50] This American College of Obstetricians and Gynecologists Committee Opinion also states "the supracervical approach should not be recommended by the surgeon as a superior technique for hysterectomy for benign disease."[50] Because of concerns about underlying carcinoma, a supracervical hysterectomy should not be performed; removal of the cervix and lower uterine segment along with the uterine corpus permits staging of any incidentally discovered cancers and reduces the risk of leaving behind residual disease. Consultation with a physician experienced in the management of these lesions should help the gynecologist choose the appropriate surgical procedure.

The surgical approach depends on the extent of the planned procedure and skill of the surgeon. Clinical studies indicate that, in the correct hands, total laparoscopic hysterectomy, robotic-assisted hysterectomy, or vaginal hysterectomy are associated with less pain, earlier hospital discharge, and quicker recovery compared with abdominal hysterectomy.[51,52]

Surgical staging is possible with minimally invasive approaches. Currently, in the United States, only one third of hysterectomies are performed either vaginally or laparoscopically. Laparoscopy is the preferred approach in patients with frank endometrial carcinoma, based on shorter patient stay, fewer inoperative and postoperative complications, and improved quality-of-life compared with abdominal approach.[20,21,27] Uterine morcellation is contraindicated in patients with a suspected or proven uterine malignancy. Regardless of the surgical approach, patients should be clearly informed of the possibility of having to undergo additional surgery if a carcinoma is identified.

The scope of the operation may be changed based on intraoperative assessment, with caveats. Intraoperative assessment requires an understanding of endometrial pathology and effective communication between the surgeon and the pathologist. At minimum, evaluation should include opening the specimen to assess for gross evidence of a tumor mass or myoinvasion. If invasive cancer is suspected, then the pathologist should exercise judgment in deciding if frozen-section analysis is indicated. Discordance between frozen-section interpretation of endometrial tissue and the final diagnosis based on permanent section is problematic. The distinction between atypical endometrial hyperplasia or endometrial intraepithelial neoplasia and well-differentiated endometrial carcinoma can be difficult, even for experienced pathologists. Ultimately, management decisions should be made based on final diagnoses rendered on formalin-fixed tissue.

Very little published data exist regarding the value of intraoperative frozen-section assessment atypical endometrial hyperplasia or endometrial intraepithelial neoplasia to help guide decisions about the need for lymphadenectomy. Even in the case of grossly obvious tumor, congruence between intraoperative assessment of tumor grade and final histologic diagnoses made on permanent sections ranges from 40% to 70%, depending on the expertise available at a given institution.[53,54] Similarly, intraoperative assessment of depth of myoinvasion is congruent with final histopathologic diagnoses of approximately 70% of cases.[53,55,56] A recent retrospective analysis comparing intraoperative frozen section (n=146) with final pathology found that frozen section frequently understaged low risk endometrial

cancer.[53] Another recent report included only 23 relevant cases; in this small series, the accuracy of frozen section in identifying carcinoma was only 65%.[57] Moreover, any potential benefit of frozen-section assessments must be weighed against the additional costs, which include additional operative time while awaiting the frozen-section diagnosis and the potential for overtreatment. One reasonable strategy is to await final pathologic assessment of the uterus to better-select patients who would benefit from a lymphadenectomy. This procedure can be performed in a minimally invasive fashion by experienced surgeons. Intraoperative assessment of sentinel lymph nodes is an attractive alternative to complete lymphadenectomy but currently should be considered investigational. The sensitivity of frozen-section assessment to identify endometrial carcinoma in the setting of a preoperative biopsy diagnosis of either atypical endometrial hyperplasia or endometrial intraepithelial neoplasia is low, in the range of 40–50%.[58,59]

Lymphadenectomy at the time of hysterectomy surgery for atypical endometrial hyperplasia would result in overtreatment and increased surgical risk for the majority of patients. Endometrial carcinoma associated with atypical endometrial hyperplasia or endometrial intraepithelial neoplasia diagnosed in the hysterectomy specimen are usually low-grade, early-stage lesions that have a low risk of lymphovascular dissemination.[16–18] The risk of a concurrent high-risk uterine carcinoma (high grade, high stage) in women with a biopsy diagnosis of either atypical endometrial hyperplasia or endometrial intraepithelial neoplasia ranges from 5% to 7%.[16–18] Thus, the consideration of lymphadenectomy as a routine part of treatment for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia would result in 93–95% of patients unnecessarily subjected to the risks associated with a pelvic lymphadenectomy. Simple hysterectomy, with or without oophorectomy and without lymphadenectomy, is the most appropriate surgical treatment for atypical endometrial hyperplasia. Cases should be staged when an underlying carcinoma is identified.

One potential disadvantage of vaginal hysterectomy is the technical difficulty, in some instances, of removing the ovaries. These technically challenging cases can be aided by the use of either laparoscopic or robotic assistance in conjunction with a vaginal approach. Comprehensive surgical staging, if indicated, is not feasible with a vaginal approach. Bilateral salpingo-oophorectomy is not absolutely required, especially in premenopausal women. In premenopausal or perimenopausal women without a confirmed gynecologic malignancy, removal of both ovaries may result in increased overall morbidity and mortality.[1] The risks of surgical menopause must be weighed against the risk of an underlying carcinoma that would require subsequent surgery to remove the ovaries. Oophorectomy is not indicated in patients who have already undergone a hysterectomy in whom no cancer was found. Patients who have no evidence of endometrial cancer after hysterectomy should undergo routine postoperative care.

Consensus Recommendation. When clinically appropriate, total hysterectomy is curative of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia and provides a definitive standard for assessment of a concurrent carcinoma (classification AI, Table 2).

Consensus Recommendation. Supracervical hysterectomy is unacceptable for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia treatment (classification AII, Table 2).

Consensus Recommendation. If hysterectomy is performed for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, then intraoperative assessment of the uterine specimen for occult carcinoma is preferred (classification AII, Table 2). When performed, this should be directed by a qualified pathologist and should include gross examination with or without frozen section (classification BIII, Table 2).

NONSURGICAL MANAGEMENT OPTIONS

Nonsurgical management is acceptable for patients who desire future fertility or patients with sufficient medical comorbidities precluding surgical management. The therapeutic goal for the first group of patients is complete clearance of disease, reversion to normal endometrial function, and the prevention of invasive adenocarcinoma. The therapeutic goals for patients who are poor surgical candidates include disease stabilization, reduction of the risk of development of endometrial cancer, and conversion to chronic medical management. Much of the available clinical data are derived from retrospective cohort studies analyzing clinical outcomes based on practice patterns in specific provider groups, or in referral populations. Because these studies are based on interventions with modalities that are commercially available, not investigational agents, the majority of data report clinical outcomes of progestin-based interventions.

Current nonsurgical management options of disorders of the endometrial lining include hormonal therapy and endometrial ablation. Endometrial

ablation using thermal or electric cautery devices has been used for nonprecancerous endometrial lesion and cancerous diagnoses, but it is not recommended for the treatment of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia. There are no available methods to confirm the completeness of ablation. Moreover, subsequent adhesions may render the cavity partly inaccessible for follow-up surveillance.

Several studies have tried to manipulate the hormonal nature of hyperplasia and cancer by targeting hormonal receptors expressed in lesions to initiate tumor cell death. Similarly, studies also have used hormonal targets to reverse hyperplastic or precancerous lesions. Hormonal classes with potential in both practice and theory include progestins, selective estrogen receptor modulators, aromatase inhibitors, sulfatase inhibitors, and gonadatropin-releasing hormone antagonists. Hormonal therapy using progesterone derivatives is of great interest, because it has an acceptable toxicity profile (eg, infrequent edema, gastrointestinal disturbances, and thromboembolic events). It is a desired option for any patient wanting to retain fertility, a reasonable option for any patient with a hyperplastic or precancerous lesion who desires uterine retention, and certainly is a consideration for most elderly patients with medical comorbidities who have the diagnosis of atypical endometrial hyperplasia or a low-grade malignancy.

In the normal endometrium, progesterone counterbalances the mitogenic effects of estrogens and induces secretory differentiation.[7] In preneoplastic lesions, the mechanisms of therapeutic effect are likely to include induction of apoptosis in neoplastic endometrial glands in concert with tissue sloughing during withdrawal shedding.[60] Activation of progestin receptors is thought to lead to stromal decidualization and thinning of the endometrial lining.[61] Clinical studies of progesterone therapy have limitations. To date, neither the dose nor the schedule for progestational agents has been well-standardized. Published studies tend to be medium in size (with less than 100 participants) and descriptive clinical series administering oral or local progestins for 6 months or more. Overall, these studies offer limited value in guiding management because of heterogeneous cohorts and inconsistent outcome monitoring.

However, several studies have suggested clinical effect of progestins for the treatment of endometrial hyperplasia (Table 5). Medroxyprogesterone acetate and megestrol acetate, with different doses and schedules, are the most commonly used progestin therapies used in the clinical setting (Table 6). Regression of hyperplasia has been observed in 80–90% of individuals receiving medroxyprogesterone acetate, 10 mg daily for 12–14 days per month, or micronized progesterone in vaginal cream, when treated for 3 months.[60,62–64] Daily medroxyprogesterone acetate doses of 600 mg resulted in 82% complete responses among 17 women at a multicenter trial with 25 to 73 months of follow-up.[65–67] Wheeler et al[66] observed that individuals who responded to progestins had decreased gland-to-stroma ratio, decreased glandular cellularity, decreased mitotic activity, loss of cytologic atypia, and other histologic or cytoplasmic changes, as well as architecture changes. The effect of progestins on endometrial cells has been observed as early as 10 weeks posttreatment initiation, with Saegusa and Okayasu observing morphologic changes in approximately 70% of treated endometrial cancers.[68]

The optimal route of progesterone administration remains to be determined. In addition to systemic administration of hormonal agents, some studies have investigated the use of intrauterine devices for the delivery of progestins. The levonorgestrel-releasing intrauterine system provides a potential alternative to oral progesterone. Local-acting progesterone has an effect on the endometrium several times stronger than that exerted by systemic products and with less systemic effect. These effects have been demonstrated in several studies (Table 5).

These studies highlight a number of unresolved issues with hormonal therapy trials. Optimal treatment doses and duration of treatment need to be defined. Some trials have investigated continuous treatment, whereas others use cyclic administration. Another confounder is the variability in length of follow-up after treatment. Many studies of hormonal treatment of endometrial intraepithelial neoplasia have small sample sizes or have different patient populations, further complicating interpretation of the studies.

Although studies to date show high response rates, these studies lack therapeutic standardization and have variable end points. One primary issue that remains to be clarified is the definition of response and regression. Historically, therapy has been directed toward reversal of the effects of unopposed estrogen by the progestin administration. After 50 years of this therapeutic approach, the frequency, duration, and mechanisms of response to progestin intervention all remain unclear. It is unknown whether the therapeutic effect of progestin is by terminal differentiation of glandular cells, shedding after hormone withdrawal, or hormonally mediated direct cell death.

Pathologic interpretation of endometrial tissue from patients before completion of a withdrawal bleed

Table 5. Selected Clinical Trials of Hormonal Therapy for Women With Atypical Endometrial Hyperplasia or Endometrial Intraepithelial Neoplasia

Study	Design	Treatment and Follow-up	Results
Perino 1987[77]	Study of women with benign uterine pathology who were candidates for hysterectomy (group 1, n=5) and women with endometrial hyperplasia (group 2, n=14, six simple, four cystic, three nonatypical adenomatous hyperplasia, one atypical adenomatous hyperplasia)	LNG-IUS (Nova-T, 3 micrograms/d for 5 y)	In all cases, the endometrial mucosa was substantially hypotrophic or atrophic
		In the first group, the aim of the histological investigations was to determine whether the effect of the LNG-IUS was limited to the area immediately adjacent to the device	The glands were reduced in size and morphologically atrophic. The epithelial lining was cylindrico-cubic, monostratified, and without mitosis The effect of the hormones could be observed throughout the whole thickness of the endometrial mucosa, as far as the basal layer In the second group, all six cases of simple hyperplasia of the endometrial mucosa showed a morphological picture of glandular atrophy and extensive predecidual reaction from the very first control performed after 2 mo After 5 mo, the four cases of glandular-cystic hyperplasia showed that the original morphological picture had given way to the typical changes produced by LNG-IUS In the three cases without cytological atypica, hysteroscopic and bioscopic examinations after 2, 5, and 8 mo showed a gradual disappearance of the irregular proliferation of the endometrial mucosa, and the appearance of a morphological picture of predecidual transformation of the endometrial stroma and much atrophy of the glandular structures
Randall 1997[65]	Retrospective study of women with atypical endometrial hyperplasia or well-differentiated endometrial carcinoma (n=27 and 33, respectively)	Progestins (n=17 for atypical endometrial hyperplasia, n=12 for well-differentiated endometrial carcinoma) or hysterectomy (n=27) or neither (n=4)	All women were alive without disease at 40 mo (mean)
		Progestins included megestrol acetate or medroxyprogesterone acetate at various doses and schedules	94% patients with atypical endometrial hyperplasia treated with progestins regressed

(*continued*)

Table 5. Selected Clinical Trials of Hormonal Therapy for Women With Atypical Endometrial Hyperplasia or Endometrial Intraepithelial Neoplasia (*continued*)

Study	Design	Treatment and Follow-up	Results
			75% patients with well-differentiated endometrial carcinoma treated with progestins regressed Median length of treatment required for regression: 9 mo Twenty-five women attempted to become pregnant; five delivered healthy full-term newborns
Vereide 2006[78]	Study of pretreated and posttreated paraffin-embedded specimens from women with endometrial hyperplasia (n =50)	LNG-IUS (n=21) vs oral medroxyprogesterone (10 mg for 10 d per cycle)	All the patients in the LNG-IUS group responded to treatment with no sign of hyperplasia after 3 mo, whereas only approximately half of the patients who were administered medroxyprogesterone orally responded
		Immunohistochemical evaluation for PRA, PRB, ER-a, ER-h, and androgen receptor expression after 3 mo of treatment	Expression of PRA, PRB, ER-a, and ER-h were markedly reduced after progestin treatment in both treatment groups but the reduction was much more pronounced in the LNG-IUS group Weak and focal stromal expression of androgen receptor was demonstrated in 22% of the specimens before but not after therapy There was a statistically significant reduction in both PR and ER among the responders, whereas nonresponders showed no statistical change after treatment
Wheeler 2007[66]	Study of women with complex atypical hyperplasia or well-differentiated endometrial carcinoma (n=18 and 26, respectively)	Oral progestins or a progesterone or LNG-IUS device	Among women with complex atypical hyperplasia, 67% had complete resolution, 11% had regression to hyperplasia without atypia, and 22% had persistent disease
		3-mo to 6-mo follow-up intervals after progesterone treatment, for a maximum of 25 mo	Among women with well-differentiated endometrial carcinoma, 42% had complete resolution, 58% had persistent disease, and there were three episodes of disease progression only after progestin discontinued
Wildemeersch 2007[79]	Noncomparative study of women with endometrial hyperplasia (n=20; eight with atypical hyperplasia)	LNG–IUS (Femilis; 20 micrograms/d) Follow-up ranged from 14–90 mo	All women had development of normal endometrium, except one asymptomatic woman with atypical hyperplasia who still had focal residual nonatypical hyperplasia at 3-y follow-up in the presence of a thin (smaller than 4 mm) endometrium

(*continued*)

Table 5. Selected Clinical Trials of Hormonal Therapy for Women With Atypical Endometrial Hyperplasia or Endometrial Intraepithelial Neoplasia (*continued*)

Study	Design	Treatment and Follow-up	Results
Varma 2008[80]	Prospective observational study of women aged 40 y or older with endometrial hyperplasia (n=105; nine with atypical hyperplasia)	LNG-IUS (Mirena; 20 micrograms/d)	Endometrial regression in 90% (94 of 105) of cases by 2 y, with a significant proportion (96%, 90 of 94) achieving this within 1 y
		22 patients received LNG-IUS in combination with hormone replacement therapy*	Regression occurred in 88 of 96 (92%) of nonatypical and in 6 of 9 (67%) of atypical hyperplasias, and in all 22 cases of endometrial hyperplasia associated with HT
		Histological surveillance was performed at 3 mo and 6 mo after insertion, with 6-month intervals thereafter	Regression rates did not differ between histological types of hyperplasia
		The study presents 1-y and 2-y postinsertion outcomes	23 women (22%) underwent hysterectomy, of which 13 were indicated and 10 were performed at patient request despite regressed endometrium
			Two cases of cancer (one uterine and one ovarian) were identified
Orbo 2008[81]	Prospective, randomized trial of women with endometrial hyperplasia (n=258)	LNG-IUS (20 micrograms/d) compared with low-dose oral medroxyprogesterone (10 mg, 10 d per cycle for 3-6 mo) compared with observation only	After 6 mo of treatment, LNG-IUS proved significantly superior to oral medroxyprogesterone treatment and observation only
		6-mo and long-term (56-108 mo) follow-up	After 56-108 mo, LNG-IUS proved significantly superior to oral medroxyprogesterone treatment and to the observation group
			Comparison of oral therapy to observation only showed no significant differences at any time point
Lee 2010[82]	Prospective observational study of women with endometrial hyperplasia diagnosed (n=12; four simple nonatypical, seven complex nonatypical, and one complex atypical)	LNG-IUS (Mirena; 20 micrograms/d))	Complete regression of endometrial hyperplasia was achieved in all cases, with the significant proportion (66%, 8 of 12) achieving it within 3 mo
			The mean follow-up duration was 12 mo (range 3-27 mo)
		Follow-up endometrial biopsies were undertaken at 3-mo intervals	The mean duration to regression was 4.5 mo
			All cases had regression within 9 mo; in the case of complex atypical hyperplasia, the regression was attained at the 9th mo after treatment initiation
			As long as LNG-IUS was maintained, endometrial hyperplasia did not recur

LNG-IUS, levonorgestrel-releasing intrauterine system; PRA, progesterone receptor A; PRB, progesterone receptor B; ER, estrogen receptor; PR, progesterone receptor; HT, hormone therapy.
*Either estrogen replacement therapy or continuous combined preparations.

Table 6. Hormonal Treatment for Atypical Endometrial Hyperplasia or Endometrial Intraepithelial Neoplasia

Treatment	Dosage or Length
Medroxyprogesterone acetate	10–20 mg daily or cyclic 12–14 d/mo
Depot medroxyprogesterone	150 mg intramuscularly every 3 mo
Micronized vaginal progesterone	100–200 mg daily or cyclic 12–14 d/mo
Megestrol acetate	40–200 mg per d, usually reserved for women with atypical hyperplasia
Levonorgestrel-containing intrauterine device	1–5 y

can be confounded by histologic changes induced by hormone treatment.[15] The interpretation of clinical trial end points has been complicated by the need to sample the endometrium periodically to estimate response and the absence of good definitions of response. Currently, the definition of response is based on histopathologic criteria extrapolated from untreated patients. However, the hormonal agents themselves produce changes that are not physiologic, and no gold standard for histologic response exists. For example, progestin exposure can reduce nuclear size, erroneously suggesting disappearance of a preexisting atypical hyperplasia that has merely undergone a change in cytologic appearance.[69] Further, expansion of the stromal compartment by pseudodecidualization pushes glands apart, creating a lower gland density that may no longer resemble that of the same glands before treatment.[70] For menopausal women, stabilization of endometrial intraepithelial neoplasia and prevention of progression change from endometrial intraepithelial neoplasia to carcinoma may be considered a response, whereas in young women desiring the opportunity to bear children, a return to normal cycling histology is needed. Histologic examination after completion of therapy and a withdrawal bleed provides the greatest information on response and generally should be included in clinical trials. A consensus definition of response rates with the use of continuous therapy is problematic. Additionally, because 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 the "gold standard" but is not an option for patients who receive nonsurgical management. A reliable serum or tissue surrogate marker is needed for patients treated with hormonal therapy. Repeated endometrial sampling may eliminate atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, yielding false-positive responses for hormonal therapy. The role of imaging to monitor hormonal interventions is not clear, particularly in premenopausal women.

Hormonal therapy resistance has been reported in up to 30% of cases, often attributed to the decreased availability of progestin receptors and alteration of the apoptotic signaling pathway of the endometrial glandular cells.[60,71] Progestin resistance also can be induced by prolonged progestin treatment through downregulation of progesterone receptor and activation of the transforming growth factor signaling pathway.[72] Less likely, resistance to hormonal therapy could result from mutations in progestin resistance or possibly paracrine effects. The histologic response of the glands of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia is strongly coupled to the decidual response in the stroma, so the possibility of a paracrine effect is plausible, but the epithelial–stromal interactions of the endometrium are incompletely understood.

There is no consensus on the preferred nonsurgical treatment of endometrial intraepithelial neoplasia. It is difficult to recommend a standard treatment regimen. Treatment with an oral progestin or levonorgestrel-releasing intrauterine system is a reasonable first option. Treatment should be continued for 6 months or more unless progression is identified. In one approach, currently being evaluated in a prospective clinical trial (GOG-224), patients undergo an endometrial biopsy at 12 weeks, with treatment continuing for 12 additional weeks if the biopsy result is positive. In this protocol, longitudinal endometrial sampling, either by curettage or by biopsy, is performed at 3- to 6-month intervals, until a minimum of three negative biopsy results are obtained, after which sampling frequency is reduced. If persistence or progression to carcinoma is detected, then hysterectomy is performed. Histologic diagnoses are determined 1–2 weeks after a progestin withdrawal bleed. Endometrial shedding minimizes cytologic and architectural effects of progesterone that could otherwise confound histologic interpretation. It is important to note that progestin treatment can reduce benign hormonal field effects, but true neoplastic lesions–even if intraepithelial–are not as likely to respond to progestin therapy.

For many women, the underlying hormonal cause of hyperplasia or endometrial intraepithelial neoplasia remains after therapy is completed. Sloughing of the target lesion may be followed by recurrence if treatment is not continued indefinitely. Long-term medical treatment to prevent reappearance of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia requires awareness of potential side effects. Edema, gastrointestinal disturbances, and thromboembolic events are infrequent, thereby providing a reasonable therapeutic window option for patients for whom surgical management is not desired.[73] Further, single-agent compared with multiagent therapy for endometrial intraepithelial neoplasia deserves consideration. Multiagent therapy could act as an estrogen antagonist at multiple sites, such as preventing peripheral conversion of androstenedione to estrone and local inhibition of steroid sulfatase in the endometrium. A better understanding of the biology of endometrial carcinoma could inform diagnostic, prognostic, and therapeutic targets. Rational therapy could be directed toward repairing or correcting the pathway, potentially at any one of multiple sites. To date, no trials have been completed using nonhormonal agents. Well-designed, large, multicenter trials will be needed to answer many of these questions and to determine the best treatment course for women requiring nonsurgical interventions.

Consensus Recommendation. Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy, which may be appropriate for women who are poor surgical candidates or who desire to retain fertility (classification BI, Table 2).

Consensus Recommendation. Endometrial ablation (thermal or electrocautery) is not recommended for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia treatment (classification DII, Table 2).

Consensus Recommendation. Follow-up of women treated hormonally should include multiple endometrial samplings during a posttreatment surveillance interval, preferably performed after withdrawal of the treating drug and completion of a withdrawal bleed (classification AII, Table 2).

CONCLUSIONS

With high rates of endometrial carcinoma, sensitive and accurate diagnosis of true premalignant endometrial lesions is imperative to reduce likelihood of development of invasive endometrial cancer. Diagnosis should use criteria and terminology that clearly distinguish between clinic pathologic entities that are managed differently, relying on examination by experienced pathologic examination of premalignant lesions. Diagnostic tissue sampling may be successfully accomplished in a number of formats, including curettage and biopsy. The clinical utility of biomarkers has yet to be determined. Exclusion of concurrent carcinoma is a necessary diagnostic goal of the patient with newly diagnosed atypical endometrial hyperplasia or endometrial intraepithelial neoplasia. Total hysterectomy is curative of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia and provides a definitive standard for assessment of a concurrent carcinoma, when clinically appropriate. If hysterectomy is performed for endometrial intraepithelial neoplasia, then intraoperative assessment of the uterine specimen for occult carcinoma is desirable, but optional. Nonsurgical management may be appropriate for patients who wish to preserve fertility or those for whom surgery is not a viable option. Treatment with progestin therapy may well provide a safe alternative to hysterectomy; however, clinical trials of hormonal therapies for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia have not established a standard regimen. Definition of standardized therapeutic end points for progestin-treated patients and standard dosing and route of administration will require future studies to determine optimal nonsurgical management of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia.

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