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Management of Endometrial Precancers

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Abstract

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 schema are in use; the 4-class WHO94 hyperplasia system, based on morphologic features of architectural complexity and nuclear atypia, and more recently, the 2-class endometrial intraepithelial neoplasia system, which is quantitative. Diagnosis should employ criteria and terminology which distinguish between clinicopathologic entities that can be managed differently. In some instances, such as for women with hereditary nonpolyposis colon cancer (HNPCC), 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, where clinically appropriate. If hysterectomy is performed for atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, 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 non-surgical management of AEH/EIN, standardizing agent, dose, schedule, clinical outcomes, and appropriate follow-up.

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Diagnosis of Endometrioid Endometrial Cancer Precursor Lesions

Burden of Disease

Adenocarcinoma of the endometrium is the most common pelvic cancer among American women, with an estimated incidence of 43,470 and 7,950 deaths due 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 histological subtype, endometrioid endometrial cancer, in which prolonged estrogenic stimulation plays a causal role. This review will not address the diagnosis or management of uterine papillary serous carcinomas, which comprise approximately 5–10% of newly diagnosed uterine carcinomas.

Endometrioid endometrial carcinoma (ECa) 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 ECa 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 BMI above 25 kg/m^2.[9] Current data from the National Health and Examination Survey (NHANES) indicate that one-third of U.S. adults are obese (BMI > 30), and that the prevalence of overweight and obesity continues to increase. The increased risk of endometrial cancer in overweight (BMI >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 ECa and its precursors.

Clinicians have long recognized the indolent nature of the lesion considered to be the precursor to ECa; 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, which uses architectural features and cytologic atypia to identify precursor lesions, termed *atypical endometrial hyperplasia* (AEH).[13] 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* (EIN).[14],[15]

Despite a growing understanding of the biology of ECa, the ability to accurately distinguish precursor lesions from invasive cancer based on tissue biopsies 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 AEH/EIN 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 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 (EIN), 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 impact, as their differing cancer risks must be matched with an appropriate intervention to avoid under- or over-treatment.

Consensus Recommendation—Sensitive and accurate diagnosis of true premalignant endometrial lesions can reduce likelihood of developing 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 4-Class WHO schema (WHO94), and the EIN diagnostic schema.[3] The WHO94 is based upon a seminal, albeit small and retrospective study in 1985 by Kurman and colleagues, which correlated cytological atypia with increased risk for cancer.[13] WHO94 classifies histology based on glandular complexity and nuclear atypia, and is comprised of 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, non-invasive growth, and risk of concurrent or incipient carcinoma.[14, 22] Histomorphological, 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 EIN 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 EIN schema to routinely obtained and stained endometrial tissues, pathologists present the clinician with disease-specific classification suited to treatment decisions. EIN diagnosis has been confirmed as prognostic in several retrospective and one prospective study.[26–28] Recent studies suggest that clinical outcome prediction and inter-observer reproducibility using the EIN system can be greater than for the WHO94 schema.[26, 28] Case-control studies reviewing histopathology of either atypical hyperplasia [29] or EIN [30] demonstrate positive predictive value of both of these diagnoses [31]. While a diagnosis of either atypical hyperplasia or EIN has predictive value in terms of identifying risk for carcinoma, as 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 employ criteria and terminology which clearly distinguish between clinicopathologic entities that are managed differently. These include true premalignant lesions, diffuse hormonal effects, and their mimics. At present, the EIN schema is most closely tailored to this objective, incorporating modified pathologic criteria based upon 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 co-existing 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 EIN or atypical hyperplasia in fact have carcinoma diagnosed in a hysterectomy specimen.[27, 32] 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 123/289 (42.6%) evaluable cases, 43 of which had features of risk, including myoinvasion or grade 2 or grade 3 carcinomas.

The accuracy of dilatation and curettage (D&C) compared to 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-institution retrospective series found that AEH diagnosed by D&C compared to pipelle was less likely to miss cancer evident only on subsequent hysterectomy (27% compared to 46%, respectively).[35] Mass lesions which impinge upon the uterine cavity, such as polyps or uterine leiomyomata, 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 EIN diagnostic criteria are predicated on a minimal lesion diameter of 1mm.

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

While 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 EIN, for now is best accomplished by an experienced pathologist using routinely stained (hematoxylin and eosin) sections at 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 newly diagnosed with AEH or EIN. (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 AEH/EIN

The primary objectives in the patient newly diagnosed with EIN/AEH are 1) ruling out a concurrent adenocarcinoma and 2) 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 AEH/EIN can be divided into surgical and non-surgical options. Although total hysterectomy is an effective means of treating a biopsy diagnosis of AEH/EIN, parameters guiding non-surgical 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 (BSO) in patients with a biopsy diagnosis of AEH/EIN. Total hysterectomy is the current standard of care for AEH/EIN, providing definitive assessment of a possible concurrent carcinoma, and effectively treating premalignant lesions.[32]

The American College of Obstetrics and Gynecology (ACOG) has commented that “women with known or suspected gynecologic cancer,…, or endometrial hyperplasia are not candidates for a supracervical procedure.”[50] This ACOG Committee Opinion also states that “the supracervical approach should not be recommended by the surgeon as a superior technique for hysterectomy for benign disease.”[50] Due to 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 right hands, total laparoscopic hysterectomy, robotic-assisted hysterectomy or vaginal hysterectomy are associated with less pain, earlier hospital discharge, and quicker recovery compared to 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 to 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, 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 AEH/EIN 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 AEH/EIN 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 40–70%, depending on the expertise available at a given institution.[53, 54] Similarly, intraoperative assessment of depth of myoinvasion is congruent with final histopathologic diagnoses in the range of 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 patients with 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 that 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 ECa in the setting of a preoperative biopsy diagnosis of either AEH or EIN is low, in the range of 40–50%.[58, 59]

Lymphadenectomy at the time of hysterectomy surgery for AEH would result in overtreatment and increased surgical risk for the vast majority of patients. ECa associated with AEH/EIN diagnosed in 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 AEH or EIN ranges from 5–7%.[16–18] Thus, the consideration of lymphadenectomy as a routine part of treatment for AEH/EIN 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 AEH. Patients 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. BSO is not absolutely required, especially in pre-menopausal women. In pre- or peri-menopausal 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 which no cancer was found.

Patients who have no evidence of endometrial cancer after hysterectomy should undergo routine postoperative care.

Consensus Recommendation—Where clinically appropriate, total hysterectomy is curative of AEH/EIN and provides a definitive standard for assessment of a concurrent carcinoma. (Classification AI, Table 2)

Consensus Recommendation—Supracervical hysterectomy is unacceptable for AEH/EIN treatment. (Classification AII, Table 2)

Consensus Recommendation—If hysterectomy is performed for AEH/EIN, intraoperative assessment of the uterine specimen for occult carcinoma is preferred. (Classification AII, Table 2) When done, this should be directed by a qualified pathologist and 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 developing endometrial cancer, and conversion to chronic medical management. Much of the available clinical data is 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 great majority of data reports clinical outcomes of progestin-based interventions.

Current non-surgical management options of disorders of the endometrial lining include hormonal therapy and endometrial ablation. Endometrial ablation using thermal or electrical cautery devices has been employed for non-precancerous endometrial lesion and cancerous diagnoses, but it is not recommended for the treatment of AEH/EIN. 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 have also used hormonal targets to reverse hyperplastic or pre-cancerous lesions. Hormonal classes with potential in both practice and theory include progestins, selective estrogen receptor modulators (SERMS), aromatase inhibitors, sulfatase inhibitors, and gonadatropin-releasing hormone (GNRH) antagonists. Hormonal therapy using progesterone derivatives is of great interest, as it has an acceptable toxicity profile (e.g., 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 pre-cancerous lesion who desires uterine retention, and certainly a consideration for most elderly patients with medical comorbidities who carry the diagnosis of AEH and/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-sized, with less than 100 subjects, descriptive clinical series administering oral or local progestins for 6 months or more. Overall, these studies offer limited value in guiding management due to 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 (MPA) 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 subjects receiving MPA, 10 mg daily for 12–14 days per month, or micronized progesterone in vaginal cream, when treated for 3 months.[60, 62–64] Daily MPA 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 and colleagues observed that subjects who responded to progestins had decreased gland-to-stroma ratio, decreased glandular cellularity, decreased mitotic activity, loss of cytologic atypia, and other histological/cytoplasmic changes, as well as architecture changes.[66] The impact of progestins on endometrial cells has been observed as early as 10 weeks post-treatment 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 (LNG-IUS) 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)

The above 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, while others use cyclic administration. Another confounder is the variability in length of follow-up after treatment. Many studies of hormonal treatment of EIN have small sample sizes or have different patient populations, further complicating interpretation of the studies.

While studies to-date show high response rates, these studies lack therapeutic standardization and have variable endpoints. One primary issue which 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 following hormone withdrawal, or by hormonally-mediated direct cell death.

Pathologic interpretation of endometrial tissue from patients prior to completion of a withdrawal bleed can be confounded by histologic changes induced by hormone treatment.[15] The interpretation of clinical trial endpoints has been complicated by both the need to sample the endometrium periodically in order 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 pre-existing atypical hyperplasia which 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 pre-treatment.[70] For menopausal women, stabilization of EIN and prevention of progression change from EIN to carcinoma may be considered a response, while 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, as full examination of the endometrium is required to measure regression, persistence, or progression of EIN, examination of the entire uterus after hysterectomy is considered the “gold standard”, but is not an option for patients who receive non-surgical management. A reliable serum or tissue surrogate marker is needed for patients treated with hormonal therapy. Repeated endometrial sampling may eliminate AEH/EIN, yielding false positive responses for hormonal therapy. The role of imaging to monitor hormonal interventions is not clear, particularly in pre-menopausal 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 down-regulation of progesterone receptor and activation of the transforming growth factor signaling pathway.[72] Less likely, resistance to hormonal therapy could result from mutations in PR or possibly paracrine effects. The histologic response of the glands of AEH/EIN 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 non-surgical treatment of EIN; it is difficult to recommend a standard treatment regimen. Treatment with an oral progestin or LNG-IUD 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 (GOG224), patients undergo an endometrial biopsy at 12 weeks, with treatment continuing for 12 additional weeks if the biopsy is positive. On this protocol, longitudinal endometrial sampling, either by curettage or biopsy, will be performed at 3–6 month intervals, until a minimum of 3 negative biopsies are obtained, after which sampling frequency will be reduced. If persistence or progression to carcinoma is detected, hysterectomy will be performed. Histological diagnoses will be determined 1–2 weeks following a progestin withdrawal bleed. Endometrial shedding will minimize 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 EIN 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 AEH/EIN 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 versus multi-agent therapy for EIN deserves consideration. Multi-agent 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 ECa could inform diagnostic, prognostic, and therapeutic targets. Rational therapy could be directed toward repairing/correcting the pathway, potentially at any one of multiple sites. To date, no trials have been completed using non-hormonal agents. Well designed, large, multicenter trials will be needed to answer many of these questions and determine the best treatment course for women requiring non-surgical 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 desire to retain fertility. (Classification BI, Table 2)

Consensus Recommendation—Endometrial ablation (thermal or electrocautery) is not recommended for AEH/EIN treatment. (Classification DII, Table 2)

Consensus Recommendation—Follow-up of women treated hormonally should include multiple endometrial samplings during a post-treatment 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 ECa, sensitive and accurate diagnosis of true premalignant endometrial lesions is imperative to reduce likelihood of developing invasive endometrial cancer. Diagnosis should employ criteria and terminology which 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 newly diagnosed with AEH or EIN. Total hysterectomy is curative of AEH/EIN and provides a definitive standard for assessment of a concurrent carcinoma, where clinically appropriate. If hysterectomy is performed for EIN, intraoperative assessment of the uterine specimen for occult carcinoma is desirable, but optional. Non-surgical 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 AEH/EIN have not established a standard regimen. Definition of standardized therapeutic endpoints for progestin-treated patients, as well as standard dosing and route of administration will require future studies to determine optimal non-surgical management of AEH/EIN.

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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

	Description
Strength of recommendation	
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 1 randomized, controlled trial.
II	Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 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 1 option is available.
Preferred	Option is the best (or 1 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.

Table 3

Functional, diagnostic, and therapeutic aspects of the endometrial intraepithelial neoplasia (EIN) classification

EIN Nomenclature	Topography	Functional Category	Treatment
Benign architectural changes of unopposed oestrogens (endometrial hyperoplasia)	Diffuse	Oestrogen 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 EIN criteria. All criteria must be fulfilled for a diagnosis of EIN to be made

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

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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 mcg/day for 5 years) ○ In the first group, the aim of the histological investigations was to determine whether the effect of the LNG-IUSwas limited to the area immediately adjacent to the device	• In all cases, the endometrial mucosa was substantially hypotrophic or atrophic ○ 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 the six cases of simple hyperplasia of the endometrial mucosa showed a morphological picture of glandular atrophy and extensive predecidual reaction from the very 1st control performed after 2 months ○ After 5 months, 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 months showed agradual 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 studyof women with atypical endometrial hyperplasia or well-differentiated	• Progestins (n = 17 for atypical endometrial hyperplasia, n = 12 for well-differentiated endometrial	• All women were alive without disease at 40 mos (mean)

Study	Design	Treatment and Follow-up	Results
	carcinoma (n = 27and 33, respectively)	carcinoma) or hysterectomy (n =27) or neither (n = 4) • Progestins included megestrol acetate or MPA at various doses and schedules	• 94% patients with atypical endometrial hyperplasia treated with progestins regressed • 75% patients with well-differentiated endometrial carcinoma treated with progestins regressed • Median length of treatment required for regression: 9mos • Twenty-five women attempted to become pregnant; five delivered healthy full-term infants
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 10fays/cycle) • Immunohistochemical evaluation forPRA, PRB, ER-a,ER-h, and androgen receptor expression after 3 months of treatment	• All the patients in the LNG-IUS group responded to treatmen twith no sign of hyperplasia after 3 months, while only about half of the patients given medroxyprogesterone orally responded • 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 wasd emonstrated 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=18and 26, respectively)	• Oral progestins or a progesterone or LNG-IUS device • 3–6 month follow-up intervals following progesterone treatment, for a maximum of 25 months	• Among women with complex atypical hyperplasia, 67% had complete resolution, 11% regressed to hyperplasia without atypia, and 22% had persistent disease • 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 ug/day) • Follow-up ranged from 14–90 months	• All women developed a normal endometrium, except one asymptomatic subject with atypical hyperplasia who still had focal residual non-atypical hyperplasia at 3 years follow-up in the presence of a thin (smaller than 4 mm) endometrium
Varma 2008 [80]	Prospective observational	• LNG-IUS (Mirena; 20 ug/day)	• Endometrial regression in 90% (94/105) of cases by 2 years, with

Study	Design	Treatment and Follow-up	Results
	studyof women aged 40 years or older with endometrial hyperplasia (n =105; nine with atypical hyperplasia)	• 22 patients received LNG-IUS in combination with hormone replacement therapy * • Histological surveillance was performed at 3- and 6-months following insertion, with 6-monthly intervals thereafter • The study presents 1 and 2 years postinsertion outcomes	a significant proportion (96%, 90/94) achieving this within 1 year • Regression occurred in 88/96 (92%) of non-atypical and 6/9 (67%) of atypical hyperplasias, and in all 22 cases of endometrial hyperplasia associated with HT • Regression rates did not differ between histological types of hyperplasia • 23 women (22%) underwent hysterectomy, of which 13 were indicated and 10 were performed at patient request despit eregressed 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 (20ug/day) vs. low dose oral medroxyprogesterone(10 mg, 10 days per cycle for 3–6months) vs. observation only • 6-month and long-term (56–108 months) follow-up	• At 6 months treatment, LNG-IUS proved significantly superior to oral medroxyprogesterone treatment and observation only • After 56–108 months, 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 diagnosed with endometrial hyperplasia (n = 12;four simple nonatypical, seven complex nonatypical, and one complex atypical)	• LNG-IUS (Mirena) • Follow-up endometrial biopsies were undertaken at 3-month intervals	• Complete regression of endometrial hyperplasia was achieved in all cases, with the significant proportion (66%, 8/12) achieving it within 3 months. • The mean follow-up duration was 12 months (range, 3 to 27 months) • The mean duration to regression was 4.5 months. • All cases had regression within 9 months. In the case of complex atypical hyperplasia, the regression was attained at the 9th month after treatment initiation • As long as LNG-IUS was maintained, endometrial hyperplasia did not recur

* Either estrogen replacement therapy or continuous combined preparations.

LNG-IUS, levonorgestrel-releasing intrauterine system; PRA, progesterone receptor A; PRB, progesterone receptor B; ER-a, estrogen receptor-a; ER-h, estrogen-receptor-h; PR, progesterone receptor; ER, estrogen receptor; HT, hormone therapy.

Table 6

Hormonal Treatment for Atypical Endometrial Hyperplasia or Endometrial Intraepithelial Neoplasia

Medroxyprogesterone acetate	10–20 mg qd, or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every three months
Micronized vaginal progesterone	100–200 mg qd or cyclic 12–14 days per month
Megestrol acetate	40–200 mg per day, usually reserved for women with atypical hyperplasia
Levonorgestrel-containing intrauterine device	1–5 years