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Clinical Expert Series CME

Endometrial Hyperplasia

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The objectives of this Clinical Expert Series on endometrial hyperplasia are to review the etiology and risk factors, histologic classification and subtypes, malignant progression risks, prevention options, and to outline both surgical and nonsurgical treatment options. Abnormal uterine and postmenopausal bleeding remain the hallmark of endometrial pathology, and up to 10–20% of postmenopausal bleeding will be either hyperplasia or cancer; thus, immediate evaluation of any abnormal bleeding with either tissue procurement for pathology or imaging should be undertaken. Although anyone with a uterus may develop atypical hyperplasia, also known as *endometrial intraepithelial neoplasia* (EIN), genetic predispositions (eg, Lynch syndrome), obesity, chronic anovulation, and polycystic ovarian syndrome all markedly increase these risks, whereas use of oral contraceptive pills or progesterone-containing intrauterine devices will decrease the risk. An EIN diagnosis carries a high risk of concomitant endometrial cancer or eventual progression to cancer in the absence of treatment. The definitive and curative treatment for EIN remains hysterectomy; however, the obesity epidemic, the potential desire for fertility-sparing treatments, the recognition of varying rates of malignant transformation, medical comorbidities, and an aging population all may factor into decisions to employ nonsurgical treatment modalities.

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Abnormal uterine bleeding remains the hallmark of endometrial pathology and up to 10–20% of postmenopausal bleeding will be either hyperplasia or cancer.[1] Uterine cancer is expected to affect 65,950 individuals in the United States in 2022,[2] accounting for 7% of all women's cancers; U.S. women have a 1 in 32 lifetime chance of developing uterine cancer. Endometrial cancer remains the most common gynecologic malignancy, and every practicing obstetrician–gynecologist (ob-gyn) needs expertise in the prevention, diagnosis, histology, and treatment of this common entity as well as the precursor lesions.

Historically, endometrial hyperplasia was classified as simple or complex with or without atypia, with a 1–43% risk of malignant progression. There was overlap of the terminology and not necessarily uniform definitions among gynecologists about malignant potential. Currently, the term *endometrial intraepithelial neoplasia* (EIN) has been recognized as the prior atypical endometrial hyperplasia and is considered the precursor lesion for endometrioid endometrial carcinoma; all other variations of endometrial hyperplasia are benign variants that can be medically managed. Endometrial intraepithelial neoplasia must not be confused with endometrial intraepithelial carcinoma (EIC), which is a precursor lesion for the more aggressive papillary serous uterine cancer.

The definitive and curative treatment for EIN remains hysterectomy. However, the obesity epidemic, the potential desire for fertility-sparing treatments, the recognition of varying rates of malignant transformation, medical comorbidities, and an aging population all may factor into decisions to employ nonsurgical treatment modalities. The objectives of

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this Clinical Expert Series on endometrial hyperplasia are to review the histologic classification and subtypes, etiology and risk factors, malignant progression risks, prevention options, and diagnostic work-up, and to outline both surgical and nonsurgical treatment options.

ENDOMETRIAL HYPERPLASIA HISTOLOGIC TYPES

Endometrial hyperplasia is microscopically defined as crowded proliferative endometrium and can be subdivided into nonatypical hyperplasia (benign endometrial hyperplasia) and atypical hyperplasia (also known as *endometrial* or *endometrioid intraepithelial neoplasia*). This two-tiered schema was endorsed by the World Health Organization Classification for Female Genital Tract Tumors in 2014 and represents an evolution of the four-tiered approach proposed in 1994. The previous system accounted for both cytologic atypia and glandular complexity, resulting in four categories: simple hyperplasia without atypia, simple hyperplasia with atypia, complex hyperplasia without atypia, and complex hyperplasia with atypia. This classification system came under scrutiny in large part because the highest risk category, complex hyperplasia with atypia, failed to capture a significant subset of lesions associated with a high rate of concomitant or future endometrioid carcinoma.[3–5] This was in part because the requirement for overt cytologic atypia meant that more subtle morphologically distinct subclones were overlooked. The newer binary classification shows more robust prognostic power, reproducibility, and alignment with treatment options, and is therefore recommended.[3] Nonetheless, some gynecologic pathologists and oncologists remain most familiar with and continue to reference the outmoded terminology; therefore, it remains important to recognize the language and implications of both systems.

Nonatypical Hyperplasia (Benign Endometrial Hyperplasia)

Although nonatypical hyperplasia carries an up to fourfold increase in endometrial cancer risk, those progression rates still remain low, and most cases can be managed or cured with hormonal treatment or curettage or both.[6,7] Microscopically, nonatypical hyperplasia is characterized by glands lined by simple epithelium reminiscent of normal proliferative endometrium, but with increased crowding (Fig. 1). The precise glands/stroma ratio required for a hyperplasia diagnosis remains controversial. A 2:1 ratio is used as the threshold for diagnosis by many pathologists, although in some systems a glandular contribution exceeding 55%—which corresponds to a glands/stroma ratio just barely above 1:1—can be considered compatible in the appropriate morphologic milieu.[5,8] As with normal proliferating glands, the glands of nonatypical hyperplasia may show scattered mitoses and nuclear enlargement, but prominent nucleoli should be absent. Critically, the appearance should be fairly uniform through the entire proliferation, and the presence of a morphologically distinct subclone raises concern for atypical hyperplasia.

Atypical Hyperplasia (Endometrial–Endometrioid Intraepithelial Neoplasia)

When compared with nonatypical hyperplasia, atypical hyperplasia bears a markedly elevated risk of carcinoma, with up to one-third of patients receiving a carcinoma diagnosis within a year.[9] Atypical hyperplasia includes proliferations previously classified as complex atypical hyperplasia, as well as a subset of those that fell into other categories based on their lack of either glandular complexity or frank cytology atypia. Its diagnosis requires glandular crowding with either cytologic atypia beyond what is expected in proliferative endometria, or a morphologically distinct subclone of glands not attributable to benign metaplasia (Fig. 2).

The argument for classifying some hyperplasia as "atypical" on the basis of morphologically distinct proliferations that lack prominent cytologic atypia is

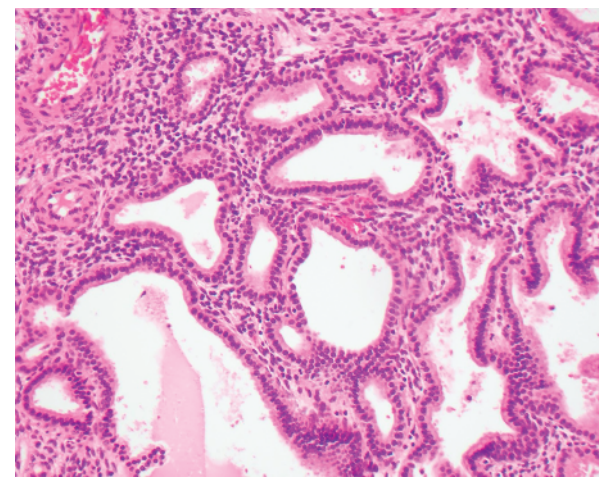

Fig. 1. Hyperplasia without atypia is comprised of crowded glands lined by cells similar to those seen in normal proliferative endometrium, with a glands/stroma ratio of approximately 2:1 representing the lower limit of requisite crowding for diagnosis for many pathologists.
Ring. Endometrial Hyperplasia. Obstet Gynecol 2022.

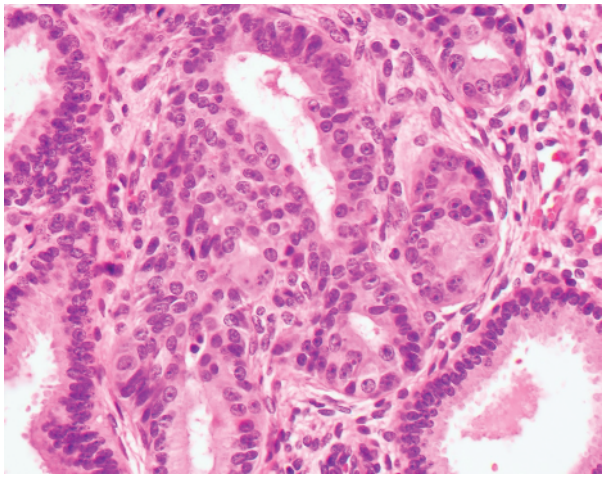

Fig. 2. Atypical hyperplasia–endometrial intraepithelial neoplasia shows both glandular crowding and, in many cases, obvious cytologic atypia, including more prominent nuclear enlargement with prominent basophilic nucleoli.
Ring. Endometrial Hyperplasia. Obstet Gynecol 2022.

based on the incorporation of the EIN system for classifying endometrial precancerous lesions.[8] This system draws from detailed morphometric and molecular investigations that focus on the "D-score," a discriminant function that accounts for both nuclear and architectural features,[10,11] as well as PTEN mutations and loss of PTEN protein expression.[8,12,13] These detailed studies demonstrated that crowded, PTEN-deficient endometrial glands morphologically dissimilar from the background endometrium carry risk comparable with that of proliferations that bear more obvious cytologic atypia (Fig. 3) Given that the risk of such proliferations was underestimated by previous criteria, the World Health Organization's classification of female genital tumors now collapses both the diagnostic criteria and terminology for atypical hyperplasia and EIN such that these diagnoses are now essentially synonymous.[5]

Atypical Hyperplasia and Endometrial Intraepithelial Neoplasia and Distinction from Endometrial Carcinoma

The microscopic distinction between atypical hyperplasia and low-grade endometrioid carcinoma can be challenging because these entities occur on a spectrum and endometrioid carcinomas typically arise in a hyperplastic background, so the entities frequently coexist. Malignant progression is confirmed at the microscope when individual glands show loss of integrity, resulting in fusing and cribriform growth.[14–16] The minimum extent of such growth required to confirm a diagnosis of malignancy has not been well-established, although the somewhat arbitrary threshold of 2 mm has been enlisted historically. Because the line between atypical hyperplasia and low-grade endometrioid carcinoma can be particularly difficult on small and fragmented samples, pathologists may occasionally interpret biopsy and curettage samples as "at least atypical hyperplasia," which suggests an elevated concern for a carcinoma diagnosis on resection.

Clinical and Diagnostic Pitfall: Endometrial Intraepithelial Carcinoma is Not the Same Entity as Atypical Hyperplasia–Endometrial Intraepithelial Neoplasia

It is important to emphasize that, although atypical hyperplasia–EIN is a precursor for endometrioid neoplasia, the similarly named "endometrial intraepithelial carcinoma (EIC)" represents a precursor for the more aggressive uterine serous carcinoma and is not related to endometrioid neoplasia. Indeed, atypical hyperplasia–EIN and EIC are entirely distinct processes tied to different morphologic appearances and distinct molecular pathways of carcinogenesis. First, in contrast to hyperplasia, the diagnosis of EIC does not account for architectural crowding; rather, it is based solely on cytologic features. Moreover, unlike atypical hyperplasia–EIN, the constituent cells of EIC have lost all resemblance to normal endometrium; instead, they demonstrate marked nuclear abnormalities with rounding, prominent eosinophilic nucleoli, and loss of polarity.

Although *PTEN* mutations are considered to be defining events in the development of atypical hyperplasia–EIN, EIC is instead typified by *TP53* mutations.[17–20] To assist in differentiating between a diagnosis of EIC compared with atypical hyperplasia–EIN, pathologists can perform P53 immunostaining to support an interpretation of EIC, because the P53 stain should show either diffuse overexpression or complete absence (null pattern) in that context but should show normal patchy staining (wild-type pattern) in atypical hyperplasia–EIN (Fig. 4). Some pathologists will also apply PTEN immunostaining in this setting because loss of expression is typical of atypical hyperplasia–EIN; however, this assay is less broadly enlisted because it lacks specificity and can show loss of staining in benign proliferations.[13]

MALIGNANT PROGRESSION RISKS

Historically, the risk estimate of progression from atypical hyperplasia–EIN to endometrial cancer has

been 29% based on retrospective review of Kurman and colleagues, where patients with endometrial hyperplasia were followed for at least one year from initial biopsy until the time of hysterectomy. Overall, 10 patients with complex atypical hyperplasia developed cancer, and this retrospective cohort study was used to initially classify endometrial hyperplasia based on cytologic atypia. More recent prospective data show a 43% rate of coexistence of cancer at the time of hysterectomy.[6] In a multicenter study of 477 patients comparing the 1994 to the 2014 World Health Organization criteria, 13% of atypical hyperplasia and 2.3% of nonatypical hyperplasia progressed. Using the updated classifications, 19% of EIN progressed and 0.6% of non-EIN cases progressed.[3]

ETIOLOGY AND RISK FACTORS FOR ENDOMETRIAL HYPERPLASIA–ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA

Atypical endometrial hyperplasia–EIN is extremely common with varying rates of progression to invasive endometrial cancer and prompt recognition of risk factors as well as symptoms and signs are imperative to enable early diagnosis and effective treatment. Probabilities of developing endometrial hyperplasia are difficult to ascertain for the general population, but the probability of developing uterine corpus cancer increases with advancing age. For example, from birth to age 49 years, U.S. women have a 1 in 320 probability, and that increases 10-fold over the course of a lifetime to be 1 in 32 from birth to death.[2] A recent international study has documented that uterine cancer rates have been increasing steadily, a fact attributed to both declines in fertility and increases in excess body weight.[21] Although development of EIN and progression to endometrial cancer are closely linked to both excess estrogen and obesity, multiple other factors can also play a role including genetic predispositions, reproductive factors, and environmental exposures and it remains difficult to sort out independent risks of each as they are all so closely intertwined (Table 1).

Although the vast majority of endometrial hyperplasia and endometrial cancer cases are sporadic, there are several inherited genetic predisposition syndromes that can markedly increase the risk of developing hyperplasia and cancer. The most common is Lynch syndrome, also known as *hereditary nonpolyposis cancer syndrome*, which is caused by a pathogenic variant in one of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*). The lifetime risk of developing cancer in this population ranges from 13 to 57% depending on the specific pathogenic variant.[22–25] Of note, there is a relatively common epigenetic change (methylation of *MLH1*) that can also be acquired rather than inherited that will increase risk as well. Less common syndromes such as Cowden syndrome (*PTEN* pathogenic variant) and Peutz-Jeghers (*STK 11* pathogenic variant) can also markedly increase the uterine cancer risks as well (9–28% and 9% lifetime risks, respectively).[26,27] Early recognition of families with hereditary cancer predisposition enables clinicians to implement even more aggressive prevention and risk-reduction measures for these highest-risk individuals.

Obesity is one the strongest risk factors for endometrial hyperplasia and cancer, and risk rises with increasing levels of severity.[28–30] For example, in one study of premenopausal women, the risk for endometrial hyperplasia in an age-matched control group showed a 2.3-fold increase in women with overweight (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] 25–29), a 3.7-fold increase in women with obesity (BMI 30–39), and a 13-fold increase in women with morbid obesity (BMI 40 or higher)[31]; multiple prior reviews have demonstrated increased summary risk ratios for endometrial cancer between 1.39 and 1.62 for each 5-unit increase in BMI.[28] Production of endogenous excess estrogen is

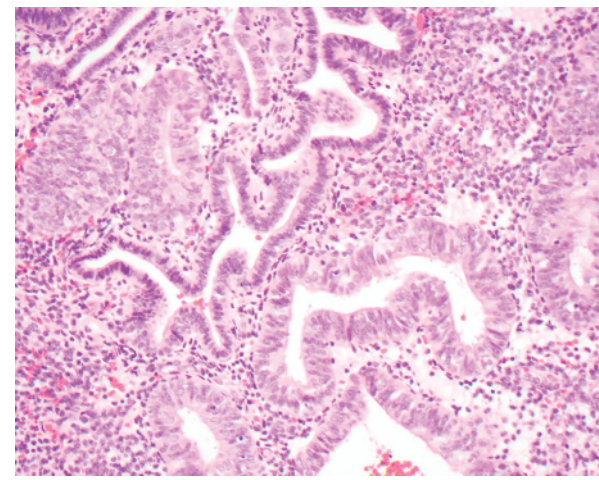

Fig. 3. Atypical hyperplasia–endometrial intraepithelial neoplasia can include crowded proliferations that lack frank cytologic atypia but that appear morphologically distinct from the background. This example shows two populations of hyperplastic glands that cannot be fully explained by benign metaplasia and therefore meet criteria for atypical hyperplasia.

Ring. Endometrial Hyperplasia. Obstet Gynecol 2022.

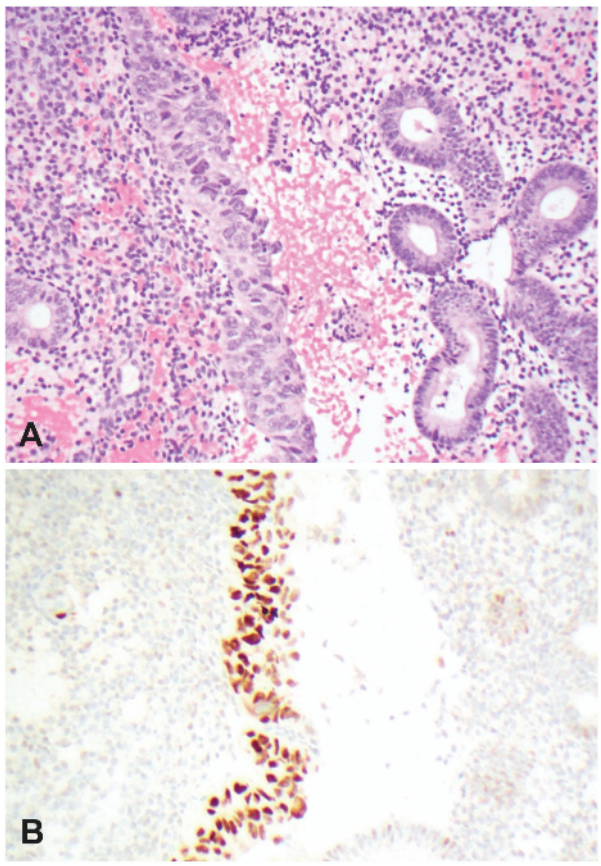

Fig. 4. Endometrial intraepithelial carcinoma (EIC) is a serous carcinoma precursor that must be distinguished from the similarly named atypical hyperplasia–endometrial intraepithelial neoplasia. **A.** This example shows a strip of EIC on the left-hand side, with normal endometrial glands on the right. **B.** The p53 immunostain shows diffuse overexpression within the EIC, supporting the presence of an underlying TP53 mutation and confirming the diagnosis. In contrast, the background endometrium shows normal patchy (wild-type) expression.

Ring. Endometrial Hyperplasia. Obstet Gynecol 2022.

thought to be the predominant obesity-related risk factor and occurs through several mechanisms, including chronic anovulation, peripheral conversion of androgens to estrogens in adipose tissue, and decreased sex hormone–binding globulin with subsequent increases in free steroid hormone levels. Additionally, obesity results in other changes that are felt to promote growth and potential carcinogenesis, including inflammatory and metabolic changes.[32]

Other reproductive factors can increase the risks of endometrial hyperplasia irrespective of obesity, including nulliparity, irregular menses, polycystic ovarian syndrome (PCOS) (PCOS carries a threefold increased risk and a 9% lifetime risk of endometrial cancer), chronic anovulation, older age at first birth and late age at menopause. Additional mechanisms that could play a role include down-regulation of progesterone regulated genes, hyperandrogenism, hypersecretion of luteinizing hormone, increased glucose, hyperinsulinemia, insulin resistance, increased insulin-like growth factor, and inflammatory responses, all of which can result in activation of multiple related pathways that accelerate tumor growth.[33–35] Protective factors include smoking, history of induced abortion, and combined oral contraceptive pill (OCP) use.[28]

PRIMARY PREVENTION OF ENDOMETRIAL HYPERPLASIA

Given that most ob-gyns are in a prime position to recognize and counsel patients with a higher risk, it is important for them to be able to provide guidance to assist with primary prevention options, specifically, obesity treatments, exercise, and medications (Table 1).

Because obesity is so closely linked to the development of endometrial hyperplasia and cancer, effective obesity treatments have been shown to both decrease the risk and even effectively treat already established hyperplasia.[35] Specific weight loss programs are beyond of the scope of this review but should be discussed and recommended to patients both for general health as well as for prevention of obesity-related cancers. Of note, bariatric surgery has been consistently shown to decrease endometrial (and other obesity-related) cancer risk.[36–39] Further, in this same population, patients who had hyperplasia at the time of bariatric surgery (up to a 10% rate of concomitant hyperplasia) were found to have resolution after bariatric surgery and subsequent weight loss.[40] Exercise, even in the absence of weight loss, has been associated with decreased cancer incidence and should be recommended, per standard practice, for all patients.[41–43]

Hormonal medications are commonly used in this patient population to improve symptoms and decrease the risk of endometrial cancer, including OCPs, Depo-Provera (medroxyprogesterone acetate), oral progestins and progesterone-containing intrauterine devices (IUDs). Oral contraceptive pills, if taken for 5 years, can decrease the population risk of endometrial cancer by 50%. Similarly, in patients with PCOS, OCP use has been associated with a 50–70% risk reduction that increases with longer duration of treatment.[33] Progesterone-containing IUDs are likewise associated with decreased endometrial cancer rates in ever users with

Table 1. Risk Factors for Endometrial Intraepithelial Neoplasia and Risk-Reduction Options

Baseline and Increased-Risk Populations	Risk of Hyperplasia or Cancer	Endometrial Cancer Screening Recommendations	Endometrial Cancer–Prevention Options
General population	1 in 32 women in the United States will develop endometrial cancer in their lifetime; continued rising incidence in U.S. women; comprises 7% of all annual cancer diagnoses in women	None currently but prompt evaluation of symptoms recommended	Maintain or attain normal body weight Attain recommended weekly exercise for cancer prevention by American Cancer Society 150–300 min/wk of moderate-intensity exercise 75–150 min/wk of vigorous-intensity exercise OR 30 min of exercise daily or a combination of the 2 intensity types OCPs decrease lifetime risk by 50%; progesterone IUDs decrease lifetime risk
Genetic predisposition		Can consider biopsy but not mandated; immediate evaluation of any abnormal bleeding	General population recommendations as above; OCP or IUD consideration before surgery; risk-reducing surgery with hysterectomy if fertility is not desired
Lynch syndrome	13–57% lifetime risk		
Cowden syndrome	9–28% lifetime risk		
Peutz-Jeghers syndrome	9% lifetime risk		
Obesity	Hyperplasia: BMI 25–29: 2.3-fold risk BMI 30–39: 3.7-fold risk BMI higher than 40: 13-fold risk Cancer: every 5-unit BMI increase is associated with 1.39–1.62 increased risk of cancer	None currently; immediate evaluation of any abnormal bleeding	General population recommendations as above; OCP or progestin IUD, especially for cycle regulation; bariatric surgery; could consider metformin if other medical indications
PCOS	Hyperplasia: threefold increased risk Cancer: 9% lifetime risk of cancer	None recommended	General population recommendations as above; OCPs shown to have 50–70% risk reduction in PCOS; progesterone IUD shown to have 50% risk reduction and persists for at least 5 y; could consider metformin if other medical indications

OCP, oral contraceptive pill; IUD, intrauterine device; BMI, body mass index; PCOS, polycystic ovarian syndrome.

a 50% decreased risk in the general population during use and persisting for at least 5 years after discontinuation.[44–46] The PROTEC trial (PROgesterone Therapy for Endometrial Cancer Prevention in Obese Women) assessed the feasibility of enrolling patients with higher risk (BMI higher than 40) into a clinical trial of the levonorgestrel-releasing IUD (LNG-IUD). This trial found a baseline 9% rate of hyperplasia in 35 patients enrolled; of the 25 patients who were not excluded and received an IUD, 96% opted to continue the IUD past the study period. Use of the IUD was associated with improved bleeding, mental well-being, and decreased endometrial proliferation markers.[47] A cost-effectiveness analysis study concluded that the use of a progesterone IUD in women older than age 50 years with BMIs higher than 40 would be efficacious and cost effective in the prevention of deaths from endometrial cancer.[48] Similarly, a prior study in 51 women with Lynch syndrome were randomized to receive either OCPs or medroxyprogesterone acetate and both showed a dramatic decrease in the epithelial proliferation markers within the endometrium, confirming this as a viable prevention option to discuss with patients at a higher risk.[49]

SCREENING FOR ENDOMETRIAL HYPERPLASIA OR CANCER

Even for the highest-risk groups with Lynch syndrome or extreme obesity, there is not a strong or

evidence-based recommendation for screening asymptomatic patients with either endometrial biopsy or ultrasonography.[50,51] The National Comprehensive Cancer Network (NCCN) guidelines for high-risk genetic mutation carriers (eg, Lynch, Cowden's or Peutz-Jeghers) state that screening with endometrial biopsy can be considered, but most expert opinion simply stresses the need for education and prompt evaluation of symptoms (eg, irregular bleeding, heavy bleeding, or postmenopausal bleeding). No guidelines exist that endorse screening in the general patient population. Despite this, a common scenario will be that a thickened endometrial stripe is incidentally noted on imaging, leaving clinicians to ascertain need for further investigation. In asymptomatic, postmenopausal women, an endometrial stripe greater than 10 mm does require further evaluation with biopsy[52]; under that threshold, biopsy is not required. This differs markedly from recommendations in postmenopausal women with bleeding, the stripe must be under 4–5 mm to be reassuring in terms of low risk for cancer and initially to omit endometrial sampling; however, if bleeding persists, biopsy will be required.

DIAGNOSTIC WORKUP FOR SUSPECTED ENDOMETRIAL HYPERPLASIA OR CANCER IN SYMPTOMATIC WOMEN

Once endometrial hyperplasia or cancer is suspected, endometrial sampling is imperative and endometrial biopsy, dilation and curettage (D&C), or D&C with hysteroscopy can effectively make the diagnosis. If the biopsy shows definitive cancer, no further histologic sampling is indicated and the patient should be referred to a gynecologic oncologist for definitive management. If the biopsy shows endometrial hyperplasia or EIN, there remains some controversy regarding the need for an additional hysteroscopy or D&C to exclude cancer before proceeding with definitive therapy. Even with a preoperative D&C showing only hyperplasia, 27% of the time an endometrial cancer will be found at the time of hysterectomy (compared with a 46% rate with only a prehysterectomy biopsy), so adding the additional procedure still does not guarantee the absence of cancer on the final hysterectomy specimen.[53–55] In general, if hysterectomy is planned and intraoperative assessment or intervention can be performed (frozen section with the ability to do nodes for a deeply invasive endometrial cancer), a further D&C will simply add cost and an additional procedure under anesthesia and potentially could be omitted. Even with the relatively high rate of concomitant cancer with a preoperative EIN–hyperplasia diagnosis, the chance of lymph node involvement is exceedingly small. One study from Dr. Plante's group, pioneers in sentinel lymph nodes, showed a 0% overall rate of lymph node involvement with a preoperative hyperplasia diagnosis that was not, "cannot rule out cancer"; the positivity rate was 3.3% for the entire population, in whom a concomitant cancer was found in more than 50% of the patients.[56]

Ultrasonograms have become integral in the gynecologic care of women due to the easy availability (the majority of ob-gyn offices have them), the comfort of most practicing ob-gyns in using them, the ease and acceptability of use and the lack of radiation, in addition to their efficacy. Ultrasonography is often the imaging modality of choice to evaluate abnormal bleeding or assess the presence of other pelvic pathology, such as adnexal or uterine masses, and in the workup for pelvic pain or infections. In postmenopausal women with bleeding, an endometrial stripe under 4–5 mm has a 99% negative predictive value and can exclude hyperplasia or cancer.[57] On a cautionary note, an ultrasound cutoff of 4 mm in Black women may not be as safe or reliable; it missed fivefold more cases compared with White women.[58] This disparity is attributed to the greater prevalence of leiomyomas and nonendometrioid histology; thus, the gold standard for symptomatic women will always be endometrial biopsy. In asymptomatic postmenopausal women having an ultrasonogram and stripe evaluation, one review–meta-analysis with almost 5,000 patients found that the mean prevalence of having a thickened endometrial stripe of 11 mm or greater was 25.5% (ranging from 2% to 67%). Further, within the total population, the prevalence of atypical hyperplasia or cancer was 2.4% (range 0.1–6.0%); notably, it was significantly higher only when the endometrial stripe was 11 mm or greater.[59] Additional modeling studies support an increased risk of endometrial carcinoma of 6.7% in asymptomatic patients with an endometrial thickness greater than 11 mm.[60,61]

Computed tomography scans are of limited utility in the initial evaluation of endometrial pathology and should not be used outside of staging purposes as needed for confirmed endometrial cancer. If abnormalities are incidentally found on computed tomography scans ordered for other reasons, an ultrasonogram or magnetic resonance imaging scan is almost always recommended for better characterization of endometrial pathology.

Magnetic resonance imaging is an excellent modality but should not supplant ultrasonography as the initial study given the cost, time, and need for contrast. Given this, magnetic resonance imaging is most often used to assess potential myometrial invasion or extrauterine disease for patients proceeding with fertility-sparing treatment options in the setting of endometrial cancer.

MANAGEMENT OPTIONS

The management strategy for atypical hyperplasia–EIN should take into account the patient's age, desire for future fertility, as well as individual medical comorbidities. As a reminder, if there is a diagnosis of EIC (considered a precursor to uterine papillary serous cancers), only definitive surgical management with a gynecologic oncologist should be offered.

Surgical Treatment Options

For patients with a uterus who have completed childbearing and have no medical contraindication to surgery, the standard of care for the treatment of atypical hyperplasia–EIN remains total extrafascial hysterectomy and bilateral salpingectomy with consideration of bilateral oophorectomy. Hysterectomy is generally completed through a minimally invasive surgical approach unless previous abdominal surgery or uterine size prevents completion of the surgery without a laparotomy or specimen morcellation. Support for the minimally invasive surgical approach is extrapolated from prospective evidence validating minimally invasive surgery in the surgical staging of endometrial cancer.[62] A vaginal approach may be considered; however, complete evaluation of the adnexa and potential need for lymphadenectomy preclude this as the standard approach to the treatment of atypical hyperplasia–EIN. Hysterectomy in this setting is both diagnostic and therapeutic–diagnostic in that final pathology can further define EIN compared with an invasive endometrial carcinoma, and therapeutic in that it removes the abnormal tissue and is curative for EIN.

Hysterectomy is supported by a prospective cohort study completed by the Gynecologic Oncology Group (GOG) of 302 women who presented with either simple or complex hyperplasia and went on to have a hysterectomy within 12 weeks of diagnosis. This study was designed with two primary endpoints: the reproducibility of the diagnosis of atypical hyperplasia as well as to determine the risk of concurrent invasive adenocarcinoma at the time of hysterectomy. It should be noted that this study used the previous nomenclature of atypical hyperplasia. The mean age of diagnosis in the patient population was 57, but 30% of patients were less than 50 at the time of hysterectomy. Biopsy and hysterectomy specimens were reviewed by GOG pathologists and evaluated for consensus. Interestingly, the three pathologists agreed on the diagnosis in only 40% of cases and there was lack of agreement with the original diagnosis from the enrolling institution. Importantly, 43% of patients were found to have an invasive adenocarcinoma at the time of hysterectomy. The majority of patients (80/123, 65%) with endometrial cancer had disease confined to the endometrium, but 43 cases had risk factors for metastatic disease including myometrial invasion (31%) and grade 2 or 3 histology (6.5%).[9]

Although the decision for oophorectomy seems like a relatively straightforward clinical decision, the nuances of the surgical management of EIN can be challenging in this patient population given the risk of concurrent endometrial carcinoma as well as the age of the patient, family history, potential risk for synchronous primary tumors, and other medical comorbidities. An informed discussion of the risks and benefits of ovarian preservation compared with oophorectomy should be clearly outlined with the patient preoperatively with a defined plan in the instance of endometrial carcinoma identified at the time of hysterectomy. Preoperative use of genetic counseling and testing for Lynch syndrome may also identify patients who would benefit from oophorectomy at the time of hysterectomy.

Lastly, given the higher-than-expected number of concurrent endometrial cancers in the GOG study, surgical intervention for EIN is now often performed by gynecologic oncologists (or by ob-gyns with oncology back-up) to enable either sentinel lymph node mapping or frozen section with selective lymphadenectomy based on intraoperative uterine factors. Despite the risk of concurrent endometrial cancer with a diagnosis of atypical hyperplasia–EIN, the majority of endometrial cancers associated with EIN are low-grade, early-stage lesions with an exceedingly overall low risk of lymphatic spread. Given this, routine pelvic and para-aortic lymphadenectomy would result in overtreatment for the overwhelming majority of patients with a preoperative diagnosis of atypical hyperplasia–EIN.

Sentinel lymph node mapping with biopsy is now standard of care in the surgical staging of endometrial cancer, but high-quality evidence is not available to support routine sentinel lymph node

mapping in cases with a preoperative diagnosis of atypical hyperplasia–EIN. Retrospective analysis of sentinel lymph node mapping in atypical hyperplasia–EIN cases showed that 53% of patients did have an endometrial carcinoma on final pathology. The majority of patients had stage IA disease and no patients had positive lymph nodes.[56] An additional retrospective study showed that sentinel lymph node mapping decreased the number of unnecessary full lymphadenectomies, but did not provide node positivity rates for EIN specifically.[63] A review of the Perspective database showed that approximately 6% of patients with EIN had sentinel lymph node mapping performed between 2012 and 2018, with rates increasing over the study period to 14%. There was no increased rate of complications for patients who had sentinel lymph node mapping, but there was an associated increased cost.[64] Given this, intraoperative frozen section and subsequent use of uterine factors to help guide selective lymphadenectomy is an alternative in this patient population to maximize outcomes and minimize unnecessary additional procedures until further evidence is available. This option also has limitations including increase time in the operating room and frequent discordance of frozen and final pathology reports. A last option is to perform the hysterectomy and simply base any further interventions on the final pathologic results.

Nonsurgical Treatment Options

Appropriately counseled patients who desire future fertility, are medically inoperable, or refuse definitive treatment with hysterectomy are candidates for hormonal therapy with an LNG-IUD or systemic progesterone therapy.[65] There are no expert evidence-based guidelines to outline the appropriate candidates and subsequent evaluation in the conservative management of patients with atypical hyperplasia–EIN; however, the NCCN does provide expert guidance for the conservative management of low-grade endometrial cancers and clinical guidance can be extrapolated for the EIN patient population (Uterine Neoplasms, Version 1.2022, nccn.org).

Initial sampling should include at least D&C to ensure adequate sampling of the endometrium. In many cases, if the plan includes use of an LNG-IUD, this can be placed at the time of D&C. Expert guidance from the American College of Obstetricians and Gynecologists suggests consideration of hysteroscopy in addition to D&C to visualize any discrete lesions for optimal sampling.[66] Although there are no specific recommendations for imaging in atypical hyperplasia–EIN, a pelvic ultrasonogram is commonly obtained during the clinical evaluation of these patients.

The decision for route of administration of hormonal therapy may vary based on patient preference, compliance, and side-effect profile.[65,67] Evidence for the efficacy of hormonal therapy generally combines atypical hyperplasia–EIN with grade 1 endometrioid adenocarcinomas of the uterus, although response rates are typically better and more durable in patients with hyperplasia compared with carcinoma.[68,69] A large systemic review including 391 patients with hyperplasia or grade 1 endometrial cancer from a total of 45 studies evaluated response to progestins, although specific progestin, route of administration (systemic vs intrauterine delivery) and dosage varied across studies. Overall, 78% of patients demonstrated a response to therapy and 53% of patients had a complete response. Patients with hyperplasia had a significantly higher complete response compared with patients with a low-grade endometrial carcinoma (65% vs 48%) with a median time to complete response of 6 months. Forty-one percent of patients with hyperplasia went on to achieve pregnancy.[70]

Megestrol is the preferred systemic progestin therapy and is usually prescribed as 160 mg/day in divided doses every 6 or 12 hours; however, multiple formulations have been evaluated (Table 2). Megestrol is associated with a response rate of 80% in the treatment of complex atypical hyperplasia.[71,72] However, compliance with systemic progestins and megestrol in particular may be hindered due to the side-effect profile, including weight gain, nausea, mood changes, risk of venous thromboembolism, and irregular vaginal bleeding. These side effects, most notably weight gain, can be difficult to manage in a population of patients with obesity. Indeed, retrospective evaluation shows that approximately half of patients taking oral anticancer medications, including hormonal therapy, report nonadherence.[73]

Given side effects and decreased compliance with systemic progestin therapy, local therapy with an LNG-IUD has emerged as the hormonal treatment strategy of choice in the fertility-sparing management of atypical hyperplasia–EIN. Response rates to local therapy of the endometrium have been evaluated in the retrospective and prospective setting with encouraging results. In a multicenter trial in Norway, 170 women with endometrial hyperplasia were randomized to one of

Table 2. Hormonal Treatment Options for Endometrial Intraepithelial Neoplasia

Hormonal Agent	Dosage and Length
Medroxyprogesterone acetate	10–20 mg/d (preferred) or cyclic 12–14 d/mo
Depot medroxyprogesterone	150 mg intramuscularly every 3 mo
Micronized vaginal progesterone	100–200 mg/d (preferred) or cyclic 12–14 d/mo
Megestrol acetate	80 mg twice/d (standard dose), range 40–200 mg/d
Levonorgestrel intrauterine system	52 mg in steroid reservoir over 5 y

Modified from Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Obstet Gynecol 2012;120:1160–75. doi: 10.1097/aog.0b013e31826bb121

three treatment arms: LNG-IUD, oral medroxyprogesterone acetate (MPA) 10 mg administered 10 days per cycle, or continuous oral MPA 10 mg/day for 6 months. At the end of 6 months, women in the LNG-IUD group (100%) and the continuous MPA group (96%) showed the highest complete response rates compared with the cyclical MPA group (69%).[74] Additionally, a 12-year comparative cohort study followed 344 patients with endometrial hyperplasia who received conservative management with progestins for atypical hyperplasia. For the group of women treated with LNG-IUD (n=250), 94.8% achieved regression of hyperplasia compared with 84% of women treated with oral progestins. Of note, the patients with BMIs of 35 or higher were most likely to have a relapse of hyperplasia or fail to regress to a normal endometrium.[75] Pal and colleagues report an 80% response rate with LNG-IUD in patients with complex atypical hyperplasia. In this cohort, BMI was not related to response to IUD; however, increased uterine size was a marker of nonresponse.[76] Most recently, a phase II prospective trial of the LNG-IUD in women with complex atypical hyperplasia and early-stage endometrial cancer reported a response rate of 90.6% in patients with complex atypical hyperplasia with a primary endpoint of pathologic response at 12 months. Quality of life was not significantly impaired. From a pathology standpoint, the majority of responders had evidence of progesterone effect on biopsy by 3 months, whereas only 25% of nonresponders demonstrated pathologic progesterone effect.[77]

An important focus of future studies includes identifying markers for nonresponse to progesterone therapy in EIN as well as low-grade uterine cancer, and several prospective studies are ongoing to evaluate whether the addition of other targeted therapies may improve response rates in this patient population.[78] One retrospective analysis using the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) algorithm in patients with endometrial cancer or EIN treated with LNG-IUD evaluated whether Cancer Genome Atlas molecular classifications were predictive for treatment nonresponse.[79] Interestingly, 6.9% were *p53* mutated consistent with a copy number high tumors, which would not be generally expected in this generally indolent and grade 1 tumor type.[80] Prospective studies of women with hyperplasia are needed for further validation. It is interesting to note that postmenopausal women are less likely to respond to progesterone therapy. In one retrospective study of 41 postmenopausal women with atypical hyperplasia and endometrial carcinoma who were treated with the LNG-IUD, a complete response was noted in only 50%. Additionally, 4 of 18 patients (22%) with a complete response later experienced relapse of hyperplasia or cancer.[81]

It is paramount that patients understand that conservative therapy with systemic or local hormonal therapy requires close surveillance with frequent follow-up visits and repeat biopsies to monitor treatment response. There are no evidence-based guidelines for frequency and length of surveillance with hormonal therapy in EIN; however, there is consensus that regular sampling for at least the first year is needed to document response, and the follow-up schedule can be extrapolated from NCCN guidelines for low-grade endometrial cancers (Uterine Neoplasms, Version 1.2022). In general, response to hormonal therapy can be seen by 6 months of treatment. Endometrial evaluation every 3–6 months with endometrial biopsy or D&C is recommended. If there is complete response by 6–12 months, pregnancy should be encouraged. If the patient is not ready to proceed with becoming pregnant, progestin therapy should be continued. If hormonal therapy is used for a fertility-sparing indication, completion hysterectomy and bilateral salpingectomy with or without oophorectomy should be recommended after childbearing is complete. If no

treatment response is seen at 6–12 months of hormonal therapy on pathologic review, hysterectomy should be very strongly considered.

Metformin has also entered the practicing obgyns' arsenal for treatment of both PCOS and infertility and it has the additional benefit of having antiproliferative effects that potentially can also serve to function as an anticancer agent and may also function to sensitize cells to progestin.[35] Although several small studies found associations between metformin use and improved endometrial hyperplasia risk and outcomes, a 2017 Cochrane Review concluded that the, "evidence is insufficient to support or refute the use of metformin alone or in combination with standard therapy–specifically megestrol acetate compared with megestrol acetate alone, for treatment of endometrial hyperplasia."[82] Yet, almost simultaneously, another 2017 review and meta-analysis concluded that metformin, "may assist in the reversal of atypical endometrial hyperplasia to normal endometrial histology, in the reduction of cell proliferation biomarkers implicated in tumor progression, and in the improvement of overall survival in endometrial cancer."[83] Since those reviews were published, a further randomized controlled trial comparing megestrol with megestrol/metformin in atypical hyperplasia and patients with endometrial cancer in China demonstrated significantly improved complete response rates at 24 weeks (39.6 vs 20%; P=.04) in the 102 patients with atypical endometrial hyperplasia.[84] Lastly, a 2021 review concluded again that there were similar remission rates for reproductive-aged women with atypical endometrial hyperplasia or early endometrial cancer when treated with progestin and metformin therapy compared with progestin therapy alone, but did assert that the combination was associated with lower relapse rates.[85] Metformin could prove to be an additional option for those pursuing hormonal and nonsurgical therapy in terms of treatment and potentially could assist in prevention if other indications exist for use (eg, diabetes).

CONCLUSION

Atypical endometrial hyperplasia–EIN is an incredibly common clinical entity, and every ob-gyn should be well versed in recognizing high risk women to allow implementation of risk-reduction strategies in addition to being facile with diagnosis, treatment options and outcomes for all women to decrease the endometrial cancer burden in the population.

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