

**Detecting Concurrent Carcinoma****RECOMMENDATION STATEMENT**

Gynecologists should attempt to exclude concurrent carcinoma in individuals with a working diagnosis of EIN/AEH. Hysteroscopic examination with further sampling of the endometrium is the most accurate method for detecting a concurrent carcinoma.

**SUPPORTING EVIDENCE****Category I***Systematic Reviews*

Doherty 2020: In pooled analysis of 11 studies of atypical hyperplasia, the pooled prevalence of concurrent endometrial cancer was 32.6% (95%CI: 24.1%, 42.4%) while no studies evaluated concurrent cancer in nonatypical hyperplasia. The risk of progression to cancer was high in atypical hyperplasia (n=5 studies, annual incidence rate=8.2%, 95%CI: 3.9%,17.3%) and only one study reported on nonatypical hyperplasia (annual incidence rate= 2.6%,95%CI: 0.6%,10.6%).

**Category II***Observational Studies*

Bedner 2007: Hysteroscopy and biopsy was followed by dilatation and curettage in 442 patients with abnormal perimenopausal bleeding or sonographically revealed endometrial pathology. Of these 442 patients, 64 were cases of endometrial polyps, 60 cases of endometrial hyperplasia, and 49 cases of endometrial cancer. Hysteroscopy left just 4 cases of endometrial pathology undiagnosed as opposed to 21 cases using dilatation and curettage.

Costales 2014: Fifty-five of the 150 patients (36.7%) had an incidental endometrial carcinoma at the time of hysterectomy. Among patients with a preoperative office biopsy compared to dilation and curettage, the rate of an incidental finding of cancer was 43.5% and 28.1%, respectively (p=0.054). Given the high rates of underlying endometrial cancer and the potential need for lymphadenectomy, care for patients with a preoperative diagnosis of CAH desiring definitive management with hysterectomy should be referred to a gynecologic oncologist.

Dolanbay 2015: A total number of 82 women; 48 (58.5%) postmenopausal and 34 (41.5%) premenopausal were determined to have EH on histopathological evaluation of

**Category III**

endometrial tissues obtained by endometrial curettage performed for evaluation of various bleeding abnormalities. Mean-age of patients was  $54.6 \pm 8.7$ . Among 82 patients found to have EH on curettage specimens 39 had EC on hysterectomy specimens (39/82. 47.5%). Consequently, we determined well differentiated endometrial adenocarcinoma in 66% (35/53) of the patients with hyperplasia with atypia (17/35. 48.5% Grade 1 and 18/35.51.4% Grade 2) and 13.7% (4/29) hyperplasia without atypia (4/4.100% Grade 1).

Dueholm 2020: Addition of HY<sub>biopsy</sub> may improve diagnosis when preoperative OES identifies AH or is insufficient for explicit diagnosis of tumor type and grade. However, there is limited benefit of the addition of HY<sub>biopsy</sub> in the presence of definite diagnosis of grade 1–2 endometrioid tumors by OES.

Suh-Burgmann 2009: Dilation and curettage lowered the risk of unexpected cancer compared with biopsy, but 18% of women still had invasive cancer found at hysterectomy. The risk of unexpected cancer is strongly related to age. Dilation and curettage can help detect cancer preoperatively but is not reliable for excluding cancer.

Trimble 2006: The prevalence of endometrial carcinoma in patients who had a community hospital biopsy diagnosis of AEH was high (42.6%). When considering management strategies for women who have a biopsy diagnosis of AEH, clinicians and patients should take into account the considerable rate of concurrent carcinoma.

## Surgical Management

### RECOMMENDATION STATEMENT

- Hysterectomy is the definitive treatment for EIN/AEH. Gynecologists should not perform supracervical hysterectomy for the treatment of EIN/AEH.
- Gynecologists should not perform endometrial ablation (thermal or electrocautery) for EIN/AEH due to high persistence and recurrence rates, as well as potential difficulty in evaluating future bleeding episodes.

### SUPPORTING EVIDENCE

ACOG Committee Opinion No. 774: Opportunistic salpingectomy as a strategy for epithelial ovarian cancer prevention

- Counseling women who are undergoing routine pelvic surgery about the risks and benefits of salpingectomy should include an informed consent discussion about the role of oophorectomy and bilateral salpingo-oophorectomy

Trimble 2012: Management of Endometrial Precancers (Society of Gynecologic Oncology Clinical Practice Committee)

- Where clinically appropriate, total hysterectomy is curative of AEH/EIN and provides a definitive standard for assessment of a concurrent carcinoma. (Classification AI)
- Supracervical hysterectomy is unacceptable for AEH/ EIN treatment. (Classification AII)
- If hysterectomy is performed for AEH/EIN, intraoperative assessment of the uterine specimen for occult carcinoma is preferred. (Classification AII) When done, this should be directed by a qualified pathologist and include gross examination with or without frozen section. (Classification BIII)
- Endometrial ablation (thermal or electrocautery) is not recommended for AEH/EIN treatment. (Classification DII)

#### Category I

##### *Systematic Reviews*

Doherty 2020: In pooled analysis of 11 studies of atypical hyperplasia, the pooled prevalence of concurrent endometrial cancer was 32.6% (95%CI: 24.1%, 42.4%) while no studies evaluated concurrent cancer in nonatypical hyperplasia. The risk of progression to cancer was high in atypical hyperplasia (n=5 studies, annual incidence rate=8.2%, 95%CI: 3.9%,17.3%) and only one study reported on nonatypical hyperplasia (annual incidence rate= 2.6%,95%CI: 0.6%,10.6%).

#### Category II

##### *Observational Studies*

Attard Montalto 2008: Intraoperative frozen section is a useful procedure to identify poor prognostic pathological factors as well as to diagnose endometrial cancer in patients undergoing hysterectomy for a preoperative biopsy diagnosis of atypical hyperplasia.

Chaiken 2022: In our cost-effectiveness model, hysterectomy with a gynecologic-oncologist for patients with EIN was associated with cost savings and increased quality-adjusted life years. Our study supports that patients undergoing hysterectomy for EIN at institutions using Mayo criteria to determine need for lymphadenectomy may benefit from surgery with a gynecologic-oncologist rather than a general gynecologist to reduce costs and adverse events associated with a second surgery.

Dolanbay 2015: A total number of 82 women; 48 (58.5%) postmenopausal and 34 (41.5%) premenopausal were

#### Category III

determined to have EH on histopathological evaluation of endometrial tissues obtained by endometrial curettage performed for evaluation of various bleeding abnormalities. Mean-age of patients was  $54.6 \pm 8.7$ . Among 82 patients found to have EH on curettage specimens 39 had EC on hysterectomy specimens (39/82, 47.5%). Consequently, we determined well differentiated endometrial adenocarcinoma in 66% (35/53) of the patients with hyperplasia with atypia (17/35, 48.5% Grade 1 and 18/35, 51.4% Grade 2) and 13.7% (4/29) hyperplasia without atypia (4/4, 100% Grade 1).

Suh-Burgmann 2009: Dilation and curettage lowered the risk of unexpected cancer compared with biopsy, but 18% of women still had invasive cancer found at hysterectomy. The risk of unexpected cancer is strongly related to age. Dilation and curettage can help detect cancer preoperatively but is not reliable for excluding cancer.

## Nonsurgical Management

### RECOMMENDATION STATEMENT

- Clinicians should recommend progestational agents as treatment for EIN/AEH for patients in whom hysterectomy is not an option.
- Data on the superiority of either oral or intrauterine progestational agents are lacking, though limited data suggests that intrauterine progestational administration may be associated with a higher rate of disease regression when compared with oral administration in patients with EIN/AEH.
- There is insufficient evidence to recommend any one formulation of oral progestational agent over another.

### SUPPORTING EVIDENCE

#### Category I

##### *Systematic Reviews*

Baker 2012: There is a lack of high-quality evidence for the efficacy of progestin in CAH or EC. The available evidence however suggests that treatment with oral or intrauterine progestin is similarly effective. The risk of progression during treatment is small but longer follow-up is required.

Gallos 2010: There were 24 observational studies (1001 women), of low methodologic quality, evaluating the outcome of regression of endometrial hyperplasia with oral progestogens or levonorgestrel-releasing intrauterine system. Meta-analysis showed that oral progestogens achieved a lower pooled regression rate compared with levonorgestrel-releasing intrauterine system for complex (pooled rate, 66% vs 92%;  $P < .01$ ) and atypical hyperplasia (pooled rate, 69% vs 90%;  $P .03$ ). There was no statistical difference in simple hyperplasia (pooled rate, 89% vs 96%;  $P .41$ )

Gallos 2012: 34 observational studies evaluating the regression, relapse, and live birth rates of early-stage EC (408 women) and ACH (151 women) with fertility-sparing treatment. Fertility-sparing treatment for EC achieved a pooled regression rate of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28%. For ACH the pooled regression rate was 85.6%, a relapse rate of 26%, and a live birth rate of 26.3%. Twenty women were diagnosed with ovarian cancer (concurrent or metastatic) during follow-up (3.6%) and 10 progressed to higher than stage I EC (1.9%) from which 2 women died.

#### Category II

##### *Observational Studies*

Barr 2021: We assessed uptake of bariatric surgery; weight lost during progestin treatment; and the impact of more than 10% total body weight loss on progestin treatment response at 12 months. Forty-three women (61%) responded to progestin, while 23 (32%) showed stabilized and 5 (7%) progressive disease. Response at 12 months was not predicted by age or baseline BMI, but women who lost more than 10% of their total body weight were more likely to respond to progestin than those who did not (adjusted odds ratio 3.95; 95% CI 1.3, 12.5;  $P = 0.02$ ).

Cholakian 2016: Oral progestin therapy for conservative treatment of young EMC/CAH survivors is associated with increased weight gain, especially when megestrol acetate is utilized. Utilization of LNG-IUD may result in less weight gain.

Gallos 2013a: Relapse of hyperplasia occurred in 13.7% (21/153) of women treated with LNG-IUS compared with 30.3% (20/66) of women treated with oral progestogens [adjusted odds ratio (OR) = 0.34, 95% confidence interval (CI): 0.17 –0.7,  $P = 0.005$ ]. Relapse rates over long-term follow-up were lower for complex non-atypical hyperplasia compared with atypical hyperplasia for both LNG-IUS (12.7%, 18/142 versus 27.3%, 3/11, respectively;  $P \leq 0.001$ ) and oral progestogens (28.3%, 17/60 versus 50%, 3/6, respectively;  $P \leq 0.001$ ).

Gallos 2013b: The follow-up rate was 95.3%. The mean length of follow-up in the two groups was 66.9+SD 35.1 months for the LNG-IUS and 87.2+SD 45.5 months for the oral progestogen

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Gunderson 2012: Based on this systematic review of the contemporary literature, endometrial hyperplasia has a significantly higher likelihood of response (66%) to hormonal therapy than grade 1 endometrial carcinoma (48%). Disease persistence is more common in women with carcinoma (25%) compared to hyperplasia (14%). Reproductive outcomes do not seem to differ between the cohorts.

#### *Randomized Controlled Trials*

Fang 2021: Before treatment, there was no significant difference in PBAC score and endometrial thickness between patients with AEH or EEC in the con group and those in the com group, but after 3 months and 6 months of treatment, the com group got a better PBAC score and better changes of endometrial thickness than the con group, and the incidence of adverse drug reactions in the com group was also significantly lower than that in the con group.

Janda 2021: Ninety-six patients were diagnosed with endometrial adenocarcinoma (EAC) (58%) and 69 patients with endometrial hyperplasia with atypia (EHA) (42%). Thirty-five participants were randomized to OBS (observation), 36 to WL (weight loss) and 47 to M (metformin) (10 patients were withdrawn). After 6 months the rate of pCR was 61% (95% CI 42% to 77%) for OBS, 67% (95% CI 48% to 82%) for WL and 57% (95% CI 41% to 72%) for M. Across the three treatment groups, the pCR was 82% and 43% for EHA and EAC, respectively.

Orbo 2014: After 6 months all three treatment regimens showed significant effect when the outcome was evaluated as therapy response or not ( $P < 0.001$ ). Responses were obtained for all the women in the LNG-IUS group (53/53, 95% CI 0.93–1.0) and for 96% of the women in the continuous oral group (46/48, 95% CI 0.86–0.99). Only 69% of the women in the cyclic oral group were responders (36/52, 95% CI 0.55–0.81). Adverse effects were relatively common with minimal differences between therapy groups.

group. Regression of hyperplasia was achieved in 94.8% (237/250) of patients with the LNG-IUS compared with 84.0% (79/94) of patients treated with oral progestogens (adjusted odds ratio (OR) = 3.04, 95% CI 1.36 –6.79,  $P = 0.001$ ). Hysterectomy rates were lower in the LNG-IUS group during follow-up (22.1, 55/250 versus 37.2%, 35/94, adjusted OR = 0.48, 95% CI 0.28 – 0.81,  $P < 0.004$ ). Endometrial cancer was diagnosed in 8 (33%) women who had hysterectomy because of a failure to regress to normal histology during follow-up ( $n = 24$ ).

Mandelbaum 2020: Our study suggests that local therapy with the levonorgestrel-releasing intrauterine device may be more effective than systemic therapy for women with complex atypical hyperplasia who opt for nonsurgical treatment, particularly in morbidly obese women. Shifts in treatment paradigm during the study period toward increased levonorgestrel-releasing intrauterine device use also led to improved complete response rates despite increasing rates of obesity.

Westin 2021: The Levonorgestrel Intrauterine Device has substantial activity in complex atypical hyperplasia and grade 1 endometrioid endometrial cancer, with a modest proportion demonstrating upfront progesterone resistance. Potential biomarkers were identified that may correlate with resistance to therapy, further exploration is warranted.

## Follow-up

### RECOMMENDATION STATEMENT

- For those initially treated with progestational agents, gynecologists should perform repeat histologic assessment for response to treatment for EIN/AEH within 3 to 6 months.
- Following initial progestin treatment, gynecologists may consider long-term maintenance therapy with progestational agents for those patients with continuing risk factors for endometrial cancer.

### SUPPORTING EVIDENCE

Trimble 2012: Management of Endometrial Precancers (Society of Gynecologic Oncology Clinical Practice Committee)

- Sensitive and accurate diagnosis of true premalignant endometrial lesions can reduce likelihood of developing invasive endometrial cancer. (Classification AII)
- 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)
- Diagnostic tissue sampling may be successfully accomplished in a number of preferred tissue formats, including curettage and biopsy (Pipelle). (Classification AII) Devices that yield crushed (jawed devices), cauterized (hot loops), or very small (jawed devices) samples are unacceptable. (Classification DIII) 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)
- Exclusion of concurrent carcinoma is a necessary diagnostic goal of the patient newly diagnosed with AEH or EIN. (Classification AII)
- Where clinically appropriate, total hysterectomy is curative of AEH/EIN and provides a definitive standard for assessment of a concurrent carcinoma. (Classification AI)
- If hysterectomy is performed for AEH/EIN, intraoperative assessment of the uterine specimen for occult carcinoma is preferred. (Classification AII) When done, this should be directed by a qualified pathologist and include gross examination with or without frozen section. (Classification BIII)
- 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)
- 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)

#### Category I

##### *Systematic Reviews*

Gallos 2012: 34 observational studies evaluating the regression, relapse, and live birth rates of early-stage EC (408 women) and ACH (151 women) with fertility-sparing treatment. Fertility-sparing treatment for EC achieved a pooled regression rate of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28%. For ACH the pooled regression rate was 85.6%, a relapse rate of 26%, and a live birth rate of 26.3%. Twenty women were diagnosed with ovarian cancer (concurrent or metastatic) during

#### Category II

##### *Observational Studies*

Gallos 2013c: This study found that poor expression of estrogen receptor (ER) and progesterone receptor (PR) is weakly associated with persisting endometrial hyperplasia and COX-2, Mh1, and Bcl-2 expressions are not predictive. None of the biomarkers is predictive for relapse in women with endometrial hyperplasia treated with LNG-IUS.

Gunderson 2014: In women with complex atypical hyperplasia or well differentiated endometrioid adenocarcinoma of the uterus, the overall response rate to progestin therapy was 65%;

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follow-up (3.6%) and 10 progressed to higher than stage I EC (1.9%) from which 2 women died.

Gunderson 2012: Based on this systematic review of the contemporary literature, endometrial hyperplasia has a significantly higher likelihood of response (66%) to hormonal therapy than grade 1 endometrial carcinoma (48%). Disease persistence is more common in women with carcinoma (25%) compared to hyperplasia (14%). Reproductive outcomes do not seem to differ between the cohorts.

Koskas 2014: The 12- and 24-month recurrence probabilities were 9.6% and 29.2%, respectively. In multivariate analysis, none of the factors studied was associated with higher recurrence probability. Twenty-two studies totaling 351 patients were used to assess pregnancy rate; 111 subjects (32%) had one pregnancy or more. In multivariate analysis, none of the factors were associated with pregnancy probability. Fertility-sparing management should not be contraindicated in older patients with previous infertility or obesity.

#### *Randomized Controlled Trials*

Orbo 2016: Histological relapse was observed in 55/135 (41%) women who had an initial complete treatment response. The relapse rates were similar in the three therapy groups ( $P = 0.66$ ). In the multivariable analyses relapse was dependent on menopausal status ( $P = 0.0005$ ) and estrogen level ( $P = 0.0007$ ).

pretreatment estrogen/progesterone receptor status did not predict response to treatment.

Lacey 2010: Cumulative 20-year progression risk among women who remain at risk for at least 1 year is less than 5% for nonatypical EH but is 28% for AH.

Mandelbaum 2020: Our study suggests that local therapy with the levonorgestrel-releasing intrauterine device may be more effective than systemic therapy for women with complex atypical hyperplasia who opt for nonsurgical treatment, particularly in morbidly obese women. Shifts in treatment paradigm during the study period toward increased levonorgestrel-releasing intrauterine device use also led to improved complete response rates despite increasing rates of obesity.

Mentrikoski 2012: the presence of cytologic atypia on 6-month posttreatment follow-up biopsy was strongly associated with treatment failure. In the current study, 7 cases showed progression or persistence of disease on the final available specimen. The only cases showing retained cytologic atypia after at least 6 months of treatment were these aforementioned 7 cases which showed disease progression or persistence; this indicates that persistence of cytologic atypia is strongly linked to treatment failure.

Mitsuhashi 2019: MPA plus metformin is efficacious in terms of RFS and post treatment conception. Moreover, metformin may be more efficacious for patients with BMI  $\geq 25$  kg/m<sup>2</sup>.

Pal 2018: In this retrospective case series, non-response following six months of treatment with the LNG-IUD was associated with increased uterine diameter (9.3 vs. 8 cm).

Sletten 2019: Pre-treatment endometrial expression of PR-A and PR-B is a valuable predictor of relapse in endometrial hyperplasia

Vaugon 2021: The probability of 2-year recurrence was 37.7% (SD 10.41%) in the IVF group and 55.7% (SD 14.02%) in the no IVF group ( $P=0.13$ ). Obesity, nulliparity, polycystic ovary syndrome, age and tumoral characteristics were not associated with recurrence. Pregnancy was a protective factor for recurrence, with 2-year recurrence probabilities of 20.5% and 62.0% in the pregnancy and no pregnancy groups, respectively ( $P=0.002$ , 95% CI 0.06–0.61). In contrast, the number of cycles, maximum serum estradiol concentration during ovarian stimulation, ovarian stimulation protocol, total dose of gonadotrophin administered and thickness of the endometrium showed no significant differences in terms of the risk of recurrence in the IVF subgroup.



Westin 2021: The Levonorgestrel Intrauterine Device has substantial activity in complex atypical hyperplasia and grade 1 endometrioid endometrial cancer, with a modest proportion demonstrating upfront progesterone resistance. Potential biomarkers were identified that may correlate with resistance to therapy, further exploration is warranted.

## Counseling Patients on Lifestyle Modifications

### RECOMMENDATION STATEMENT

Gynecologists and other clinicians should counsel patients that lifestyle modification resulting in weight loss and glycemic control can improve overall health and may decrease the risk of EIN/AEH and endometrial cancer.

### SUPPORTING EVIDENCE

#### Category I

##### *Systematic Reviews*

Linkov 2008: Obesity and inactivity are two of the major risk factors associated with the development of endometrial cancer and endometrial hyperplasia. Other modifiable risk factors include dietary habits, exercise and the use of hormonal therapy. Similar factors, along with cancer biomarkers, may play an important role in the early detection of endometrial cancer and survival after the diagnosis. The majority of these factors fit well with the unopposed estrogen theory. Diet and exercise programs are currently not integrated into a standard treatment programs for patients with endometrial hyperplasia or endometrial cancer.

Raffone 2020: Twelve retrospective studies with 1579 EH were included. Diabetes mellitus showed significant association with the presence of cancer coexistent with endometrial hyperplasia (OR = 1.96; 95% CI, 1.07–3.60; p = 0.03)

##### *Randomized Controlled Trials*

Haggerty 2016: A technology-based weight loss intervention is feasible in women with type I endometrial cancer/hyperplasia. Both interventions produced weight loss, although more person-to-person contact produced more significant outcomes. Reductions in expression of IL-2 were related to weight loss.

#### Category II

##### *Observational studies*

Barr 2021: We assessed uptake of bariatric surgery; weight lost during progestin treatment; and the impact of more than 10% total body weight loss on progestin treatment response at 12 months. Forty-three women (61%) responded to progestin, while 23 (32%) showed stabilized and 5 (7%) progressive disease. Response at 12 months was not predicted by age or baseline BMI, but women who lost more than 10% of their total body weight were more likely to respond to progestin than those who did not (adjusted odds ratio 3.95; 95% CI 1.3, 12.5; P = 0.02).

Haggerty 2017: Eighty-one women with early stage (71.6% stage I) and grade (41.7% grade 1) disease completed the survey. The median BMI was 35.4kg/m (IQR32.2–43.5kg/m) and the average age was 59.3 (SD11.1) years. 76.25% of women were unable to categorize their BMI correctly and 86.9% of those incorrectly underestimated their BMI category. One-third (35.9%) were unaware of any association between obesity and endometrial cancer and 33.3% responded that obesity decreased or did not significantly increase the risk of endometrial cancer. 59% expressed interest in a weight loss intervention.

Jernigan 2015: Weight-loss counseling is well received by these women. After being offered bariatric referral, only 17% comply, but most women (59%) subsequently initiate a weight loss attempt. Referrals should be offered early in the course of cancer care to maximize acceptance.

#### Category III

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