

Management of endometrial hyperplasia

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Endometrial hyperplasia (EH) - Importance

- ❑ Cause of AUB**
- ❑ Risk factor for the development of endometrial cancer (EC)**

Endometrial hyperplasia (EH) - Definition

- ❑ EH is an abnormal proliferation of the endometrium, greater than the normal proliferation that occurs during the menstrual cycle**
- ❑ In EC, prolonged estrogenic stimulation plays a causal role**

Epidemiology of EH

- ❑ Women aged 18 to 90 over an 18-year period , the overall incidence of EH was **133 per 100,000 woman-years**
- ❑ The diagnosis is most commonly made in woman age 50 to 54 years
- ❑ The incidence of simple and complex EH without atypia were highest in women age 50 to 54 years
- ❑ **The rate of AEH was highest in women age 60 to 64 (56 per 100,000 woman-years)**

❑ Reed SD, Newton KM, Clinton WL, et al. Incidence of endometrial hyperplasia. Am J Obstet Gynecol 2009; 200:678.e1.

Risk faktors for EH

- ❑ Same as those for EC**
- ❑ Obesity, unopposed estrogen, DM, and nulliparity**

Clinical presentation

- EH typically presents with AUB and is most common in women who are postmenopausal and with increasing age in premenopausal women**
- Occasionally, women with no abnormal uterine bleeding present with abnormal findings on cervical cytology or TVUS findings in postmenopausal women**

Evaluation of women with suspected EH

- ❑ Physical and pelvic exam**
- ❑ TVUS to exclude another etiology of AUB or to assess endometrial thickness in postmenopausal women**
- ❑ Evaluation is the same as for women with suspected EC**

Diagnosis of endometrial precancer

❑ Hysteroscopy does not significantly increase detection of occult cancers

- ❑ Garuti G, et al. Hysteroscopically targeted biopsies compared with blind samplings in endometrial assessment of menopausal women taking tamoxifen for breast cancer. *J Am Assoc Gynecol Laparosc.* 2004;11(1):62–67

❑ Moreover, not all precancerous lesions can be visualized by hysteroscopy

- ❑ Elliott J, Connor ME, Lashen H. The value of outpatient hysteroscopy in diagnosing endometrial pathology in postmenopausal women with and without hormone replacement therapy. *Acta Obstet Gynecol Scand.* 2003;82(12):1112–1119

❑ Current diagnostic schema should include assessment of sample adequacy

- ❑ Allison KH, et al. Diagnosing endometrial hyperplasia: why is it so difficult to agree? *Am J Surg Pathol.* 2008;32(5):691–698

Diagnosis of EH

- ❑ **AUB symptoms may be due to an etiology other than EH**
- ❑ **TVUS, sonohysterography, or diagnostic hysteroscopy should be performed to exclude other lesions (myomas, endometrial polyp)**

Endometrial thickness and prediction of EH in patients with PCOS

- BMI is predictive of sonographic endometrial stripe thickness, which in turn is predictive of EH in patients with PCOS
- For every 1-mm increase in endometrial stripe, the odds ratio of hyperplasia increased by 1.48 (95% confidence interval, 1.04-2.10)
- McCormick BA, Wilburn RD, Thomas MA, Williams DB, Maxwell R, Aubuchon M. Endometrial thickness predicts endometrial hyperplasia in patients with polycystic ovary syndrome. *Fertil Steril*. 2011, 95(8):2625-7

Endometrial thickness and prediction of EH

- ❑ Evaluation of endometrial sampling in asymptomatic, bleeding-free postmenopausal women with endometrial thickness greater or equal to 5 mm
- ❑ Retrospective study, mean endometrial stripe thickness was 8.7 mm
- ❑ 5 cases of EC (0.9%) and 65 (12.2%) cases of simple/complex atypical hyperplasia were diagnosed
- ❑ 106 investigations were performed to detect one case of EC

- ❑ Saatli B, Yildirim N, Olgan S, Koyuncuoglu M, Emekci O, Saygılı U. The role of endometrial thickness for detecting endometrial pathologies in asymptomatic postmenopausal women. Aust N Z J Obstet Gynaecol. 2014 ;54(1):36-40

The time course from a diagnosis of EH to EC

- ❑ It is not well established
- ❑ The case control study reported that the average time to diagnosis of cancer was six years in women with all types of EH
- ❑ Lacey JV Jr, Sherman ME, Rush BB, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol* 2010; 28:788

EC risk among women EH: the 34-year experience

- ❑ Classifying EH as ,simple hyperplasia (SH) vs complex hyperplasia (CH), and nuclear atypia (simple atypical hyperplasia (SAH) vs complex atypical hyperplasia (CAH)
- ❑ **AH significantly increased carcinoma risk (RR=14)**
- ❑ Risk was highest 1-5 years after AH
- ❑ Remained elevated 5 or more years after AH
- ❑ Progression risks for SH (RR=2.0) and CH (RR=2.8) were substantially lower
- ❑ Lacey JV Jr, Ioffe OB, Ronnett BM, Rush BB, et al, Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. Br J Cancer. 2008;98(1):45-53

Progestin treatment for women with the low risk of progression to EC

Treatment	Dosage and length
MPA	10-20 mg daily or cyclic 12-14 d/mo
DMPA	150 m IM every 3 month
Micronized vaginal progesterone	100-200 mg daily or cyclic 12-14 d/mo
LNG containig IUD	1-5 y

Progestin treatment for women with the low risk of progression to EC

□ Regression of hyperplasia

- 80–90% of subjects receiving MPA, 10 mg daily for 12–14 days per month**

Effect of LNG IUD with oral MPA on simple EH and fertility preservation

- ❑ Endometrial thickness was reduced in both groups ($p < 0.001$), but further reduction in LNG group was seen
- ❑ Side-effects of MPA were more and reached significance ($p < 0.003$)
- ❑ The rate of satisfaction with LNG was higher than MPA ($p < 0.048$)
- ❑ Karimi-Zarchi M, Dehghani-Firoozabadi R, Tabatabaie A, Dehghani-Firoozabadi Z, et al, A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation. Clin Exp Obstet Gynecol. 2013;40(3):421-4

Identification of precursor lesions of EAC

- The classification systems most widely used
 - Use of architectural features and cytologic atypia, termed atypical endometrial hyperplasia (AEH)
 - Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer*. 1985;56(2):403–412
 - Use of quantitative morphologic measures associated with clonality, and terminology, endometrial intraepithelial neoplasia (EIN) is defined
 - Mutter GL, et al. Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. *J Pathol*. 2000;190(4):462–469
 - Mutter GL, et al. Benign endometrial hyperplasia sequence and endometrial intraepithelial neoplasia. *Int J Gynecol Pathol*. 2007;26(2):103–114

Endometrial precancer Classification Systems WHO94

	EAC Risk %
Simple hyperplasia without atypia	1
Complex hyperplasia without atypia	3
Simple atypical hyperplasia	8
Complex atypical hyperplasia	29

- Categories are descriptive in nature**
- Interpretation is subjective**
- Indicate poor reproducibility**
- Do not suggest specific management algorithms**

Endometrial precancer Classification Systems

EIN

Diameter	minimum 1 mm
Architecture	area of glands exceeds the area of stroma
Cytology	changed relative to background
Exclude mimics	polyps, secretory endometrium, effects of exogenous estrogen and cancer

EIN nomenclature

EIN nomenclature	Topography	Functional Category	Treatment
Unopposed Estrogens (EH)	Diffuse	Estrogen effect	Hormonal
EIN	Focal, later diffuse	Precancer	Hormonal or surgery
Cancer	Focal, later diffuse	Cancer	Surgery stage based

Endometrial precancer Classification Systems WH094 and EIN

- ❑ EIN diagnosis has been confirmed as prognostic in several retrospective and one prospective study**
- ❑ Clinical outcome prediction and inter-observer reproducibility using the EIN system can be greater than for the WH094**
- ❑ Case-control studies reviewing histopathology of either AEH or EIN demonstrate positive predictive value of both of these diagnoses**
- ❑ Both diagnostic schema are limited by the quality of the diagnostic tissue specimen**

Coexistent EC with AEH

- ❑ Many women with AEH have coexistent EC
- ❑ A literature review noted the frequency of concurrent EC among patients with AEH ranged from **17 to 52%** across studies
- ❑ **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 AEH
- ❑ Concurrent EC was diagnosed in **123 (42.6%)** of cases, 43 of which had high risks including myoinvasion or grade 2 or grade 3 carcinomas
- ❑ **Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006; 106:812**

Coexistent EC with AEH

- ❑ EC associated with AEH/EIN diagnosed in hysterectomy specimen are usually low grade, early stage lesions that have a low risk of LVI
- ❑ The risk of a concurrent high-risk uterine carcinoma (high grade, high stage) in women with a biopsy diagnosis of AEH ranges from **5–7%**
- ❑ Beutler HK, Dockerty MB, Randall LM. Precancerous lesions of the endometrium. *Am J Obstet Gynecol.* 1963;86:433–443
- ❑ Campbell PE, Barter RA. The significance of a typical endometrial hyperplasia. *J Opt Soc Am.* 1961;68:668–672
- ❑ Gore H, Hertig AT. Carcinoma in situ of the endometrium. *Am J Obstet Gynecol.* 1966;94(1):134–155

Management of AEH/EIN

- ❑ The primary objectives with EIN/AEH are
 - ❑ Ruling out a concurrent EC
 - ❑ Prevention of progression to EC
- ❑ Management of AEH/EIN can be surgical and non-surgical

Intraoperative assessment of AEH/EIN

- 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**

Intraoperative assessment of AEH/EIN

- ❑ The distinction between AEH/EIN and well-differentiated endometrial carcinoma can be difficult even for experienced pathologists**
- ❑ Patients should be staged when an underlying carcinoma is identified**
- ❑ Otherwise management decisions should be made based on final diagnoses rendered on formalin-fixed tissue**

Intraoperative assessment of AEH/EIN

- ❑ **Intraoperative assessment of tumor grade and final histologic diagnoses made on permanent sections ranges from 40–70%**
 - ❑ Kumar S, et al. The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS One*. 2011;6(9):e21912
 - ❑ Sanjuan A, et al. Preoperative and intraoperative assessment of myometrial invasion and histologic grade in endometrial cancer: role of magnetic resonance imaging and frozen section. *Int J Gynecol Cancer*. 2006;16(1):385–390
- ❑ **Intraoperative assessment of depth of myoinvasion is congruent with final histopathologic diagnoses in the range of 70% of cases**
 - ❑ Kumar S, et al. The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS One*. 2011;6(9):e21912 55.
 - ❑ Wang X, et al. Clinical factors affecting the diagnostic accuracy of assessing dilation and curettage vs frozen section specimens for histologic grade and depth of myometrial invasion in endometrial carcinoma. *Am J Obstet Gynecol*. 2009;201(2):194. e1–194 e10.
 - ❑ Case AS, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol*. 2006;108(6):1375–1379.

Management of AEH/EIN

- ❑ **Surgical options include abdominal, vaginal, and minimally invasive procedures (laparoscopy or robotic surgery)**
- ❑ **Hysterectomy with or without BSO is standard**
- ❑ **Total hysterectomy is the current standard of care for AEH/EIN**
- ❑ **ACOG Committee Opinion No. 388 November 2007: supracervical hysterectomy. Obstet Gynecol.2007;110(5):1215–1217**

Without hysterectomy and nonsurgical management of AEH/EIN

- The therapeutic goal**
 - Complete clearance of disease**
 - Reversion to normal endometrial function**
 - The prevention of invasive EC**

Endometrial ablation for the management of AEH/EIN

- ❑ Not recommended for the treatment of AEH/EIN**
 - ❑ There are no available methods to confirm the completeness of ablation**
 - ❑ Subsequent adhesions may render the cavity partly inaccessible for follow-up**

Nonsurgical Management of AEH/EIN

- Progestins**
- SERMS**
- Aromatase inhibitors**
- Sulfatase inhibitors**
- GNRH antagonists**

Nonsurgical Management of AEH/EIN

❑ Progestins

- ❑ Acceptable toxicity profile**
- ❑ Option for any patient wanting to retain fertility**
- ❑ Option for any patient who desires uterine retention**
- ❑ Option for elderly patients with medical comorbidities**
- ❑ Therapy have limitations, neither the dose nor the schedule for progestational agents has been well standardized**

Effectiveness of progestin treatment for AEH/EIN

- ❑ Histologic examination after completion of therapy and a withdrawal bleed provides the greatest information on response**
- ❑ 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**

Relapse of EH after conservative treatment LNG-IUS vs oral progestogens

- ❑ A cohort study of 219 women with complex nonAEH or AEH who were treated and achieved initial regression with LNG-IUS or oral progestogens and followed >5 years
- ❑ Relapse of EH occurred in 13.7% of women treated with LNG-IUS compared with 30.3% of women treated with oral progestogens, OR=0.34, (0.005)
- ❑ Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up. Hum Reprod. 2013;28(5):1231-6

Effectiveness of progestin treatment for AEH/EIN, with oral progestin or LNG-IUD

- 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**
- Longitudinal endometrial sampling, either by curettage or biopsy, at 3–6 month intervals, until a minimum of 3 negative biopsies are obtained**
- If persistence or progression to carcinoma is detected, hysterectomy will be performed**

Oncologic and reproductive outcomes in fertility-sparing management of AEH and EC: systematic review and meta-analysis

- ❑ 22 studies, totaling 351 patients were used to assess pregnancy rate; 111 subjects (32%) had one pregnancy or more
- ❑ Among the 263 patients used to assess progression rate, 39 (15%) had a tumor with at least myometrial invasion on the hysterectomy specimen
- ❑ Fertility-sparing management should not be contraindicated in older patients with previous infertility or obesity
- ❑ Koskas M, Uzan J, Luton D, Rouzier R, Daraï E: Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. *Fertil Steril*. 2014 Mar;101(3):785-94. doi: 10.1016/j.fertnstert.2013.11.028. Epub 2014 Jan 2

Summary

- EH without atypia is treated with progestins**
- Total hysterectomy is curative of AEH/EIN and provides a definitive assessment of a concurrent EC**
- If hysterectomy is performed for AEH/EIN, intraop. assessment of the uterine specimen for occult EC is preferred**
- Evaluation by a qualified pathologist with gross examination with or without frozen section is necessary**
- Endometrial ablation is not recommended for AEH/EIN**
- Follow-up of women treated hormonally should include multiple endometrial samplings**

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Tedavide progesteron – progestinler

- **Düşük doz, ayda 12-14 gün**
 - **MPA, 10-20 mg/gün**
 - **Nor ethidron asetat, 5 mg/gün**
 - **Mikronize progesteron (oral , vajinal)
200 mg/gün**
 - **Megesterol asetat, 20-40 mg/gün**
- **Yüksek doz, ayda 21 gün**
 - **MPA, 40-100 mg /gün**
 - **Mikronize progesteron (oral , vajinal)
300-400 mg/gün**
 - **Megesterol asetat, 80-160 mg /gün**

Türkiye'deki Preperatlar – fiyatları 01.04.2014

❑ **LNG-IUS, Mirena, 239.44 TL**

❑ **Progesteron**

❑ **Progestan 100 mg, 30 kap/kutu, 13.53 TL**

❑ **Progestan 200 mg, 30 kap/kutu, 26.97 TL**

❑ **Progestan 50 mg, ampul, 5x1 amp, 18.18 TL**

❑ **Progynex kapsül 100 mg, 30 kap/kutu, 13.53TL**

❑ **Progynex kapsül 200 mg, 30 kap/kutu, 26.97TL**

❑ **Progynex ampul 50 mg, 5x1 amp, 19.70**

Türkiye'deki Preperatlar – fiyatları 01.04.2014

□ Progesteron analogları

□ Didrogesteron (Duphaston 10 mg, 20 tab/kutu), 9.97 TL

□ MPA (Tarlusal 5mg, 12 tab/kutu, 3.87 TL

□ Nomegesterol Asetat (Lutenyl 5mg, 10 tab/kutu), 7.82 TL

□ Megesterol asetet (Megace 160 mg, 30 tab/kutu) 44,03 TL

□ Testosteron analogları

□ Noretisteron (Primolut-N 5mg, 30 tab/kutu), 9.71TL

□ Linestrenol (Orgametril 5mg, 30 tab/kutu), 8.28 TL