Non-surgical Management of Premalignant Conditions of the Endometrium

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Disclosure
Case # 1

30 yo G0P0, referred for assessment of abnormal bleeding. Prior to the current bleeding she was having “menses” every 4-5 months. Pap and pelvic exam reported as normal 10 months ago. Married for four years and has never used contraception.

PMH: HTN, Diet controlled diabetes mellitus (sort of)

V/S: Ht. = 65”, Wt. = 100 Kg. B/P 138/92  BMI 36.7 (Kg/M2)

Examination: Obese patient with central obesity and hirsutism.
Objectives

1. Nomenclature
2. Diagnosis
3. Natural History
4. Management
5. Follow-up
Nomenclature
Endometrial Cancer Precursors

- Atypical endometrial hyperplasia
- EIN (Endometrial Intraepithelial Neoplasia)
Endometrial Cancer Precursors
WHO Criteria

- Proliferative Endometrium
- Endometrial Hyperplasia (simple/complex)
- Atypical Endometrial Hyperplasia
- Endometrial Carcinoma

Kurman et al. Cancer 1985;56:403-12
Proliferative Endometrium

Complex Endometrial Hyperplasia

Atypical Endometrial Hyperplasia
Endometrial Cancer Precursors
WHO Criteria

Regardless of simple or complex architecture, nuclear cytologic atypia is the dominant risk assessment.

Cytologic atypia diagnoses are difficult to reproduce between pathologists.
Endometrial Intraepithelial Neoplasia
EIN

- EIN is conceptually similar to Complex Atypical Hyperplasia (CAH).
- The majority of EIN overlaps with CAH.
- EIN is not exclusive to CAH.
- Not all CAH are EIN.
- Specific to Type I endometrial cancer precursors.
Endometrial Intraepithelial Neoplasia
EIN

Clonal proliferation of architecturally and cytologically altered premalignant endometrial glands, prone to malignant transformation to endometrioid (Type I) endometrial adenocarcinoma.

Non-invasive, genetically altered neoplasms that arise focally and may convert to malignant phenotype upon acquisition of additional genetic damage.
## Endometrial Intraepithelial Neoplasia (EIN)

<table>
<thead>
<tr>
<th>EIN Criterion</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Architecture</td>
<td>Area of glands exceeds that of stroma</td>
</tr>
<tr>
<td>Cytology</td>
<td>Differs between architecturally crowded focus and background</td>
</tr>
<tr>
<td>Diameter</td>
<td>Maximum linear dimension exceeds 1mm.</td>
</tr>
<tr>
<td>Exclude Mimics</td>
<td>Benign conditions with overlapping criteria: basalis, secretory polyps, repair etc.</td>
</tr>
<tr>
<td>Exclude Cancer</td>
<td>Carcinoma if maze-like meandering glands, solid areas, or appreciable cribriforming</td>
</tr>
</tbody>
</table>

Mutter et al. J Pathol 2009;190:462-9
WHO Diagnoses Reviewed for EIN Criterion

- Atypical Hyperplasia = 78% EIN
- Complex Hyperplasia = 44% EIN
- Simple Hyperplasia = 4% EIN

Atypical Endometrial Hyperplasia vs. EIN

- The pathologist decides on the nomenclature for the diagnosis.
- The clinician needs to understand the significance of the diagnosis and propose the best therapy to fit the circumstances.
Diagnosis
Endometrial Sampling

Important Points

The extent of histological sampling will vary based on the ultimate plan of treatment.

Medical Management

vs.

Surgical Management
Endometrial Sampling

Important Points

- Conventional D&C samples < 50% of the endometrium in 60% of patients.
- Hysteroscopic guidance of curettage decreases sampling error.
- Pipelle® sampling sensitivity;
  - 82-100% for atypical hyperplasia
  - 99.6% for endometrial carcinoma

Cancer 2000;89(8):1765-1772.
Natural History
30-40% of patients diagnosed with EIN or Atypical Endometrial Hyperplasia will have a concurrent, occult carcinoma.

25% of women diagnosed with endometrial cancer are premenopausal.

3-5% of women diagnosed with endometrial cancer are age 40 or younger, 70% of whom are nulliparous.

The diagnosis of EIN or AEH is associated with a 45-fold risk of progression to endometrial cancer.

Lacey, JV et al, Cancer, 2008; 113(8):2073-2081

Trimble, CL et al, Cancer. 2006;106(4):812-819
Non-Surgical Management
Can/should surgery be avoided??

Non-surgical Management

– Weight reduction
– Progestin therapy
– Progestin + Metformin ??
– Eventual ovulation induction
Oncologic and Reproductive Outcomes With Progestin Therapy for Endometrial Hyperplasia and Grade 1 Adenocarcinoma: Systematic Review

- 45 studies with 391 (111/280) subjects from 2004-2011
- 81% treated with oral or systemic progestin, 19% with levonorgestrel IUD.
- Overall Response Rate was 77%
- Complete Response Rate was 53%
  - Hyperplasia 65%, Carcinoma 48%
- Recurrence Rate: Hyperplasia (23%), Cancer (35%)
- Persistent Disease: Hyperplasia (14%), Cancer (25%)
- Pregnancy Rate: Hyperplasia 41%, Cancer 34%
- 117 Live Births

Gunderson et al, Gynecol Oncol, 2012; 125: 477-482
Outcomes of Treatment for Endometrial Hyperplasia in Women Younger Than Age 35 Years

- Retrospective study of 233 patients, (70 AEH, 153 Non-AEH) . 20% Lost to Follow-up.
- Mean Age 29, Mean BMI 40
- Systemic Progesterone Therapy in 75% of patients
- Follow-up biopsy results with pre-treatment Non-AEH
  - Benign=62%, Non-atypical= 24%, AEH = 12%, Cancer = 1%
- Follow-up biopsy results with pre-treatment AEH
  - Benign = 53%, non-atypical = 20%, AEH = 18%, Cancer = 9%

Fertility Sparing Treatment of Complex Atypical Hyperplasia and Low Grade Endometrial cancer Using Oral Progestin

- Retrospective study of 44 patients < 45 years of age with CAH (43%) or G1EC (57%) treated with oral progestin.
  - 26% with MPA ≥ 100 mg/day or megestrol ≥ 80 mg/day
  - 74% with MPA ≤ 100 mg/day or megestrol ≤ 80 mg/day

- 55% Complete Response Rate. **Median Time to CR was 11 months**

- 11 (25%) underwent Fertility Treatment
  - 2(18%) Live Birth, 3(27%) SAB, 5(55%) No pregnancy.

- 54% ultimately underwent hysterectomy, with 63% found to have cancer

Simpson AN, et al, Gynecol Oncol 2014; 133: 229-233
Princess Margaret & Odette Cancer Centers in Toronto, Canada
Systemic and Local Hormone Therapy for Endometrial Hyperplasia and Early Adenocarcinoma

- Retrospective review of 186 patients with 153 having adequate follow-up, 1999-2011.
- Avg Age at Diagnosis 49 years (22-92)
- Non-surgical management for Medical Comorbidities (46%) and Fertility (21%)
- Therapy was with systemic progesterone or levonorgesterel IUD.
- Mean BMI 50 vs. 36 for systemic progestin vs. IUD for Hyperplasia
- Mean BMI 50 vs. 40 for systemic progestin vs. IUD for Cancer
- Hyperplasia patients had a 66-70% Complete Response Rate and 11-23% Recurrence Rate
- Cancer patients had 6-13% Complete Response Rate and 19-30% Recurrence Rate.
- One patient with Hyperplasia three patients with Cancer died of disease.
Systemic and Local Hormone Therapy for Endometrial Hyperplasia and Early Adenocarcinoma

- There was no difference in response rates between systemic progestin and levonorgestrel-IUD except during the 9-12 month assessment.
- 32 (21%) patients cited fertility as the reason for non-surgical therapy.
  - Of the 32, 6 pursued ART, and three achieved pregnancy.

Non-Surgical Therapy

- Insulin resistance, obesity, and Metabolic Syndrome are risk factors for endometrial cancer.

- Adding an insulin sensitizing agent to progestin for treatment of AEH/EIN has been reported in case reports and small studies and may be beneficial, but, has not been proven.
Prospective Study of 16 Subjects, 8 treated with Megestrol and 8 treated with Megestrol and Metformin

- Megace 160 mg/day, Metformin 500 mg TID

D&C after 12 weeks of therapy

Megestrol Only

- 4 Non-responses, 2 Partial Responses, 2 Complete Responses

Megestrol/Metformin

- 2 Non-responses, 6 Complete Responses

### Hormonal Therapy of EIN/AEH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage &amp; Length</th>
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<tbody>
<tr>
<td>Medroxyprogesterone Acetate</td>
<td>10-20 mg daily or cyclic 12-14 d/month.</td>
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<tr>
<td>Depo Medroxyprogesterone</td>
<td>150 mg IM every 3 months</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>40-200mg/d</td>
</tr>
<tr>
<td>Micronized vaginal progesterone</td>
<td>100-200 mg/d or cyclic 12-14 d/month</td>
</tr>
<tr>
<td>Levonorgestrel IUS</td>
<td>1-5 years</td>
</tr>
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</table>
Hormone Therapy of EIN/AEH
Unanswered Questions

- Duration of therapy 12 months seems reasonable (Underlying risk is unchanged)

- Methods of surveillance
  - Repeat biopsy
  - TV sonography

- Ovulation induction in the fertility patient

- Hysterectomy when treatment or pregnancy is complete
Medical Management of AEH/EIN and Grade 1 Endometrial Cancer is a cautious option.

Active patient participation and consent are essential.

Fertility preservation is a short-term goal.

A 12 month trial of medical therapy is reasonable.

Oral progestin or levonorgestrel-IUD are probably equally effective.

Follow-up biopsy and sonography scheduled on a three to six month basis is reasonable.

Following pregnancy or failed treatment, hysterectomy, BSO should be recommended.
EIN/ Atypical Endometrial Hyperplasia
Surgical Therapy

- Total Hysterectomy (By the least morbid route)
- BSO in menopausal women
- ?? Preserving ovaries in pre-menopausal women. (I wouldn’t)
- Supracervical hysterectomy and morcellation are inappropriate.
- Staging lymphadenectomy is not needed
Discussion
Endometrial Intraepithelial Neoplasia

EIN Criteria

1. EIN differs from normal tissues
2. EIN shares some, but not all features with carcinoma
3. EIN can be diagnosed (D-score < 1)
4. EIN increases risk for cancer
5. Genetic and hormonal mechanisms of carcinogenesis converge in EIN
6. Introducing EIN genotype into an animal model produces premalignant lesions
Endometrial Intraepithelial Neoplasia
EIN

**PTEN** (phosphatase and tensin homologue deleted on chromosome ten) tumor suppressor gene normally increases in an estrogenic environment. However, 63% of EIN is PTEN-defective.
WHO Hyperplasia Rediagnosed by EIN Criteria

- Atypical hyperplasia: 79%
- Complex non-atypical hyperplasia: 44%
- Simple non-atypical hyperplasia: 5%
- Endometrial intraepithelial neoplasia (EIN): 63%
- Other: 10%

Key:
- Green: Atypical hyperplasias rediagnosed as EIN
- Pink: Complex non-atypical hyperplasias rediagnosed as EIN
- Blue: Simple non-atypical hyperplasias rediagnosed as EIN
- Yellow: Hyperplasias not diagnosed as EIN

© 2006 Elsevier Inc. Crum CP and Lee KR. Diagnostic Gynecologic and Obstetric Pathology
AEH or EIN

GOG 167

- Post-hysterectomy findings in women with atypical endometrial hyperplasia.
- 123/289 (42.6%) women found to have endometrial carcinoma on final pathology.
- 43/123 (34%) demonstrated myometrial invasion or Grade 2 or Grade 3 carcinomas.

Cancer 2006;106:812-819.
Non-surgical Therapy of AEH

- Multiple small studies in select patient populations are reported.
- Multiple regimens of oral progestin (medroxyprogesterone acetate, megestrol acetate) in addition to levonorgestrel-IUS have been reported.
- Regression rates of 67-100%
- Duration or response varies.
Reference

Management of Endometrial Precancers
Trimble et al. Obstet Gynecol
2012;120:1160-75.