Endometrial Intraepithelial Neoplasia (EIN) and/or Atypical Endometrial Hyperplasia: …another step in the evolution of gynecologic pathology terminology
Richard Lieberman, M.D.

Endometrial Cancer Statistics

- New cases in 2015 = 54,870
- 80-85% are endometrioid (i.e. Type 1)
  - precursor lesions common
  - chronic estrogen excess*
- Endometrial cancer deaths in 2015 = 10,170
  - 1.7% of cancer deaths in women

SEER Fact Sheet: Endometrial Cancer
http://seer.cancer.gov

ATTENTION:
!!! EIN is not EIC !!!

- EIN – endometrial intraepithelial neoplasia
- EIC – endometrial intraepithelial carcinoma
  - aka serous carcinoma in situ
  - precursor of uterine papillary serous carcinoma
  - Type 2 endometrial carcinoma prototype

EIC is not EIN

COMMITTEE OPINION

This document reflects emerging clinical and scientific as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Endometrial Intraepithelial Neoplasia (EIN)

- terminology should reflect cancer risk
- EIN schema “seems” to be preferred over WHO four-class schema
- hysteroscopy with directed biopsy more sensitive than D&C

Disclosure

Nothing to disclose…
Serous Carcinoma “Type 2”

Classification of pre-cancerous lesions of the uterine corpus

WHO 1994
- Non-atypical hyperplasia
  - simple
  - complex
- Atypical hyperplasia
  - simple
  - complex
- Type I Endometrial Adenocarcinoma

WHO 2014
- Benign hyperplasia
- EIN: endometrial intraepithelial neoplasia
- Type I Endometrial Adenocarcinoma

WHO 2014 OR
- Non-atypical hyperplasia
  - simple
  - complex
- Atypical hyperplasia
  - simple
  - complex
- Type I Endometrial Adenocarcinoma

EIN v. AH: Why now?

- Diagnostic terminology?
  - histopathological tags that infer:
    1. growth potential
      - i.e. high grade v. low-grade
      - regression - persistence – progression
    2. pathophysiology
      - allow intervention
    3. potential underlying molecular-genetic alteration

How did we get here? Terminology Timeline

- late 1800’s: hypertrophy… cystic hyperplasia
- 1900-1980’s: adenomatous hyperplasia…
- 1960 AFIP Fascicle:
  - atypical adenomatous hyperplasia
  - carcinoma in-situ
- 1985: simple & complex hyperplasia +/- atypia
  - i.e. 1984 WHO Four Class Schema
- “2015”: AH-EIN

“tumor-like” lesions
- Polyp
- Metaplasia
- Arias-Stella reaction
- Lymphoma like lesion

“four-class WHO schema”

Type I precursor lesions of the uterine corpus

epithelial precursors
- Hyperplasia without atypia (benign hyperplasia)
- Atypical hyperplasia
  or
- Endometrial intraepithelial neoplasia (EIN)
Precursor Lesions based on WHO 1994

- **Type I Pathophysiology:**
  - succession of histological changes
  - continued chronic estrogen excess
    - defined: infrequent or no progestin withdrawal

- established criteria were subjective
  - glandular crowding
    - less than one-to-one
  - architectural & cytologic atypia
  - poorly reproducible

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Endometrial Progression to Carcinoma: A Spectrum of *Proliferative* Changes

- Hormonal
- Neoplastic

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Hyperplasia</th>
<th>Atypical Hyperplasia</th>
<th>Carcinoma</th>
</tr>
</thead>
</table>

- Continued estrogen excess

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Non-atypical Hyperplasia

- Simple
- Complex (BTB Glands)

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Hyperplasia without atypia

- Cystic (simple)
- "Complex"

---

Complex Hyperplasia?...more?
Complex Hyperplasia?...more?

- hyperplasia
- worse?
- Its “metaplastic” ... does that matter? ...subjectivity enters
- what if it’s a polyp?
- and what does it mean for the patient?

Historical Publications (1980’s):
Classify Hyperplasia & Risk

- criteria for endometrial adenocarcinoma
  - Kurman1,2, Kaminski2, and Norris1,2
    1. long term study of “untreated” hyperplasia
    2. criteria: AH vs. well differentiated carcinoma.
       Cancer 49: 2547-2559, 1982

Q: What histologic features in an endometrial biopsy or curettage predict concurrent or subsequent invasion, metastasis, and death?

Atypical Hyperplasia: Defining Features

<table>
<thead>
<tr>
<th>Glands &amp; Cells</th>
<th>Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ increased number of cells</td>
<td>✓ large, variable size/shape</td>
</tr>
<tr>
<td>✓ loss of polarity</td>
<td>✓ hyperchromatic, chromatin clumping</td>
</tr>
<tr>
<td>✓ increased N/C ratio</td>
<td>✓ irregular nuclear outlines</td>
</tr>
<tr>
<td>✓ intervening stroma retained</td>
<td>✓ prominent nucleoli</td>
</tr>
<tr>
<td>✓ cribriforming not present*</td>
<td>✓ mitoses not predictive</td>
</tr>
</tbody>
</table>

*confluent epithelial growth...more later

Follow-up of “Untreated” Hyperplasia:
Progression to Endometrial *Adenocarcinoma?

<table>
<thead>
<tr>
<th>Type</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>80%</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Complex</td>
<td>80%</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Simple Atypical</td>
<td>70%</td>
<td>23%</td>
<td>8%</td>
</tr>
<tr>
<td>Complex Atypical</td>
<td>57%</td>
<td>14%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Kurman, Kaminski & Norris
Cancer 56: 403, 1985
Atypical Hyperplasia

AH Diagnosis: Turning Point?

Reproducibility of AH
- GOG 167: Cancer 106:804, 2006
- all cases reviewed by 3 experts

Results
- overall kappa = 0.4
- panel diagnoses: 29% upgraded to carcinoma

“better criteria needed for atypical hyperplasia”

AH and Concurrent CA
- GOG 167: Cancer 106:812, 2006
- 289 patients of original with AEH
- all cases reviewed by 3 experts

Results
- overall kappa = 0.4
- panel diagnoses: 29% upgraded to carcinoma

Hysterectomy Findings
- 42.6% with concurrent carcinoma
- 64.3% from panel upgraded group

“better criteria needed for atypical hyperplasia”

when managing AEH consider the high rate of concurrent carcinoma

Atypical Hyperplasia Diagnosis: How reliable is the diagnosis?

Reproducibility of AH (criteria for study entry)
- GOG 167 – Part I
  - 306 patients with AH
  - all cases reviewed by 3 experts
  - Consensus = 2/3 experts

Results
- 39% agreed with dx (2/3)
- 29% upgraded to carcinoma
- 25% normal or b9 hyperplasia

Conclusions:
- Reproducibility of pathologists’ diagnosis of AH is poor.
- Better diagnostic criteria are needed for atypical hyperplasia

Atypical Hyperplasia Diagnosis: Is AH predictive of carcinoma?

Untreated AH (same group): Findings in Subsequent Hyst

GOG 167 – Part II
- 123/189 with endometrial carcinoma
- 43% with concurrent carcinoma!
- 31% myoinvasive

when managing AH: consider the high rate of concurrent carcinoma (43%)

Panel Results: % Cancer in Hyst
- upgraded to carcinoma: 64%
- AH consensus: 30%
- downgraded to <AEH: 19%

Cancer 106:812, 2006
Summary of Critiques of WHO AH-Schema

- subjective & poorly reproducible
  - strength: still widely used. ...familiar.

✓ fails to incorporate diagnostic advances of the last three decades

- hyperplasia and “atypical” hyperplasia are distinct biological entities

AH Problems – EIN Solutions

- defined:
  1. benign hyperplasia (hormonal effect)
  2. EIN (neoplastic)
    + PAX2 & PTEN mutations

- histologic criteria:
  - increased cancer risk
  - minimum lesion size
  - measured amount of glandular crowding
  - internal background gland size comparison

Assessment thus far:
- better predictor of disease progression... and benign behavior
- limited clinical experience

Gene Mutations & Protein Expression

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>EIN</th>
<th>endometrioid adenocarcinoma</th>
<th>“normal” latent precancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX2*</td>
<td>71%</td>
<td>77%</td>
<td>38%</td>
</tr>
<tr>
<td>PTEN -</td>
<td>44-63%</td>
<td>68-83%</td>
<td>40-49%</td>
</tr>
</tbody>
</table>

Protein Expression (IHC)

<table>
<thead>
<tr>
<th>Protein Expression (IHC)</th>
<th>proliferative</th>
<th>secretory</th>
<th>simple hyperplasia</th>
<th>complex hyperplasia</th>
<th>atypical hyperplasia</th>
<th>FIGO 1 CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX2 IHC Loss</td>
<td>0%</td>
<td>17%</td>
<td>59%</td>
<td></td>
<td>74%</td>
<td>73%</td>
</tr>
</tbody>
</table>

EIN: qualities of the clonal proliferation

1. a gland to stroma ratio of >1 : 1
   - volume percent stroma (VPS) ≤ 55%

2. cytology differs from the background glands

3. greater than 1mm in linear dimension

4. exclude mimics

5. exclude carcinoma

EIN or benign hyperplasia: VPS
EIN Images: VPS

graphic from www.endometrium.org
EIN Primer, DP George Muller

Volume Percentage Stroma, VPS: light circles are same number of gland epithelium (not known)

<table>
<thead>
<tr>
<th>90%</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF</td>
<td>INF</td>
<td>INF</td>
<td>INF</td>
<td>INF</td>
</tr>
</tbody>
</table>

EIN: VPS < 55% ...and cytology?

- a gland to stroma ratio of >1:1
- volume percent stroma (VPS) ≤ 55%
- cytology differs from the background glands
- exclude mimics: benign hyperplasia or polyp
- greater than 1mm in linear dimension
- exclude carcinoma

Benign Hyperplasia

Epithelial Atypia Suspicious for...

- a gland to stroma ratio of >1:1
- volume percent stroma (VPS) ≤ 55%
- cytology differs from the background glands
- exclude mimics: benign conditions with overlapping criteria (polyps, basalis, disordered, breakdown, etc)
- too small, recommend repeat sampling
- exclude carcinoma

Endometrial Assessments:

- Pipelle® Biopsy
- Hysteroscopy*
- Sharp Curettage
- Suction Curettage

9/15/2016
**Endometrial Biopsy Fragments**

**Endometrial curettage fragments**

**“Preferred” Endometrial Assessment**

**EIN: Clonal Growth >1.0mm**

**EIN: qualities of the clonal proliferation**

- a gland to stroma ratio of >1:1
- cytology differs from the background glands
- greater than 1mm in linear dimension
- exclude benign mimics
  - telescoped glands, basalis, polyps, metaplastic proliferations, etc.
- exclude carcinoma

**Clonal Proliferation in a Polyp**
Endometrial Polyps: AH? EIN?

**AH Terminology**
- No specific criteria
- "presumed" risk factor
- most are "hyperplastic"
- higher dx threshold
- limited data
  - ≤1% - 5% of polyps with endometrioid adenocarcinoma
  - fragmented vs. resected

**EIN Terminology**
- Criteria modification:
  - clonal growth & altered cytology & architecture
- metaplasia common
- "some" data
  - polyps more common in EIN patients
  - 43% vs. 13% (controls)
  - manage like EIN

**Maize-like:**
Not EIN… Endometrial Cancer

EIN & Carcinoma
- **EIN**: clonal proliferation immediate precursor of endometrioid endometrial adenocarcinoma
- 1/3 have concurrent adenocarcinoma
- patients who don’t develop cancer in first year
  - 45x risk of future endometrial cancer

Comparison of EIN and WHO Classifications

<table>
<thead>
<tr>
<th>EIN Class</th>
<th>WHO Class</th>
<th>Topography</th>
<th>Etiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Hyperplasia</td>
<td>Non-atypical</td>
<td>Diffuse</td>
<td>excess estrogen</td>
<td>hormonal</td>
</tr>
<tr>
<td>EIN</td>
<td>Hyperplasia</td>
<td></td>
<td>clonal (&gt;1mm)</td>
<td>hormonal or surgical*</td>
</tr>
<tr>
<td>Atypical Hyperplasia</td>
<td>precancer</td>
<td>maize-like, confluent growth, etc.</td>
<td>cancer</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>meets criteria for stromal invasion</td>
<td>cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EIN – Brief Summary**
- better reproducibility than WHO Classification
- new diagnosis of EIN: >1/3 cancer in first year
- clinical management is the same
- …and carcinoma is still carcinoma

2015: Endorsed by ACOG & SGO “Committee”
...and EIN may need more time

4-year Experience: Beth Israel, Boston
- Staff trained: conversion to "new" terminology
- Only 17% of EIN with subsequent carcinoma
- Terminology not always used

"...these results for general pathologists show a higher false positive rate for subsequent cancer."

"Educating staff pathologists was more difficult. Most felt, and still feel, that EIN puts undue burden on them to make an actionable diagnosis."

"Every negative hysterectomy brings additional angst of overdiagnosis..."

Int J Gynecol Pathol 31:160-165, 2012

Summary: EIN and AH
- EIN "preferred" by ACOG and SGO in Committee Opinion
- Acceptance not universal... for now
- Needs more input from more pathologists
- Time for another Consensus Conference

Management Keys:
- Both EIN & AH are high risk for concurrent carcinoma

1. Sample more
2. Consider hysterectomy
3. Progestins with periodic resampling

ACOG/SGO Committee Opinion #631, May 2015

Thank you!

Maize-like: Not EIN... Endometrial Cancer

FIGO 1: Latticework

"Excessive" cribriform - bridging
FIGO 1: Confluent sheets with cribriforming

Atypical Hyperplasia vs. Grade I Endometrial Adenocarcinoma

1. stromal alteration
   infiltrating glands
   desmoplasia – fibrosis and inflammatory infiltrate
2. confluent glands*
   uninterrupted by stroma
   cribriforming and aggregation
3. extensive complex papillary pattern*
4. squamous cell proliferation replacing stroma*

*must involve at least ½ a low power field (2.1 mm)

Endometrial Adenocarcinoma: Alteration of Stromal = Invasion

Desmoplasia: not always seen

Endometrial Adenocarcinoma:

Confluent Papillary Growth - Villoglandular

Well-differentiated Endometrial Adenocarcinoma, Endometrioid-type with Squamous Differentiation

Confluent epithelial growth (cribriforming) with interspersed squamous morules
Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings

<table>
<thead>
<tr>
<th>Age</th>
<th>Proportion of Uteri Containing Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=35</td>
<td>63%</td>
</tr>
<tr>
<td>36-54</td>
<td>51%</td>
</tr>
<tr>
<td>&gt;=55</td>
<td>26%</td>
</tr>
</tbody>
</table>

Invasion in Curettings

<table>
<thead>
<tr>
<th>No Invasion in Curettings</th>
<th>Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 115, mean = 55%</td>
<td>Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings*</td>
</tr>
<tr>
<td>n = 89, mean = 17%</td>
<td>Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings*</td>
</tr>
</tbody>
</table>

*based upon criteria of Kurman & Norris, Cancer 49:2547, 1982 and from Chapter 14, The Pathology of Incipient Neoplasia, 1992

WHO 2014: Classification of tumors of the uterine corpus

**type 1 tumors**
- Endometrioid carcinoma
  - squamous differentiation
  - villoglandular
  - secretory
  - Mucinous carcinoma
- adenocarcinoma with mixed cell type

**type 2 tumors (not type 1)**
- Serous carcinoma
  - EIC: endometrial intraepithelial carcinoma
  - Serous carcinoma
  - Clear cell carcinoma
  - Neuroendocrine tumors
    - Low-grade (carcinoid)
    - High-grade
    - Small cell
    - Large cell
  - Undifferentiated carcinoma
  - Dedifferentiated carcinoma

Type I Endometrioid Adenocarcinoma — Prototype

Serous Carcinoma “type 2”

WHO 2014: Classification of tumors of the uterine corpus

- epithelial precursors
  - Hyperplasia without atypia
  - Atypical hyperplasia
  - Endometrial intraepithelial neoplasia (EIN)

- tumor-like lesions
  - Polyp
  - Metaplasia
  - Arias-Stella reaction
  - Lymphoma like lesion