Endometrial Neoplasia, Including Endometrial Intraepithelial Neoplasia (EIN)

TEXAS SOCIETY OF PATHOLOGISTS ANNUAL MEETING

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Boston, MA

OUTLINE

Recognition of Precancerous Change
Metaplastic Changes – When Should I Worry?

Case History

• 59 year old woman with postmenopausal bleeding; endometrial sampling.
WHO 1994 and 2003

- Simple hyperplasia without atypia
- Simple hyperplasia with atypia
- Complex hyperplasia without atypia
- Complex hyperplasia with atypia
17 Years of Progress

- Hormonal Field Effect
  - Polyclonal
  - No mutation
  - Effects entire compartment

- Precancerous Change
  - Monoclonal
  - Mutated >> CA
  - Transformed cell

Discovery of Histologic Correlates

- 2 Groups can be biologically defined

- What is the Histology of these?

- Correlate histologic features with fundamental biologic processes and clinical cancer outcome

In EIN, Area of Glands > Stroma

[Graph showing volume percentage of glands with categories: Monoclonal, Polyclonal, and Normal]

Adapted from Baak, Mutter, and Janssen 2000-2002
Architecture and Size

- Area of glands greater than stroma (volume glands > 50%)

Cytologic Demarcation

- Cytology differs between architecturally crowded focus and background
- Size >1 mm: Maximum linear dimension exceeds 1mm.

EIN by H&E

- No Computer Required!! No brown stains!!

<table>
<thead>
<tr>
<th>EIN Criterion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Area of glands greater than stroma (volume glands &gt; 50%)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytology differs between architecturally crowded focus and background</td>
</tr>
<tr>
<td>Size &gt;1 mm</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 glands, solid areas, or significant cribriforming</td>
</tr>
</tbody>
</table>
COMMENTARY
Endometrial Intraepithelial Neoplasia (EIN): Will It Bring Order to Chaos?
George L. Matter, M.D.,1 and The Endometrial Collaborative Group3


Australia
Andrew Ostor
Canada
Alex Ferenczy
France
C. Bergeron
Great Britain
Harold Fox
Michael Wells
Netherlands
Jan P. A. Baak
Norway
Anne Orbo
Spain
F. Nogales
Taiwan
Ming-Chieh Lin

USA
Debra A. Bell
Christopher Crum
William C. Faquin
Nancy B. Kiviat
Marisa R. Nucci
Ralph M. Richart
Mark H. Stoler
Fattenah Tavassoli
William R. Welch
Clinical outcomes of 97 endometrial “hyperplasias” by WHO and EIN subjective Diagnosis

EIN Concurrent Cancer

- **39%** (43/110) Carcinoma <1 year (Retrospective, Baak 2005)
- **37%** (54/152) Carcinoma at hysterectomy (Prospective Clinical Trial: GOG167, Trimble 2006)
- **32%** (18/56) of concurrent CA myoinvasive (Prospective Clinical Trial: GOG167, Mutter 2008)
- **35.7%** (56/157) overall cancer incidence (Retrospective, Semere 2011)

>1-Year Cancer Progression Following Biopsy EIN Diagnosis

<table>
<thead>
<tr>
<th>Followup Time, Months</th>
<th>Proportion Cancer Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>50</td>
<td>0.8</td>
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<tr>
<td>100</td>
<td>0.6</td>
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<tr>
<td>150</td>
<td>0.4</td>
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<tr>
<td>200</td>
<td>0.2</td>
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</table>

Hazard Ratio: **45:1**
EIN Diagnostic Reproducibility

- Among Experts
  - Kappa 0.73-0.90  Hecht et al Mod Path 2005
  - Kappa 0.75  Usubutun et al Mod Path 2012

Interobserver Reproducibility
Collapsed 2-class WHO vs EIN

1. Sherman et al, IJGP 2008
2. Zaino et al, Cancer 2006
3. Lacey et al, Cancer 2008
4. Usubutun et al, Modern Pathology 2012
WHO 2003 Text:
Endometrial Hyperplasias

- “Reproducibility [of WHO 1994] is disappointing…”
- “It is extremely difficult to glean reliable incidence and progression data from the literature because diagnostic consistency has not been adequately maintained between studies.”
- “Moreover, the practical value of many molecular studies is similarly diminished by uncertainty about histopathological categorization.”
- Inconsistent diagnosis can be identified as a major barrier to appropriate clinical management.”

Gynecologic Oncology Group:
GOG167A
Central expert review of 300 EmBx with community diagnosis of Atypical Hyperplasia

- 7% Cycling endometrium
- 18% Non-Atypical hyperplasia
- 38% Atypical Hyperplasia
- 29% Adenocarcinoma

Zaino et al, Cancer 2006

Collapse of the WHO

Simple hyperplasia \textit{with atypia} \rightarrow \textit{Atypical Hyperplasia}

Complex hyperplasia \textit{with atypia} \rightarrow \textit{Atypical Hyperplasia}
“The histologic feature associated with the most diagnostic disagreement was cytologic atypia”
"Despite training, our focused review demonstrated that assessing ‘volume percentage stroma’ as required in the EIN system is neither easy nor reproducible (data not shown)"

Sherman et al, IJGP 2008

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Do you think that EIN classification is easy to learn?

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Absolutely disagree</td>
<td>0%</td>
</tr>
<tr>
<td>Disagree</td>
<td>0%</td>
</tr>
<tr>
<td>I have no idea</td>
<td>15%</td>
</tr>
<tr>
<td>Agree</td>
<td>50%</td>
</tr>
<tr>
<td>Absolutely agree</td>
<td>35%</td>
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n=20

Usubutun et al. Modern Pathology 2012

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“The diagnostic reproducibility of the light microscopic assessment of volume percentage stroma has not been adequately determined”

Ellenson et al, Blaustein’s Pathology of the Reproductive Tract, 2011
Gland Volume, by Cancer Outcome

Baak, Mutter, and Janssen 2000-2002

Proportion

10 20 30 40 50 60 70 80 90

Cancer
No Cancer
n=297

Baak, Mutter, and Janssen 2000-2002

VPG50
The Donut Game - Results

<table>
<thead>
<tr>
<th>Child</th>
<th>% correct (n=24)</th>
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<tbody>
<tr>
<td>CM (6 years)</td>
<td>81</td>
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<tr>
<td>JM (8 years)</td>
<td>86</td>
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<td>CM (10 years)</td>
<td>59</td>
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<td>80</td>
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<td>IM (12 years)</td>
<td>80</td>
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## The Donut Game - BWH Residents/Fellows

17 participants; 20 questions

- Range: 75-100%
- Mean: 94%
- Median: 95%
Benefits of EIN

• Two tiered classification scheme
• Benefits from 17 years of new evidence
• Clinically useful
• Diagnostically reproducible
• Easy to learn and apply
Diagnosis: Endometrial Intraepithelial Neoplasia (EIN) involving an endometrial polyp
Follow-up Hysterectomy (1 mo. later): Endometrial adenocarcinoma, endometrioid type, grade 1 (of 3) arising in association with EIN, with superficial myometrial invasion

What if the focus is not crowded enough?

Clinical outcome in diagnostically ambiguous foci of "gland crowding" in the endometrium.
Huang EC, Mutter GL, Crum CP, Nucci MR.

71,579 reports since 2001
206 (0.3%) cases with "gland crowding"
143 (69.4%) with follow-up reports
1 to 16 biopsies (median=1, avg=1.8)
Follow-up reports

- 77% Unremarkable
- 19% EIN
- 4% Carcinoma

Results

- 27 (18.9%) with subsequent EIN
  - 1 month to 7 years (median=1 yr, avg=1.5 yr)
  - 14 (51.9%) cases diagnosed within 1 yr

- 6 (4.2%) with subsequent carcinoma
  - 1 month to 5 years (median=0.5 yr, avg=1.7 yr)
  - 4 (66.7%) cases diagnosed within 1 yr

Conclusions

- 23.1% will be followed by a histologic outcome of neoplasia

- A diagnosis of “gland crowding” warrants a repeat biopsy in 4-6 months

- No histologic features to predict the outcome/progression of “gland crowding”
Diagnostic Terminology

Proliferative endometrium with a focus of gland crowding, see COMMENT.

COMMENT: The findings are not diagnostic of Endometrial Intraepithelial Neoplasia. In our experience focal gland crowding is followed by EIN on a subsequent sample in ~ 20% of cases. There is no evidence of carcinoma. Followup sampling is advised in 4-6 months to exclude EIN, or earlier if there are clinical concerns.


How do I diagnose EIN in a polyp?

- Features can overlap with EIN
- Should be excluded as mimic
Endometrial polyps are more common in women with EIN

<table>
<thead>
<tr>
<th></th>
<th>No Polyp</th>
<th>Polyp</th>
<th>n, Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>78.0%</td>
<td>12.0%</td>
<td>3584</td>
</tr>
<tr>
<td>EIN</td>
<td>56.7%</td>
<td>43.3%</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>3200</td>
<td>467</td>
<td>3667</td>
</tr>
</tbody>
</table>

Fishers Exact p<0.001
Carlson & Mutter, 2007

Uterine Polyps

- Benign stromal neoplasms
- Cytogenetic aberrations – t(6;14)

Diagnostic Criteria:
Not Basalis or LUS
2 of three:
Irregular glands
Altered Stroma
Thick Vessels
What if the EIN is in a polyp? Are there clinical repercussions for the location of the lesion?
Endometrial Intraepithelial Neoplasia Involving Endometrial Polyps. A Followup Study.
Quick CM, Mutter GL, Crum CP, Nucci MR
Mod Pathol 2012; 25: 293A

- 37 EIN in EMP diagnosed in 2009-2010
- 29/84 had followup (78%)
  - 13 (45%) NED
  - 12 (41%) persistent EIN (+/- polyp)
  - 4 (14%) EMADCA, grade 1

Non-Endometrioid Differentiation in EIN

<table>
<thead>
<tr>
<th>Metaplasia Type</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>53.0</td>
</tr>
<tr>
<td>Squamous Morules</td>
<td>18.1</td>
</tr>
<tr>
<td>Tubal Secretory</td>
<td>14.4</td>
</tr>
<tr>
<td>Tubal Ciliated</td>
<td>4.8</td>
</tr>
<tr>
<td>Mucinous</td>
<td>4.8</td>
</tr>
<tr>
<td>Secretory Vacuoles</td>
<td>4.8</td>
</tr>
<tr>
<td>Papillary</td>
<td>3.6</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>3.6</td>
</tr>
<tr>
<td>Squamous Surface</td>
<td>1.2</td>
</tr>
<tr>
<td>Total</td>
<td>n=83</td>
</tr>
</tbody>
</table>

EIN is associated with Polyps and Frequently Has Metaplastic Change
Carlson J, Mutter GL.
Histopathology 2008; 53: 325-32
How do I distinguish a benign metaplasia from a precancerous change? Or....It looks different, When Should I Worry?

Geometry of Benign, Premalignant, and Malignant lesions

Major Pathogenetic Mechanisms

- Degenerative/reparative
- Hormonal
- Neoplastic
Endometrial Metaplasia

✓ Squamous
✓ Mucinous
   Tubal
Eosinophilic

SQUAMOUS

Degenerative/Repair Category – No Risk

• Topography
   – Location → Surface
   – Usually FOCAL
Degenerative/Repair Category – No Risk

• Squamoid change associated with stromal breakdown/surface repair
  – Chronic endometritis
  – IUD
  – Infarcted Polyp
  – Trauma/prior procedure
When to be concerned:

- Abundant squamous epithelium in a postmenopausal patient +/- history of pyometra
Squamous cell carcinoma of endometrium

Rare, < 0.5% of all endometrial carcinomas

Exclusively composed of squamous epithelium with varying degrees of differentiation

May be associated with ichthyosis uteri and pyometra (cervical stenosis)

Squamous cell carcinoma of endometrium

Must exclude:
Endometrioid adenocarcinoma with extensive squamous differentiation
And
Primary squamous cell carcinoma of cervix
Neoplastic Category – High Risk

- EIN with squamous morules
- Atypical polypoid adenomyoma (morules)

Squamous Morular Metaplasia

- Categories of associated glandular alterations
  - “Normal” usually proliferative phase endometrium (isolated squamous morular metaplasia)
  - Endometrial glandular proliferation/alteration, not readily classifiable
  - Endometrial intraepithelial neoplasia (EIN)
Squamous Morular Metaplasia

Risk of subsequent endometrial neoplasia

<table>
<thead>
<tr>
<th>Pattern</th>
<th>N</th>
<th>Morphology</th>
<th>NL</th>
<th>EIN</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>29</td>
<td>Isolated/No gland crowding</td>
<td>89.7</td>
<td>6.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>28</td>
<td>Gland crowding/No cytologic change</td>
<td>57.1</td>
<td>28.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>19</td>
<td>Gland crowding/Cytologic change</td>
<td>42.1</td>
<td>42.1</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Lomo et al, Mod Pathol 2004

Isolated Squamous Morular Metaplasia

Descriptive diagnosis and follow-up sampling

- e.g. Proliferative/secretory endometrium with focal squamous morular metaplasia.
- Follow-up sampling in 9-12 months is recommended (if a curetting); earlier if biopsy
Endometrial Alteration with Squamous Morular Metaplasia

Descriptive diagnosis and follow-up sampling
• e.g. Endometrial glandular crowding and complexity associated with squamous morular metaplasia
• Note: Diagnostic features of EIN are not present, nevertheless, close clinical follow-up with repeat sampling in 6 months is recommended due to the area of glandular crowding.

Endometrial Intraepithelial Neoplasia with Squamous Morular Metaplasia

• Diagnosis: EIN with squamous morular change (or metaplasia)
  – Quantify amount of lesion
• Treatment:
  – Close clinical follow-up with hormonal ablation or hysterectomy

Atypical Polypoid Adenomyoma

• Polypoid, biphasic lesion
• Fourth and fifth decades (mean 39 years)
• Lower uterine segment
• Morular metaplasia in >90% of cases
Atypical Polypoid Adenomyoma

- Persistent, recurrent disease
- Local excision, hormonal therapy and close clinical follow-up vs. hysterectomy

Atypical Polypoid Adenomyoma

- Distinguish from EIN by:
  - Polypoid fragments
  - Distinctive stroma
- Distinguish from myoinvasive adenocarcinoma by:
  - Less architecturally complex
  - Lack of separate fragments of typical adenocarcinoma

MUCINOUS
Degenerative/Repair Category – No Risk

• Topography
  – Location → Surface
  – Usually FOCAL
  – NO epithelial complexity

Degenerative/Repair Category – No Risk

• Syncytial repair and stromal breakdown
• Hormonal therapy
• Endometrial polyp

“Papillary Syncitial Metaplasia” = Degenerative
When to be concerned:

- Any degree of epithelial complexity associated with mucinous change
- The epithelial complexity can be within the gland (e.g. papillary change) OR it can be architectural complexity in disassociated strips of epithelium (e.g. papillary or microacinar growth)

When to be concerned:

- If there is papillary change, ask if focus meets criteria for EIN
  - Meets EIN VPS and size criteria
  - Usually localizing lesion
  - May blend into more endometrioid lesion
When to be concerned:

• If it does NOT meet EIN criteria:
  
  – Consider followup sampling
    depending on amount, condition of
    sample (fragmentation), location (in
    a polyp)
When to be concerned:

- Complex mucinous epithelial proliferations

- Consider carcinoma if:
  - Complex, microglandular growth pattern
  - Villous architecture
  - Extensive papillary formation (with stromal cores)
The diagnosis of carcinoma in the biopsy/curettage depends on amount and condition (fragmentation) of sample.
Diagnosis: Complex mucinous epithelial proliferation, see NOTE.

NOTE: Findings are worrisome for a neoplastic process; however the (scant amount/fragmentation/preservation) precludes a more definitive diagnosis. Followup sampling is recommended.
Exclusion of Mimics

- Exclude cervical microglandular hyperplasia
  - Endometrial vs. endocervical stroma
  - Presence of reserve cell hyperplasia
  - Presence of sub/supranuclear vacuoles
- Exclude cervical adenocarcinoma
- Epithelial complexity associated with repair
  - Associated stromal breakdown

[Images: Subnuclear Vacuoles, Reserve Cell Hyperplasia]
CONCLUSIONS

Recognition of Precancerous Change – Benefits of EIN

Two tiered classification scheme

Benefits from 17 years of new evidence

Clinically useful

Diagnostically reproducible

Easy to learn and apply
CONCLUSIONS

Metaplastic Changes – When Should I Worry?

Be aware of the major mechanisms associated with metaplastic changes (degenerative, hormonal, neoplastic)

Understand the topography of these mechanisms (surface change vs localizing; focal vs diffuse)

Don’t ignore morules

Be wary of epithelial complexity

Ask for follow up if necessary