Endometrial Intraepithelial Neoplasia (EIN) and/or Atypical Endometrial Hyperplasia:

…another step in the evolution of gynecologic pathology terminology

Richard Lieberman, M.D.

1

Disclosure

Nothing to disclose…

2

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

3

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society of Gynecologic Oncology

COMMITTEE OPINION

Number 631 • May 2015

This document reflects emerging clinical and scientific as of the date issued and is subject to change. The information should not be contrued 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**

4

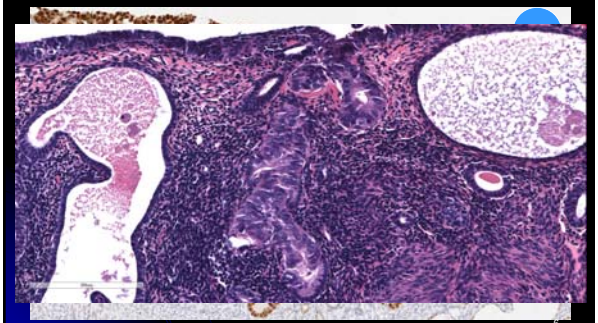
ATTENTION:

‼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*

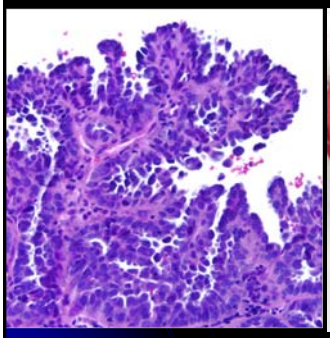
5

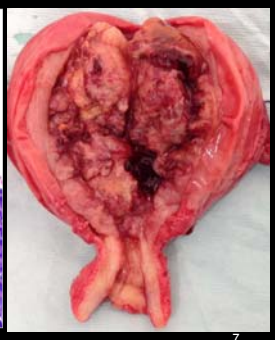
EIC is not EIN



6

Serous Carcinoma "Type 2"





7

Classification of pre-cancerous lesions of the uterine corpus

WHO 1994

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

"four-class WHO schema"

8

WHO 2014: Type I precursor lesions of the uterine corpus

- epithelial precursors
  - Hyperplasia without atypia (benign hyperplasia)
  - Atypical hyperplasia
    or
  - Endometrial intraepithelial neoplasia (EIN)
- "tumor-like" lesions
  - Polyp
  - Metaplasia
  - Arias-Stella reaction
  - Lymphoma like lesion

9

Classification of pre-cancerous lesions of the uterine corpus

WHO 2014 *OR*	**WHO 2014 → ACOG/SGO**

• Non-atypical hyperplasia
  • simple
  • complex
	• Benign hyperplasia

• Atypical hyperplasia
  • simple
  • complex
	• EIN: endometrial intraepithelial neoplasia

• Type I Endometrial Adenocarcinoma	• Type I Endometrial Adenocarcinoma

10

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.1994 WHO Four Class Schema
- "2015": AH -EIN

11

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*

12

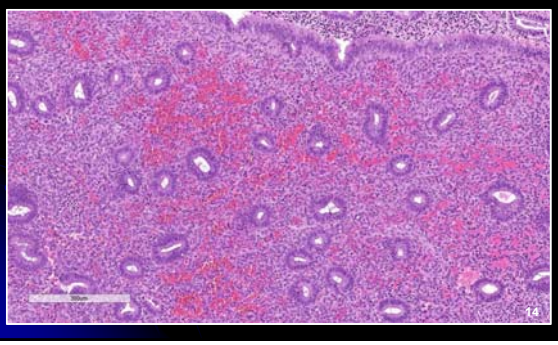
Precursor Lesions based on WHO 1994

- 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

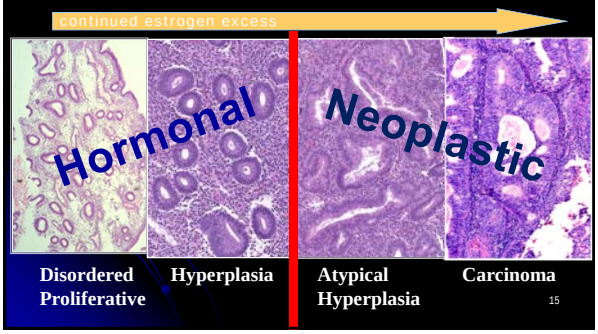
13

Proliferative = Estrogen XS
Breakdown = anovulation



14

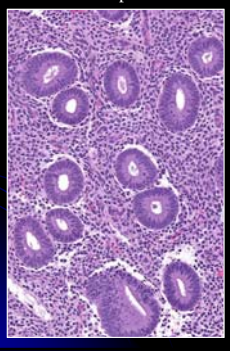
Endometrial Progression to Carcinoma: A Spectrum of *Proliferative* Changes



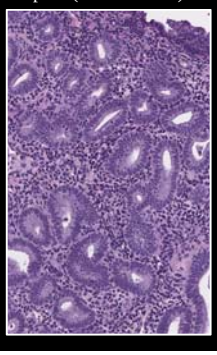
15

Non-atypical Hyperplasia

Simple



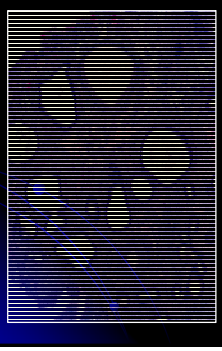
Complex (BTB Glands)



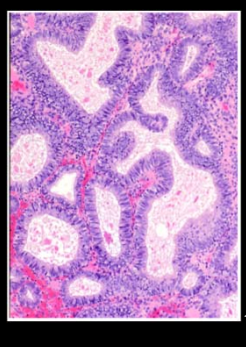
16

Hyperplasia without atypia

Cystic (simple)

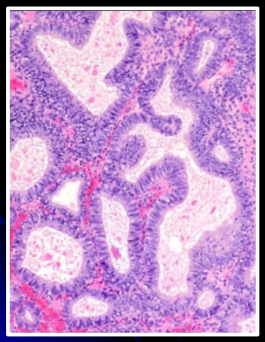


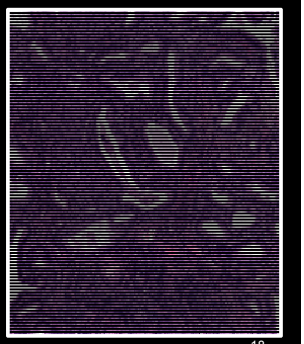
"Complex"



17

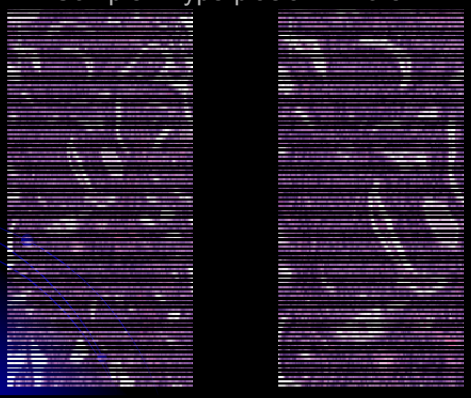
Complex Hyperplasia?…more?





18

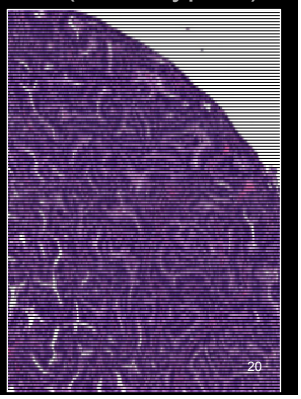
Complex Hyperplasia?…more?



19

Complex Hyperplasia (with atypia?)

- *hyperplasia ✓*
- *worse?*
- *its "metaplastic" … does that matter?*
  …subjectivity enters
- *what if it's a polyp?*
- ***and what does it mean for the patient?***



20

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

- criteria for endometrial adenocarcinoma
  - Kurman[1,2], Kaminski[2], and Norris[1,2]
    1. long term study of "untreated" hyperplasia
       Cancer 56: 403-12, 1985.
    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?

21

Follow-up of "Untreated" Hyperplasia: Progression to Endometrial *Adenocarcinoma? n=170

Type	Regression	Persistence	Progression*	
Simple	80%	19%	1%	2%
Complex	80%	17%	3%	
Simple Atypical	70%	23%	8%	23%
Complex Atypical	57%	14%	29%	

What was N=?

22

Kurman, Kaminiski & Norris Cancer 56: 403, 1985

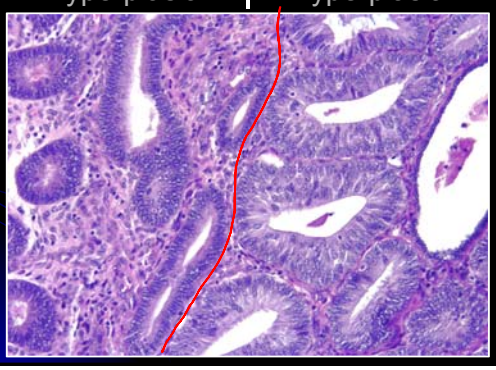
Atypical Hyperplasia: Defining Features

Glands & Cells	Nuclei
✓ increased number of cells	✓ large, variable size/shape
✓ loss of polarity	✓ hyperchromatic, chromatin clumping
✓ increased N/C ratio	✓ irregular nuclear outlines
✓ intervening stroma retained	✓ prominent nucleoli
✗ cribriforming not present*	✗ mitoses not predictive

*confluent epithelial growth…more later

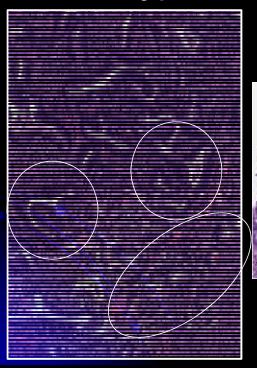
23

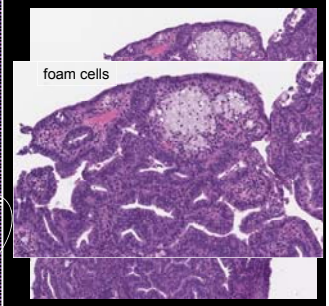
Non-atypical Hyperplasia | Atypical Hyperplasia



24

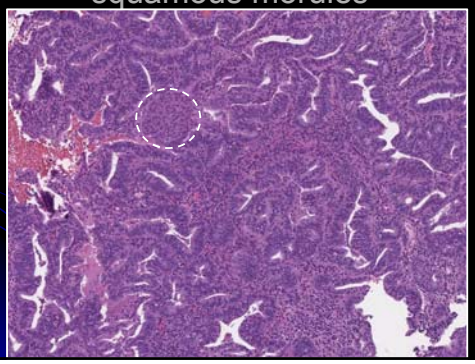
Atypical Hyperplasia





25

Atypical Hyperplasia with squamous morules



26

AH Diagnosis: Turning Point?

Reproducibility of AH

- GOG 167:
  *Cancer 106:**804**,2006*
  - 306 patients with AEH
  - 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
  - hyst in 12 weeks: no treatment
- Hysterectomy Findings
  - ***42.6% with concurrent carcinoma***
  - **64.3% from panel upgraded group**
- when managing AEH consider the high rate of concurrent carcinoma

27

AH Diagnosis: Turning Point?

Reproducibility of AH

- GOG 167:
  *Cancer 106:**804**,2006*
  - 306 patients with AEH
  - 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
  - hyst in 12 weeks: no treatment
- Hysterectomy Findings
  - ***42.6% with concurrent carcinoma***
  - **64.3% from panel upgraded group**
- when managing AEH consider the high rate of concurrent carcinoma

28

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

overall kappa = 0.3-0.4
between pathologists AND
between "experts"

Only 15% of AH were supported (3/3)

Conclusions:
Reproducibility of pathologists' diagnosis of AH is poor.

"better diagnostic criteria are needed for atypical hyperplasia"

Cancer 106:804,2006

29

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%
o AH consensus:	39%
☹ **downgraded to <AEH:**	**19%**

Cancer 106:812,2006

30

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

Obstet Gynecol 118(1):21-8, 2011 31

AH Problems – EIN Solutions

- *defined:*
  - two tiered
    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

Obstet Gynecol 118(1):21-8, 2011 32

Gene Mutations & Protein Expression

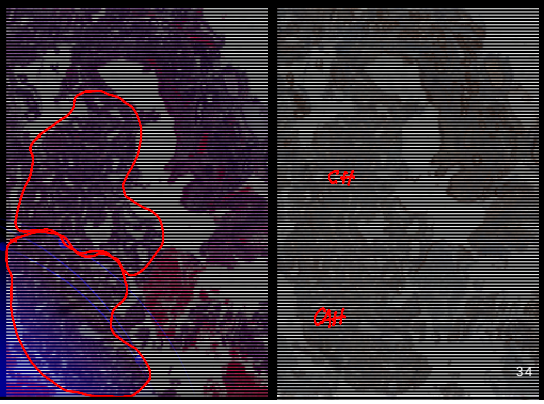
Gene Mutation	EIN	endometrioid adenocarcinoma	"normal" latent precancers
PAX2*	71%	77%	36%
PTEN - ☹	44-63%	68-83%	40-49%

Cancer Research 70:6225-32,2010

Protein Expression (IHC)	prolf or secretory	simple hyper	complex hyperplasia	atypical hyperplasia	FIGO 1 CA
PAX2 IHC Loss	0%	17%	59%	74%	73%

Sem Diag Pathol 27(4):215-225, 2010
Int J Gyn Pathol 31:151-9, 2012
33

AH & EIN: PAX-2 Loss



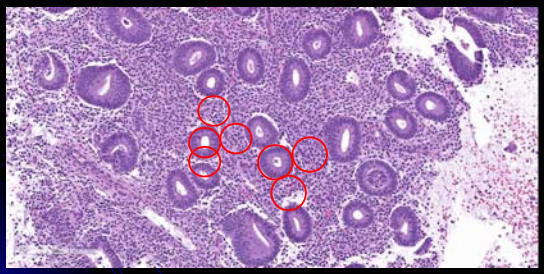
34

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

35

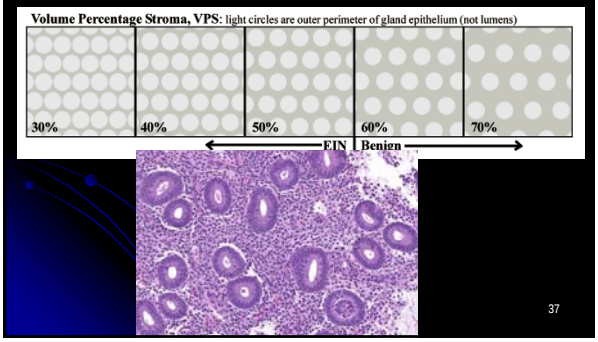
EIN or benign hyperplasia: VPS



36

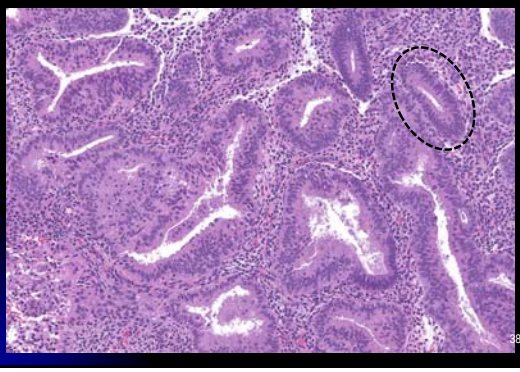
EIN Images: VPS

graphic from www.endometrium.org
EIN Primer, Dr. George Mutter



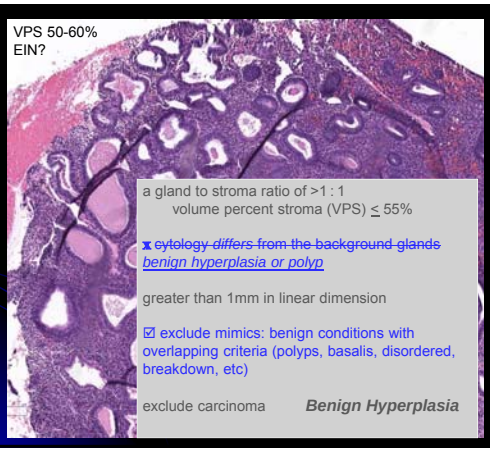
37

EIN: VPS < 55% …and cytology?



38

VPS 50-60% EIN?



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

~~x cytology *differs* from the background glands~~
benign hyperplasia or polyp

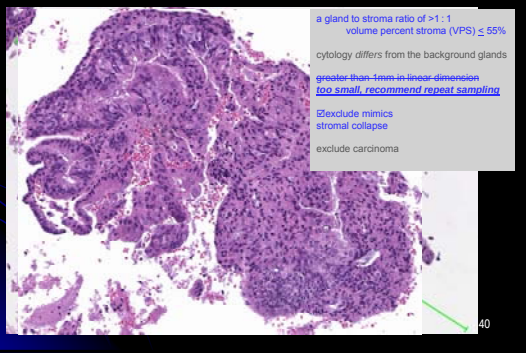
greater than 1mm in linear dimension

☑ exclude mimics: benign conditions with overlapping criteria (polyps, basalis, disordered, breakdown, etc)

exclude carcinoma **Benign Hyperplasia**

39

Epithelial Atypia Suspicious for…



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

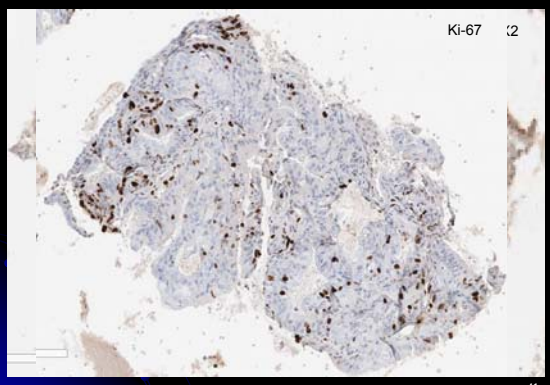
cytology *differs* from the background glands

~~greater than 1mm in linear dimension~~
too small, recommend repeat sampling

☑exclude mimics
stromal collapse

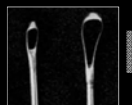
exclude carcinoma

40

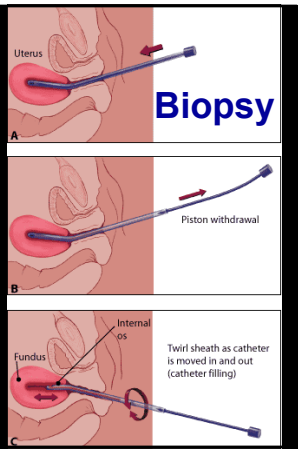


41

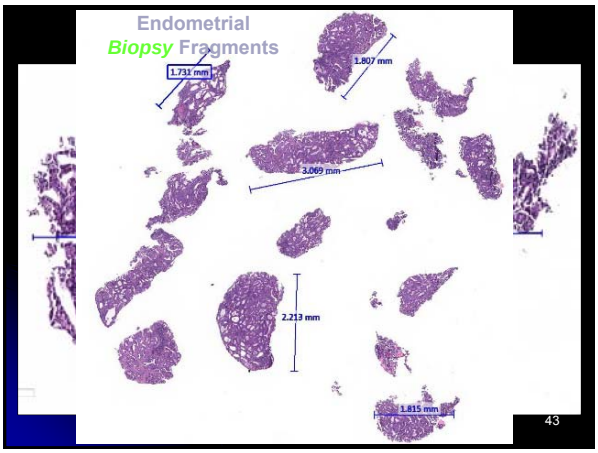
Endometrial Assessments:

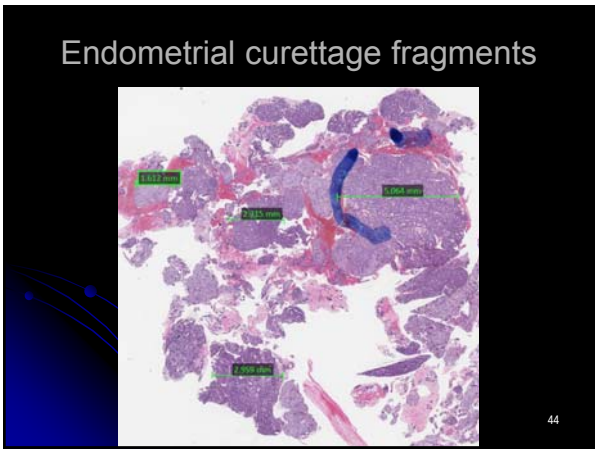


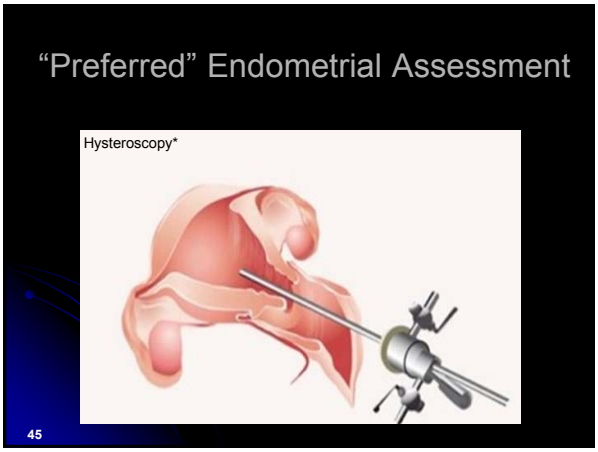
Sharp Curettage

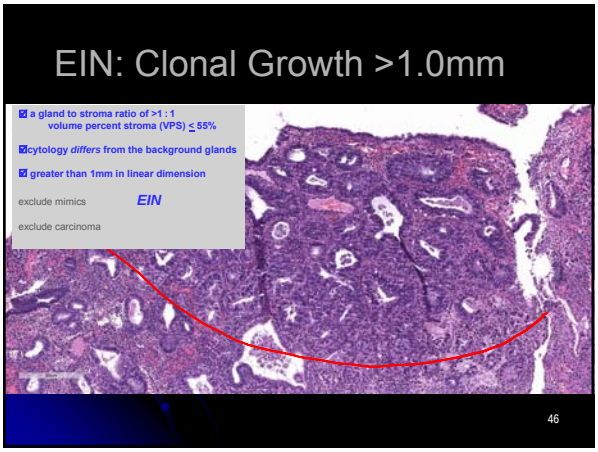


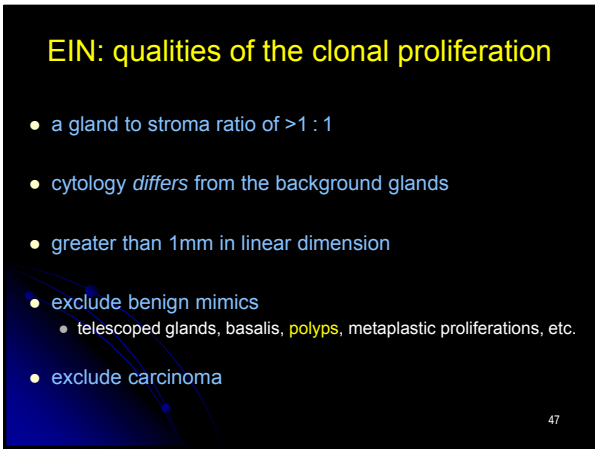
42

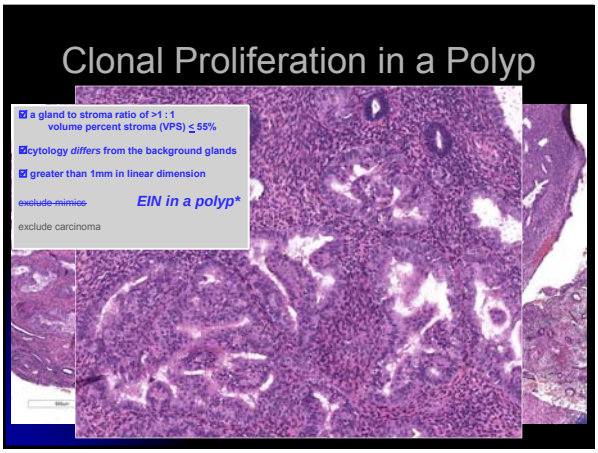

Endometrial
Biopsy Fragments
1.731 mm
1.807 mm
3.069 mm
2.213 mm
1.815 mm
43


Endometrial curettage fragments
44


"Preferred" Endometrial Assessment
Hysteroscopy*
45


EIN: Clonal Growth >1.0mm
☑ a gland to stroma ratio of >1 : 1
volume percent stroma (VPS) ≤ 55%
☑cytology differs from the background glands
☑ greater than 1mm in linear dimension
exclude mimics
EIN
exclude carcinoma
46


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
47


Clonal Proliferation in a Polyp
☑ a gland to stroma ratio of >1 : 1
volume percent stroma (VPS) ≤ 55%
☑cytology differs from the background glands
☑ greater than 1mm in linear dimension
exclude mimics
EIN in a polyp*
exclude carcinoma

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 adenoca
  - 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

Am J Obstet Gyn 188:927-31, 2003

Histopathol 53(3):325-332, 2008

49

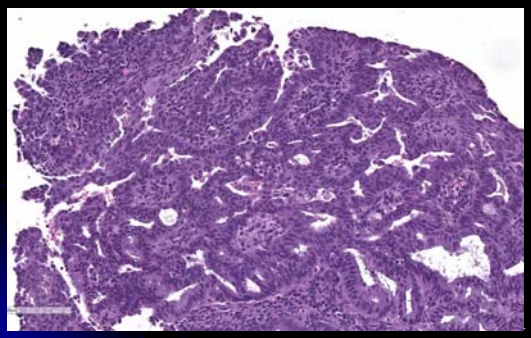
EIN & Carcinoma

- 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

Int J Gynecol Pathol 26:103-114, 2007

50

Maize-like: Not EIN… Endometrial Cancer



Comparison of EIN and WHO Classifications

EIN Class	WHO Class	Topography	Etiology	Treatment
Benign Hyperplasia	Non-atypical hyperplasia	Diffuse	excess estrogen	hormonal
EIN		clonal (>1mm)	molecular alteration	hormonal or surgical*
	Atypical Hyperplasia	<1/2 low power field	precancer	
Adenocarcinoma		maize-like, confluent growth, etc.	cancer	surgical staging procedure for either
	Adenocarcinoma	meets criteria for stromal invasion	cancer	

52

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*

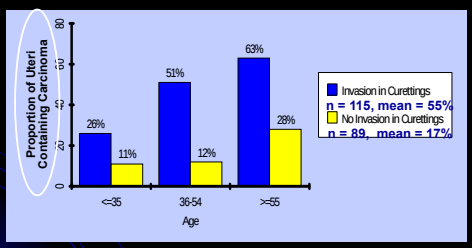
Arch Path Lab Med 138:484-491, 2014

- ***2015: Endorsed by ACOG & SGO "Committee"***

53

… but remember, WHO 1994 *still* has validity

Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings*



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

54

…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

Int J Gynecol Pathol 31:160-165,2012

- "…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…*"

55

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

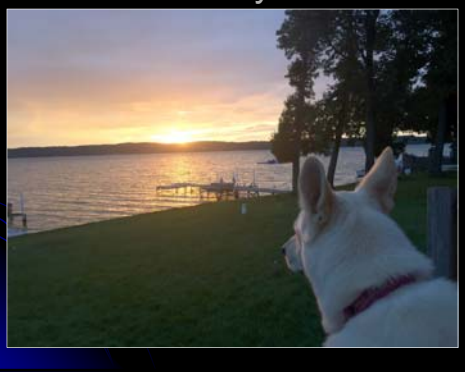
Management Keys:

- ***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

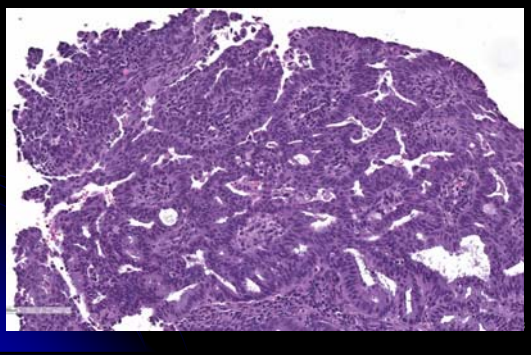
56

Thank you!

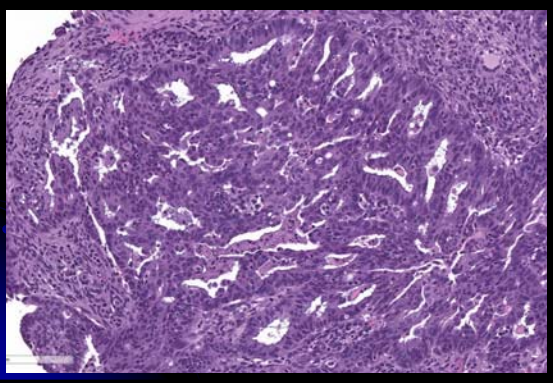


57

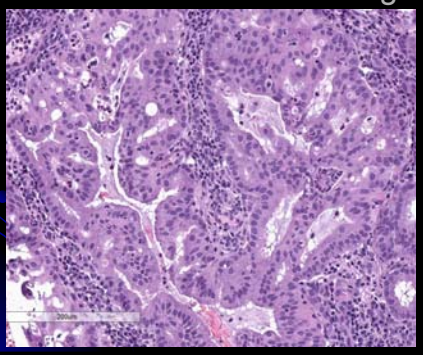
Maize-like: Not EIN… Endometrial Cancer



FIGO 1: Latticework

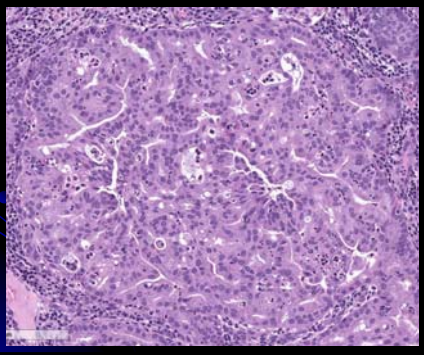


FIGO 1: "Excessive" cribriform - bridging



60

FIGO 1:
Confluent sheets with cribriforming



61

… as we transition to EIN

Atypical Hyperplasia vs. Grade I Endometrial Adenocarcinoma

***Curettage** Criteria for Stromal Invasion*

Kurman & Norris Cancer 49: 2547, 1982

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*

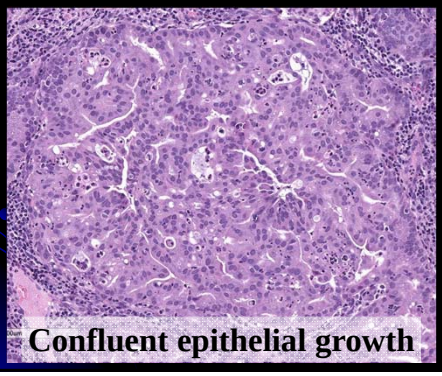
****must involve at least ½ a low power field (2.1 mm)***

62

Endometrial Adenocarcinoma: Alteration of Stromal = Invasion

Desmoplasia: not always seen

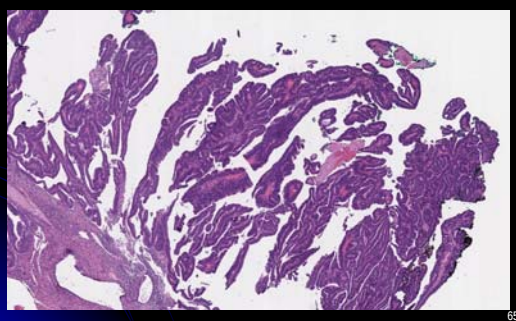
Adenocarcinoma: Cribriform Gland Formation



Confluent epithelial growth

64

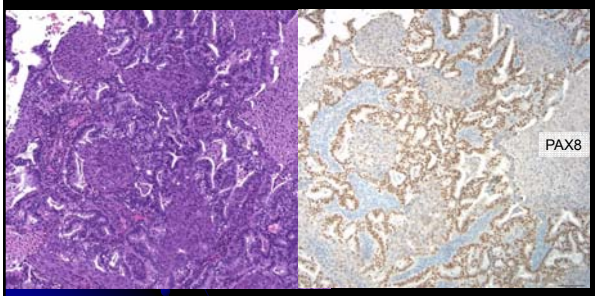
Confluent Papillary Growth - Villoglandular



65

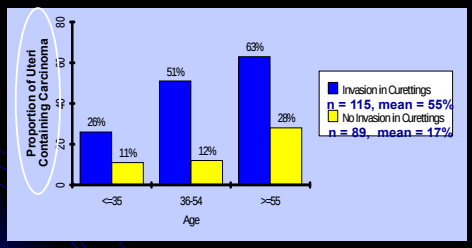
Well-differentiated Endometrial Adenocarcinoma, Endometrioid-type with Squamous Differentiation

Confluent epithelial growth (cribriforming) with interspersed squamous morules



66

Residual Carcinoma in Uterus According to Age and Presence of Stromal Invasion in Curettings*



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

67

WHO 2014: Classification of tumors of the uterine corpus

type 1 tumors

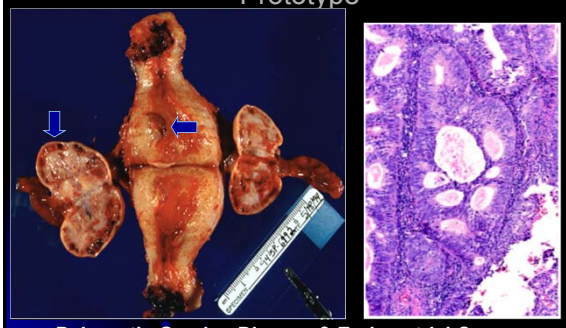
- Endometrioid carcinoma
  - squamous differentiation
  - villoglandular
  - secretory
- Mucinous carcinoma
- adenocarcinoma with mixed cell type

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

68

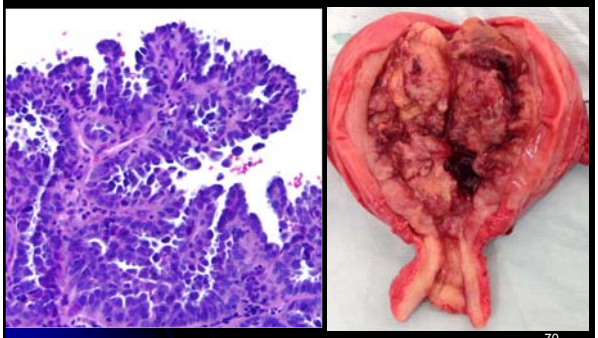
Type I Endometrioid Adenocarcinoma — Prototype



Polycystic Ovarian Disease & Endometrial Cancer

69

Serous Carcinoma "type 2"



70

WHO 2014: Classification of tumors of the uterine corpus

- epithelial precursors
  - Hyperplasia without atypia
  - Atypical hyperplasia
    or
  - Endometrial intraepithelial neoplasia (EIN)
- tumor-like lesions
  - Polyp
  - Metaplasia
  - Arias-Stella reaction
  - Lymphoma like lesion

71