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Endometrial Intraepithelial Neoplasia (EIN) Fact Sheet

Objective and Disclaimer.

This white paper summarizes previously peer-reviewed and published data regarding Endometrial Intraepithelial Neoplasia, a precursor lesion to endometrioid endometrial adenocarcinoma. It is provided as a service to assist health care professionals in their critical review of the literature.

Diagnosis and management of premalignant endometrial disease is a complex matter to be undertaken by appropriately trained clinicians within the context of an individual patient. This summary cannot replace the physician-patient relationship, nor is it tailored to be a guide for management. Patients who desire more information should direct their questions to the physician who is responsible for managing their care. A reference list at the end provides original sources to which physicians and health care professionals are referred for additional relevant details.

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Endometrial Intraepithelial Neoplasia

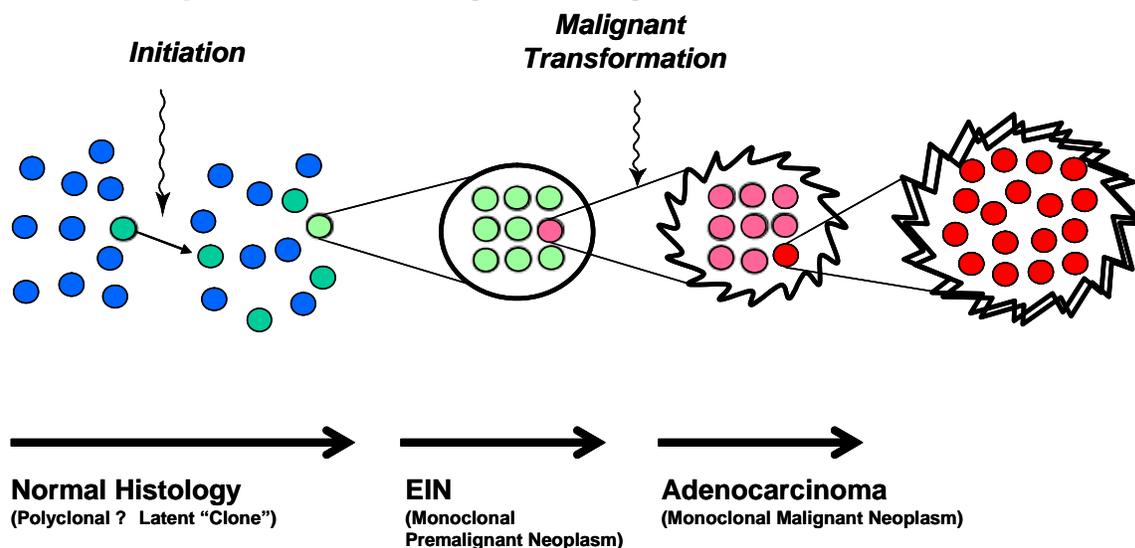
Biology of EIN: Endometrial Intraepithelial Neoplasia¹

Endometrial Intraepithelial Neoplasia (EIN) is a clonal proliferation of architecturally and cytologically altered premalignant endometrial glands which are prone to malignant transformation to endometrioid (Type I) endometrial adenocarcinoma. EIN lesions are non-invasive genetically altered neoplasms which arise focally, and may convert to malignant phenotype upon acquisition of additional genetic damage. Diagnostic criteria for EIN have been developed by histopathologic correlation with clinical outcomes, molecular changes, and objective computerized histomorphometry.

EIN should not be confused with unrelated serous intraepithelial carcinoma (serous EIC), which is an early phase of (Type II) papillary serous adenocarcinomas of the endometrium.

Management of EIN lesions follows guidelines long established for atypical endometrial hyperplasia. A high concurrent cancer rate (26%), and concern that sampling errors may miss an occult tumor, have led to a prevailing view that immediate hysterectomy is justified by its combined diagnostic and therapeutic benefits. Young patients wishing to preserve fertility, and women who are poor surgical risks, are candidates for hormonal (progestin) therapy. Systemic progestins can successfully ablate up to 90% of endometrial precancers in young women², although it is not possible in advance to predict that fraction which will respond. A decision to treat hormonally must thus be made between the clinician and patient in full light of the risks, and with the precondition that regular followup surveillance can be performed.

Figure 3: Clonal Origin of EIN. The first genetic changes (such as PTEN inactivation) which initiate



endometrial carcinogenesis are unaccompanied by any phenotypic alterations at the light microscopic level. This "latent", phase of cytologically and architecturally normal but genetically altered cells may persist for years in a normally menstruating woman. Low cancer risk, combined with lack of a rational therapeutic response, are reasons that systematic screening and treatment of these "latent" phase lesions is unwarranted at present. As additional genetic damage accumulates, higher risk morphologically altered mutant clones declare themselves by demonstrating those architectural and cytologic alterations that distinguish EIN. Malignant transformation of EIN lesions, which occurs at least 46-times more frequently than non-EIN tissues, warrants careful diagnosis and treatment. Endocrine modifiers of endometrial

cancer risk act upon the latent and EIN phases of this sequence by tipping the balance of clonal expansion vs. involution.

A combined molecular and histopathologic model for EIN.

Latent, premalignant, and malignant phases of EIN-mediated endometrial carcinogenesis are diagrammed in Figure 3. In almost half of apparently normal women, histologically unremarkable proliferative endometria contain a small fraction of (PTEN tumor suppressor gene) mutant endometrial glands. This phase may be construed as “latent” because not only do the mutated glands look completely normal under the microscope, but they progress to EIN and cancer at very low efficiency. This latent phase may persist for years, with continued presence of scattered and interspersed mutant glands after many menstrual cycles³. Mutant glands are probably represented in the reserve population of cells that regenerate a new functionalis each month. Endocrine factors act upon these “latent precancers” to modulate involution, or progression to EIN. Transition to EIN requires accumulation of additional genetic damage in at least one “latent precancer” cell, which then clonally expands from its point of origin (indicated by expanding arrows) to form a contiguous grouping of a tightly packed and cytologically altered glands recognizable as EIN. The monoclonal precancer (EIN) develops internal heterogeneity through mutation, and advantageous events selected by local conditions result in hierarchical subclones (left to right) of varying success. EIN lesions have only marginal increases in growth potential, and retain susceptibility to further growth modulation by hormonal factors. Some involute. Others, through additional mutation and selection, reach a stage where hormonal support is no longer required for survival. Malignant transformation to cancer is defined by accumulation of sufficient genetic damage to permit invasion of adjacent stromal tissues.

1.What Is EIN?

Endometrial Intraepithelial Neoplasia, EIN^{4,5}, is the histopathologic presentation of premalignant endometrial disease which confers an elevated risk for endometrial cancer. The singular category of EIN is not stratified or divided into subgroups, and must be distinguished from earlier phases of latent premalignant disease, and endometrial carcinoma. This term was proposed by The Endometrial Collaborative Group⁴ to accommodate changing concepts of premalignant endometrial disease and take advantage of revised diagnostic strategies.

EIN needs to be treated, and the type of therapy decided between the patient and treating physician. Things that may influence the choice of surgical vs. hormonal therapy include but are not limited to: diagnostic confidence that a co-existing carcinoma has been excluded, desire for maintained fertility, ability to perform followup surveillance, and patient-specific hormonal and surgical risks.

2.Clinicopathologic Foundations Of EIN

Rigorous experimental validation of clinically and biologically defined endometrial precancers, and development of correlative diagnostic criteria is a multidisciplinary process. Key predictions expected of precancers which have now been fulfilled for EIN, and practical aspects of their clinical implementation are listed in Table III:

Table III: Precancer postulates fulfilled for EIN

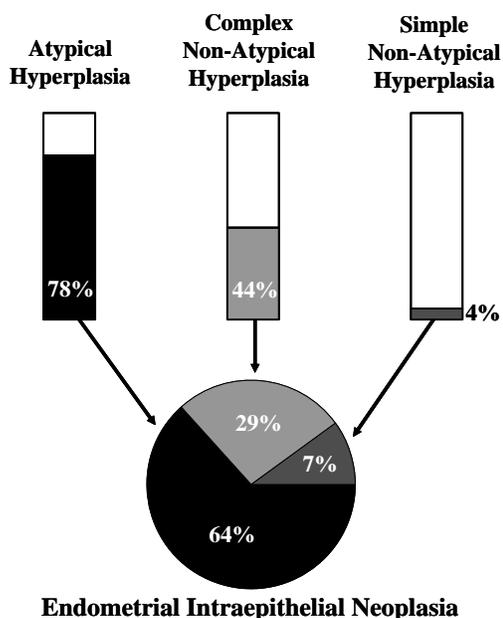
Postulate	Evidence
Precancers differ from normal tissues	Monoclonal ⁶⁻⁸ . Divergent genotype ⁹ .
Precancers share some, but not all features with carcinoma	Including PTEN ¹⁰⁻¹² , K-ras ¹³⁻¹⁵ , and MLH1 changes ¹⁶ . Both are monoclonal ^{6-8;17} . Precancer-cancer lineage hierarchy ⁹ .
Precancers can be diagnosed	Computerized morphometry reference standard for EIN ¹⁷
Precancers increase risk for carcinoma	High concurrent cancer rate in EIN ^{18;19;19} High future cancer rate in EIN ²⁰⁻²³
Epidemiologic and genetic mechanisms are linked	The PTEN gene, mutated in EIN, is subject to hormonal modulation ^{12;24}
Introducing precancer genotype into an animal produces premalignant lesions and heightened cancer risk	100% of PTEN mutant heterozygote mice get endometrial “hyperplasia” and 21% evolve to carcinoma. ²⁵

3.WHO Hyperplasia-EIN Concordances

Concordances with EIN diagnostic system and were obtained by review of cases initially diagnosed using other endometrial hyperplasia classification schemes²⁰.

Figure 4: Correlation of WHO and EIN Diagnoses.

Gray portions of Bar Graphs show approximate percentages of each WHO hyperplasia class that will be diagnosed as EIN. Remaining WHO hyperplasias not diagnostic of EIN (white) will be allocated to unopposed estrogen (anovulatory), polyp, and other categories. Pie chart shows relative contributions of each hyperplasia type to the EIN diagnostic category in a series of 97 cases with 28 EIN examples²⁰.



4.Clinical Cancer Outcomes Following EIN Diagnosis

The risk of developing endometrial cancer, as predicted by an EIN diagnosis are the basis for therapy. Although there are many previous references citing cancer outcomes of EIN patients^{18;21;22}, the two studies summarized below show cancer predictive value of subjective (Figure 5)²⁰ and objective histomorphometric (Figures 6-8)¹⁹ EIN diagnosis. Patients with EIN lesions have an overall 89-fold increased cancer risk than those without EIN. In practice, the time interval separating EIN from cancer divides these into either concurrent EIN and cancer, or progression events from EIN to cancer. For purposes of illustration we have considered cancers diagnosed within 12 months of EIN to be “concurrent” (Figure 7), and those following EIN by more than one year to be “progression events” (Figure 8).

Figure 5: Cancer outcomes (black), by followup interval (vertical axis) of 97 endometrial biopsies diagnosed by WHO hyperplasia (left) or EIN (right) schema²⁰. Endometrial hyperplasias (left panel) were rediagnosed subjectively (without morphometry) as EIN or benign, non-EIN (right panel). All 8 cancer outcomes (black symbols) followed an initial diagnosis of EIN. EIN has a better negative predictive value than atypical hyperplasia, as 2/8 cancer occurrences were seen in the non-atypical hyperplasia groups.

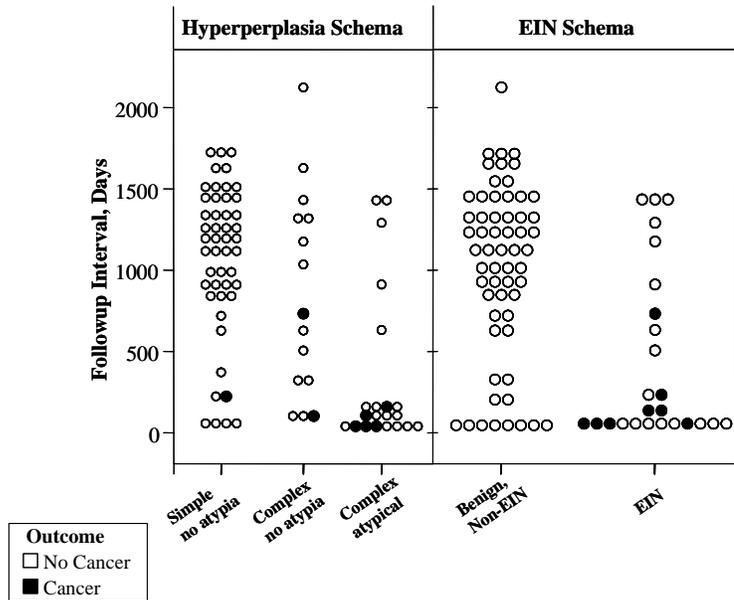


Figure 6: Overall cancer free survival of 674 patients with “endometrial hyperplasia” stratified by morphometry into EIN (D-Score <1) or benign non-EIN (D-Score >1)¹⁹. 65/67 cancer occurrences occurred in the EIN category. Elevated cancer risk of having an EIN lesions is 89 times that of women without EIN. Incidences of carcinoma following EIN diagnosis may be considered concurrent (steep part of curve in months 1-12) or future (more shallow curve > 12 months). These subsets of short and long term cancer occurrences are plotted for this dataset in Figures 3 and 4. 2/446 non-EIN and 65/228 EIN cases developed adenocarcinoma.

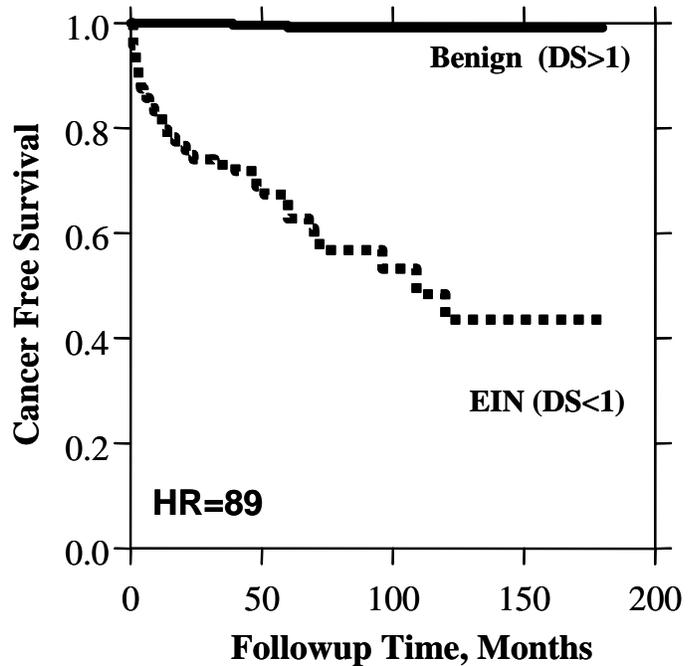


Figure 7: Concurrent Cancer in women with EIN.

“Concurrent cancers,” those diagnosed within 1 year of a baseline cancer-free endometrial biopsy, are more likely to be seen in women with EIN compared to women without EIN. Approximately half of patients with EIN lesions will have a cancer diagnosed in the first year. 197 Women with “endometrial hyperplasia re-stratified into EIN vs. non-EIN categories. 0/87 non-EIN and 43/110 EIN cases developed adenocarcinoma.

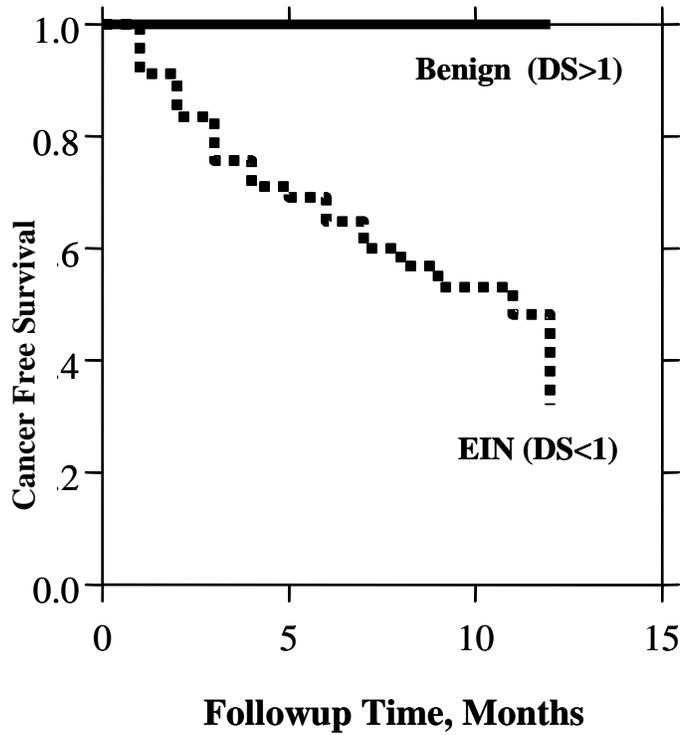
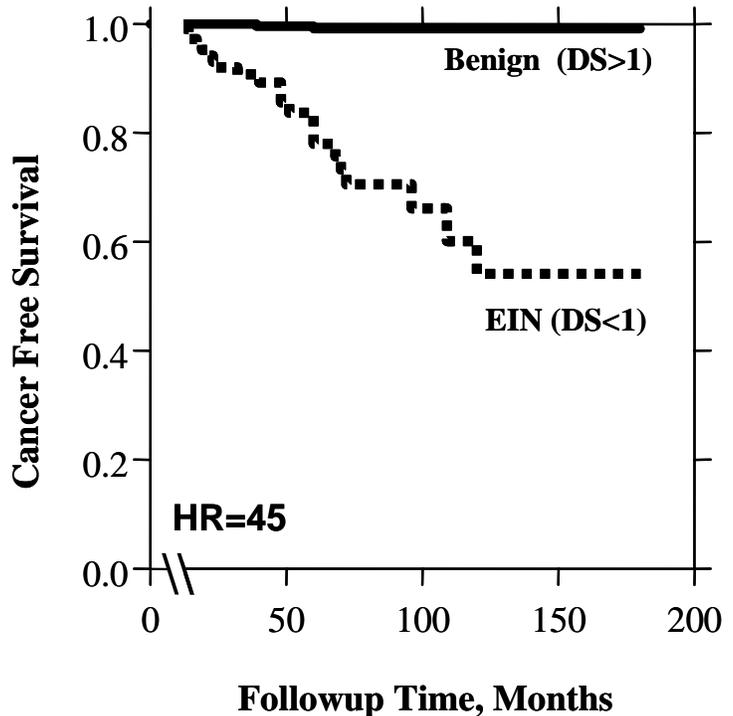


Figure 8: Long term cancer progression in women with EIN¹⁹.

Cancer outcomes that occur more than one year after EIN diagnosis are bona-fide progression events from a premalignant to malignant phase of disease. Progression to cancer more than one year following EIN diagnosis is 45 times more likely compared to women without EIN. Note the tempo of cancer appearance indicates that it can take years for an EIN to evolve into adenocarcinoma.. 477 Women with “endometrial hyperplasia re-stratified into EIN vs. non-EIN categories. 2/359 non-EIN and 22/118 EIN cases developed adenocarcinoma.



5.How Is EIN Diagnosed?

(also see www.endometrium.org)

EIN is diagnosed by a pathologist using routine (hematoxylin and eosin stained) sections prepared from a representative endometrial sample^{26;27}. It is extremely important to note that diagnostic accuracy may be severely compromised by exogenous progestin-containing hormonal therapies. For this reason, primary diagnosis or followup surveillance of a suspected EIN lesion should be based whenever possible on a sample obtained while the patient is not on therapeutic hormones. For those patients on progestins, diagnostic tissue can be obtained 2-4 weeks after stopping exogenous hormones, after completion of a withdrawal bleed. Although computerized morphometry has been a useful tool in identifying features characteristic of EIN, such equipment is not required for routine diagnosis. Rather, pathologist interpretation of stated criteria at a standard microscope is adequate.

It should be noted that EIN is a precursor of endometrioid endometrial adenocarcinomas and is unrelated to the "Endometrial Intraepithelial Carcinoma" proposed²⁸ to be the earliest stages of papillary serous type endometrial adenocarcinomas.

A framework for EIN Diagnosis is shown in Table I at the beginning of this syllabus. Notable is the clear separation of endometrial changes caused by unopposed estrogens, and carcinoma, from EIN.

1.Topography of EIN

The distribution of a lesion is useful in distinguishing between the diffuse, field-wide effects, of an abnormal hormonal environment (anovulation, or persistent estrogen effect), surface changes secondary to stromal breakdown, and more focal EIN. Clonal origin from a single cell requires EIN lesions to begin as local processes within the endometrial compartment. Early EIN lesions are easily diagnosed by their contrast in architecture and cytology with the background from which they have emerged. Over time, EIN lesions may completely overrun the background endometrium, thereby removing the convenient lesion-to-background contrast in morphology which assist in EIN diagnosis. For this reason, or because of fragmentation, many EIN lesions must be diagnosed without the benefit of comparison with companion benign tissues. Exclusion of artifact and careful evaluation of the architectural and cytologic features of EIN usually permits accurate diagnosis in these instances.

2.EIN Diagnostic Criteria

All of the diagnostic criteria of Table IV, listed as A-E below, must be met in order to make an EIN diagnosis. The entire slide should first be scrutinized under low magnification for localizing lesions, and if found, these areas examined under higher power to assess possible changes in cytology within the architecturally distinct focus. Widespread EIN lesions that have replaced the entire endometrial compartment tend to have a sufficiently atypical cytology that background normal endometrium is no longer required as a reference point for accurate diagnosis.

Size, architecture, and cytology features are easy EIN diagnostic criteria. Much more difficult are exclusion of benign mimics and adenocarcinoma from the differential diagnosis. There are no simple rules for benign mimic exclusion. The broad universe of competing entities can only be recognized on sight by one who has the easy familiarity that comes with experience. Consistent demarcation of the EIN-adenocarcinoma threshold remains important clinically because it provides a basis for the clinician to

evaluate the risks of electing hormonal rather than surgical therapy in younger patients who wish to retain fertility.

Special diagnostic challenges, such as recognition of EIN within polyps, interpretation of subdiagnostically small or fragmented lesions, and interpretation of lesions with non-endometrioid differentiation have specific caveats presented below that should be carefully studied.

Table IV: EIN Diagnostic Criteria. Modified after ⁵.

EIN Criterion	Comments
Architecture	Area of Glands greater than Stroma
Cytology	Cytology differs between architecturally crowded focus and background, or clearly abnormal.
Size >1 mm	Maximum linear dimension exceeds 1mm.
Exclude mimics	Benign conditions with overlapping criteria: Basalis, secretory, polyps, repair, etc..
Exclude Cancer	Carcinoma if mazelike glands, solid areas, polygonal “mosaic-like” glands, myoinvasion, or significant cribriforming

a.Architecture: Gland area exceeds stromal area:

A cardinal architectural feature of endometrial precancers is glandular crowding, with a threshold quantitative cutoff for EIN lesions of less than half of the tissue area occupied by stroma (Volume Percentage Stroma). Areas with large dominant cysts should always be avoided in making this assessment. Although EIN is an epithelial disease, visual assessment of the glands themselves is complicated by frequent artifactual displacement from associated stroma, pale staining of most epithelia, and visual "shimmering" between gland epithelia and lumens. These may all be avoided by focusing on the stromal compartment which has the significant advantages of a more uniform composition throughout the specimen, and superior staining qualities. By focusing on the stroma itself only intact fragments in which stroma has not been avulsed from glands will be evaluated.

Careful review of graphic and histologic examples of varying stromal densities will assist in training your eye to classify patient material as above or below the diagnostic threshold. EIN lesions tend to cluster with a median volume percentage stroma of about 40% and non-EIN (benign) lesions cluster at a median of approximately 75%. These differences are sufficiently great that visual assessment by a trained eye can be informative.

b.Cytology of architecturally crowded area is different than background, or clearly abnormal:

There is no absolute standard for cytologic features of EIN lesions, but the cytology of EIN is usually clearly demarcated as divergent from that of co-existing benign endometrial tissues in the same patient. The manner of cytologic change in EIN varies considerably from patient to patient, and can include but not be limited to, increased variation in nuclear size and contour, clumped or granular chromatin texture, change in nucleoli, change in nuclear/cytoplasmic ratio, and altered cytoplasmic differentiation. Stereotypical static descriptions of cytologic atypia, such as nuclear rounding and appearance of nucleoli are met in many but not all EIN lesions. In this sense, a fixed presentation of cytologic atypia is not a prerequisite for EIN. Attempts to define an absolute standard are confounded by

the extreme morphologic plasticity of endometrial glandular cells under changing hormonal, repair, and differentiation conditions.

Cytologic changes in some EIN lesions are manifest as a change in differentiation state to a tubal, mucinous, micropapillary, or eosinophilic phenotype. These must be distinguished from the scattered random pattern of hormonally, or surface located repair-induced “metaplasias.” Further details of how to interpret non-endometrioid EIN lesions are presented in the “Pitfalls” section below.

In those cases with no normal glands for internal reference, it is necessary to assess the freestanding cytology of relevant fragments in the context of their architectural features. Some EIN lesions occupy the entire tissue sample, and should not be underdiagnosed for lack of a convenient benign gland in the area.

c. Size >1mm in maximum dimension:

Accurate EIN diagnosis requires a contiguous field of glands sufficiently large to enable reliable assessment of architecture. A minimum lesion size of 1 mm maximum dimension was required in the previous clinical outcome studies^{18;19;21;23} for an EIN lesion to achieve elevated cancer risk. That area of an EIN lesion which meets architectural (gland area) and cytologic (changed) criteria for diagnosis must measure a minimum of 1mm in maximum dimension, a scale which usually encompasses more than 5-10 glands. Most biopsy formats produce tissue fragments in excess of 1.5-2mm. The size requirement must be met in a single tissue fragment, not added amongst multiple fragments. There is no formal evidence that once beyond the minimum 1mm, EIN lesions should be stratified by size, but if a lesion is discretely focal, it may be of interest to the clinician to know what fraction of the available curettings contain lesion.

Individual or small clusters of cytologically altered glands have an undefined natural history and are best diagnosed descriptively (See Pitfalls section below).

d. Exclusion of Benign Mimics

Patients with one of the conditions listed below may still have an EIN, but this diagnosis should be made with careful consideration into how the coexisting factor(s) may modify the criteria for EIN diagnosis. If a specimen is refractory to confident diagnosis, a comment as to the nature of the problem may be useful in directing management.

1. **Reactive changes** caused by infection, physical disruption, recent pregnancy, or recent instrumentation. These can cause piling up of the epithelium, and loss of nuclear polarity..
2. **Artifactual gland displacement.** Beware diagnosing an EIN lesion if the cytology is identical between areas with crowded compared to uncrowded glands! Many of these are artifactual disruptions where the stroma is sheared and glands pushed in apposition .
3. **Persistent Estrogen Effect:** Randomly scattered cysts of protracted estrogen exposure and occasional branching glands are commonly encountered in anovulatory or estrogen-exposed endometria. Gland density is uniformly irregular throughout the endometrial compartment, with occasional clusters of glands having a cytology identical to the uncrowded areas. These can be diagnosed as “Benign Endometrial Hyperplasia” if glands are significantly crowded, or in some mild cases as "disordered proliferative" endometrium. With increasing duration, microthrombi form and scattered stromal breakdown may be associated with epithelial piling along the collapsed stromal surfaces.
4. **Mid to late secretory endometrium** displays loss of nuclear polarity, nuclear enlargement, and variation in nuclear size which if measured objectively by computerized morphometry overlaps substantially with EIN lesions. Stromal responsiveness to progesterone is not homogenous at all endometrial depths. Lack of stromal pre-decidualization in the deeper functionalis and superficial basalis makes glands appear crowded, and these same glands may display a worrisome cytology and complicated saw-toothed luminal profiles

5. **Endometrial polyps** contain irregularly spaced glands in which scattered glands may differ from native endometrium due to their tendency to have reduced hormonal responsiveness. Benign polyps may also have low volume percentage stroma caused by cysts (senile polyps) or random aggregations of glands. Approximately 10% of EIN lesions, however, will present within an endometrial polyp and these must be diagnosed as described below in the “Pitfalls” section.
6. **Endometrial breakdown** is one of the most common settings for overdiagnosis of a benign endometrium as a precancer or cancer. Breakdown may follow an ovulatory or anovulatory cycle and persist into the transitional period between late menses and early proliferative endometrium. Altered cytology is due to piling up of epithelial cells unsupported by stroma, and associated nuclear changes such as loss of polarity which may be accentuated under certain fixation conditions which exaggerate chromatin texture (Bouin's fixative).

e.Exclusion of Carcinoma

Cancer may coexist with EIN in an individual patient, but should be always be separately diagnosed because current management of carcinoma differs from that for EIN. Keep in mind that absence of carcinoma in a tissue biopsy does not exclude the possibility of that the patient has a cancer which was unsampled during the biopsy procedure. An opinion should always be rendered based upon available material, and clearly stated.

EIN is composed of individual glands lined by an epithelium one cell layer thick. The epithelium may be pseudostratified, but should not be cribriform or composed of solid areas of epithelial cells. Presence of any of the following features involving neoplastic glands is inconsistent with EIN, and a diagnosis of carcinoma should be entertained.

1. Meandering or “mazelike” lumens
2. Solid epithelium
3. Cribriform architecture.
4. “Mosaic” gland pattern of distorted polygonal glands with threadlike intervening stroma

Myoinvasion. Unfortunately, myometrium is rarely available for evaluation in a biopsy or curettage specimen.

Pitfalls of EIN Diagnosis: A Practical Approach

Introduction:

Uncommon presentations of common diseases, and suboptimal specimens are two of the many sources of diagnostic difficulty in endometrial pathology. Combined with a "normal" reference point which changes dynamically throughout the month, and during the life cycle, the very definition of "abnormal" depends on the clinical setting. This section will serve as an introduction to some of the more common problems, with suggestions for coping strategies that will not compromise management of the patient.

Table V: Pitfalls in EIN Diagnosis.

Problem	Response
Fragmented or Distorted	Get levels and ask for a rebiopsy soon (within 3 months) if still worried
Suspicious for EIN but <1mm	Section deeper and evaluate context 1)If extends to edge of fragment <1mm, likely sampling error. recommend rebiopsy soon (within 3 months) 2)If small area in larger fragment, likely a subdiagnostic "pre-EIN". make descriptive diagnosis and recommend followup biopsy in 6 months
Suspicious for EIN but >50% VPS	Descriptive diagnosis and followup in 6 months
EIN in Polyp	Apply usual EIN criteria, using polyp itself as the background for cytologic comparison. EIN in polyps are usually discrete.
Non-Endometrioid Differentiation	If glandular, can use EIN criteria but must rule out specific cancer.
Squamous Morules	Make diagnosis based upon gland component, mentally subtracting morules. Do not consider cribriform if morule separates peripheral lumens
Progestin Effect	Withdraw hormones and rebiopsy 2-4 weeks after cessation of withdrawal bleed

If confounding factors preclude a definitive classification of the specimen at hand, make a descriptive diagnosis and clearly communicate the character of the unresolved differential and specific reason for diagnostic uncertainty. Pathologists vary in their attitudes towards making clinical recommendations for followup within the pathology report. We do this routinely, especially if the sampling instrument or strategy needs to be changed in the next diagnostic procedure, or the clinician must discontinue progestins to improve diagnostic accuracy. Whatever the venue for communication, the pathologist is often well equipped to contribute a constructive plan for resolution of the diagnostic problem. For example, the patient who is biopsied while on exogenous progestins may be easier to evaluate after withdrawal of hormones. Confusing histologies such as those obscured by extensive altered cellular differentiation ("metaplasias") should be described clearly. Other specimens may be compromised by sampling errors, or superimposed regenerative epithelial changes. All should be clarified by additional studies, deeper levels or immediate resampling to detect the presence of diagnostic areas elsewhere, or followup with rebiopsy. If the patient is symptomatic, some clinicians will elect to treat with a trial of high dose progestins followed by a post-withdrawal biopsy. Recommendations for interpretation of some commonly encountered diagnostic problems are listed in Table I.

Subdiagnostic EIN-like lesion:

Lesions suspicious for but subdiagnostic for EIN deserve clear description and if clinically appropriate, resampling. Obvious localizing lesions characterized by a changed cytology sometimes do not meet either the minimal 1 mm size or 50% volume percentage stroma EIN requirements. This is a heterogeneous group composed of examples of poorly sampled EIN lesions, very early precursors of EIN that have not yet reached the diagnostic threshold, and subtle benign mimics.

The fragment context of small or loosely packed localizing lesions should be evaluated after obtaining deeper levels. If the affected fragments in deeper levels remain <1mm in size, with densely packed lesional glands extending from edge to edge, there is a high likelihood that tissue disruption of a larger lesion is the problem. These may be diagnosed as “Fragments of crowded glands with altered cytology consistent with, but not diagnostic of, EIN” with a recommendation to resample within 3 months.

If the fragment is large, but the focus of clustered cytologically altered glands remains <1mm, or has insufficient gland density for EIN, then sampling error is unlikely. This is a small category of cases, comprising roughly one fifth or one quarter of the frequency of easily diagnosed EIN lesions. These rare lesions are probably pre-EIN precursors with a lower cancer risk than bona fide EIN. They should be diagnosed descriptively (“microscopic cluster of cytologically altered glands, See Note”) with a recommendation for followup biopsy in 6 months.

Every effort should be made to avoid overdiagnosis of small groups of contrasting glands as EIN. Patients with unopposed estrogens may randomly have a few tubal glands in proximity, polyps can contain irregular distributions of glands, and the patient with endometritis or repair can have local effects which polarize the endometrium. Examination of the background context is most helpful in these circumstances.

EIN within an Endometrial Polyp:

In general, all criteria for EIN diagnosis apply to EIN arising within a polyp, but the reference point for interpretation of EIN cytology and architecture are the background polyp itself, not the normal endometrial functionalis. EIN within polyps are best recognized as geographic regions of contiguous glands with an architecture and cytology readily distinguished from that of the background polyp. Avoid overreaction to bland dominant cysts lined by atrophic epithelium, as these are a common component of benign senile polyps or mixed endocervical-endometrial polyps.

The benign polyp will have a regularly irregular distribution of glands. Cytologic variation will not appear in geographic clusters of glands, but rather interspersed or splayed on the periphery with loose boundaries. Random apposition of glands in proximity can be recognized by a cytology identical to that of more dispersed glands elsewhere in the polyp.

On those occasions when EIN is diagnosed within a polyp, the polyp setting should be clearly mentioned in the report. If completely excised, a polypectomy may be curative. If incompletely excised, the physical bulk of a polyp can prevent adequate followup sampling by flexible devices (Pipelle).

Non-Endometrioid EIN vs. “Metaplasia”:

EIN lesions with non-endometrioid cytology must be distinguished from benign “metaplasias.” A shift in cytodifferentiation may be the cytologic change which characterizes some EIN examples, which also meet other size, architecture, and exclusion criteria. In most instances they are localizing lesions with a classic EIN geography composed of mucinous, tubal, or eosinophilic glands. A special case are those glandular lesions containing round intraluminal expansile squamous morules. These morules may be quite abundant, creating distortion of the volumetric relationships between gland and stromal compartments. Since it is the glandular, not morular component of these lesions which have premalignant

behavior, the bulk contributed by morules should be mentally excluded when assessing the size of the glandular vs. stromal compartments. If possible, search for morule poor areas with glands that meet EIN criteria.

The differential diagnosis between EIN and carcinoma may have special considerations in non endometrioid lesions. Solid morules surrounded by a peripheral garland of lumen-containing glands resemble a cribriform pattern that may easily be overinterpreted as adenocarcinomas. True cribriforming involves glandular epithelium only, and should not be diagnosed when the cells separating individual lumens are squamous. Criteria for diagnosis of a mucinous and squamous adenocarcinomas are different than those for endometrioid adenocarcinomas. The distinction between EIN and carcinoma in these cases must be made using differentiation-state appropriate criteria.

Confounding progestin exposure:

Progestins, whether endogenous or pharmacologic, alter endometrial gland cytology and variably expand the stromal compartment to modify gland-stromal relationships. EIN lesions exposed to progestins tend to display nuclear shrinkage and homogenization of coarse chromatin, with pseudodecidual change responsible for separation of glands making them appear less crowded. In contrast, nuclei of glands in normal secretory endometrium greatly enlarge, and the proportion of glands to stroma varies by height within the functionalis. The paradoxical result is that in the presence of progestins EIN lesions become more bland, and normal endometrium more worrisome. In its most extreme form, pregnant patients with Arias Stella phenomenon have dramatic epithelial atypia caused by polyploidy, and these areas typically demonstrate minimal stromal decidualization, resulting in very crowded gland architecture.

Many EIN lesions rebiopsied in the midst of a course of therapeutic progestins will no longer be diagnostic. For this reason, the pathologist should avoid providing assurance of therapeutic efficacy from a biopsy secured while still on progestins. When diagnostic features are present, EIN lesions can and should be diagnosed through a progestin effect. This may be somewhat deceptive to the clinician, however, as much of the therapeutic benefit of progestin therapy is conferred by the massive wave of apoptosis and endometrial shedding which follows withdrawal of progestins²⁹. The patient still on hormones has not yet reached the culmination of therapy, so the significance of “persistent” EIN lesions in that setting is unclear. This combination of interpretive difficulties for the pathologist, and premature endpoint for the patient, makes biopsy while still on progestins an inappropriate followup for a known EIN lesion. A recommendation for rebiopsy 2-4 weeks after withdrawal of hormones is in the best interest of the patient.

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