Endometrial Precancers:
The Benign Endometrial Hyperplasia Sequence and EIN

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INTRODUCTION

The diagnostic strategies outlined here are based upon an integrated picture of endometrial carcinogenesis from diffuse hormonal changes (benign hyperplasia sequence) to the earliest recognizable premalignant cells (Endometrial Intraepithelial Neoplasia, EIN) [26]. In the past, both generalized hormonal responses and localized premalignant lesions were lumped under the term "endometrial hyperplasia," with various modifiers such as "adenomatous", "mild, moderate, and severe", and "atypical" that had no uniform meaning. The WHO 1994 classification system subdivided hyperplasias by architectural complexity and cytologic atypia [31]. Although this practice has been widespread, and has had a benefit of unifying terminology, it fails to optimally stratify patients according to those pathologic mechanisms and cancer risks necessary for appropriate therapeutic triaging. Diagnoses are poorly reproducible [38]. Recent molecular studies have provided evidence that the use of the term hyperplasia is conceptually correct for some but not all of these lesions. For these reason, we have chosen to present a practically oriented disease classification in which the hormonal effects of unopposed estrogens (benign hyperplasia) and emergent neoplastic precancerous lesions (endometrial intraepithelial neoplasia (EIN)) are separately diagnosed using non-overlapping terminology and discrete criteria [2]. We acknowledge that the term "hyperplasia" is problematic, given its complex history and varied diagnostic application. However, the subset of largely polyclonal proliferations that result from a physiologic response of the endometrium to an abnormal estrogenic stimulus precisely fits the general definition of hyperplasia. In contrast, the clonal subset has the characteristics of a non-invasive neoplasm, and should be diagnosed as such (EIN). Compelling genetic, biologic and histologic evidence supports the use of these two diagnostic terms in a new way.

Part I: THE DISORDERED PROLIFERATIVE AND BENIGN ENDOMETRIAL HYPERPLASIA SEQUENCE

Benign endometrial hyperplasias do not have a singular histopathologic appearance, but rather demonstrate sequential changes occurring in a combination and severity that reflects the quantity and duration of unopposed estrogen exposure [37]. Characteristic histologic features include irregular remodeling of glands, variably accompanied by vascular thrombi, stromal breakdown and randomly scattered cytologic changes. Some estrogen induced changes persist, with modification, even after the estrogen level declines or is quenched by addition of progestins. This aggregate group of benign endometrial hyperplasias can thus be envisioned as a temporal sequence of estrogen-induced changes in which the appearance at any single time point is codetermined by the trajectory of prior morphologic changes and the current hormonal environment. Prolonged estrogen exposure unmitigated by opposing progestins confers a modest 2-10 fold increased

endometrial cancer risk [28;32;39]. Those benign endometrial hyperplasias that develop histologically discontinuous EIN lesions are associated with dramatically increased cancer risk. The challenge to the pathologist is to divide the diverse histologic presentations of benign endometrial hyperplasia into functionally defined subgroups, while maintaining a sharp diagnostic boundary with premalignant EIN lesions.

Table I: Endometrial Diagnostic Terminology

Nomenclature	Topography	Functional Category	Treatment
Benign Endometrial Hyperplasia	Diffuse	Prolonged Estrogen Effect	Hormonal therapy, Symptomatic
EIN Endometrial Intraepithelial Neoplasia	Focal progressing to diffuse	Precancerous	Hormonal or surgical
Endometrial adenocarcinoma, endometrioid type, well differentiated	Focal progressing to diffuse	Malignant	Surgical stage-based

Pathophysiology

Benign endometrial hyperplasia is encountered most frequently around the time of the menopause, when the normal cycle of sequentially regulated estrogen and progesterone is perturbed in tempo and amount. It can also occur, however, in young women and teenagers, in whom anovulatory cycles are also the norm. The primary pathology in all these cases is a systemic excess of estrogens, albeit one in which the endometrium is secondarily altered and a frequent source of symptomatic bleeding. The pathognomonic feature of persistent estrogen stimulation is architectural changes of individual glands distributed randomly throughout the entire hormonally responsive region of the endometrium (superficial functionalis). Prolonged proliferation as a result of unopposed estrogens first gives rise to disordered proliferative endometrium, and over time an increasingly irregular distribution of individually variable endometrial glands which are known as benign hyperplasia. Disordered proliferative endometrium and the earliest phases of benign hyperplasia of the endometrium thus share a common pathogenesis, and present a continuous spectrum of overlapping histopathologic features (Table II) rather than sharply different appearances. Precise discrimination is somewhat arbitrary.

In a woman of childbearing age, there is characteristically prolonged or excessive bleeding at intervals that are initially longer than normal. Microinfarcts and estrogen withdrawal are responsible for symptomatic bleeding [10;34]. Both mechanisms may be effective at different times in patients with benign hyperplasia. Patchy stromal breakdown secondary to estrogen-induced microthrombi can produce intermittent spotting. A relative reduction in the prolonged estrogen stimulation causes apoptosis of the endometrial glands and stroma of the hypertrophied functionalis [34], and resultant heavy shedding. Occasionally, decline in estrogen levels is sufficiently gradual that generalized apoptosis and shedding fail to take place.

Superimposition of progesterone upon a benign endometrial hyperplasia occurs in women with delayed ovulation, sporadic corpus luteum development in the perimenopausal years, or therapeutic administration of progestins following an extended follicular phase. Down-regulation of estrogen receptors by progestins leads to a dominant progestational effect, regardless of the

presence or absence of continued estrogen production. In this environment menstrual shedding is delayed, as progestins have the capacity to directly support the endometrium. Progesterone related stromal and secretory glandular changes develop within the setting of irregular glands previously developed under the influence of estrogens. Thus, the histologic appearance at diagnosis may be heavily modified by intermittent or accompanying progestins although the causal event in benign hyperplasia is unopposed estrogen.

Table II: Histological Features of Benign endometrial hyperplasia (not all are present in every case)

Feature	Comment	Disordered Proliferative	Benign Hyperplasia		Benign Hyperplasia with superimposed progestin effect	Shedding following Benign Hyperplasia
			active phase	exhausted phase		
mitotic activity	similar to normal proliferation	+	+			
scattered cysts	within functionalis, random placement	+	+	+	+	
tubal metaplasia	randomly involves scattered tubular or cystic glands. +/- cilia	+	+	+	+	
variable gland density	"regularly irregular" secondary to gland proliferation and remodeling		+	+	+	
bulky specimen	reflects prolonged proliferative activity		+	+	+	
fibrin thrombi	often separate or displaced		+	+	+	+
microinfarcts with epithelial change	randomly placed, multifocal, with intervening intact		+	+	+	
low or absent mitoses	reflects decline in estrogen			+	+	+
secretory change	variable extent depending on exposure				+	+
stromal pre-decidualization	may be patchy or lacking, depending on progestin exposure				+	+
global breakdown	architectural clues obscured, cytology degenerative					+

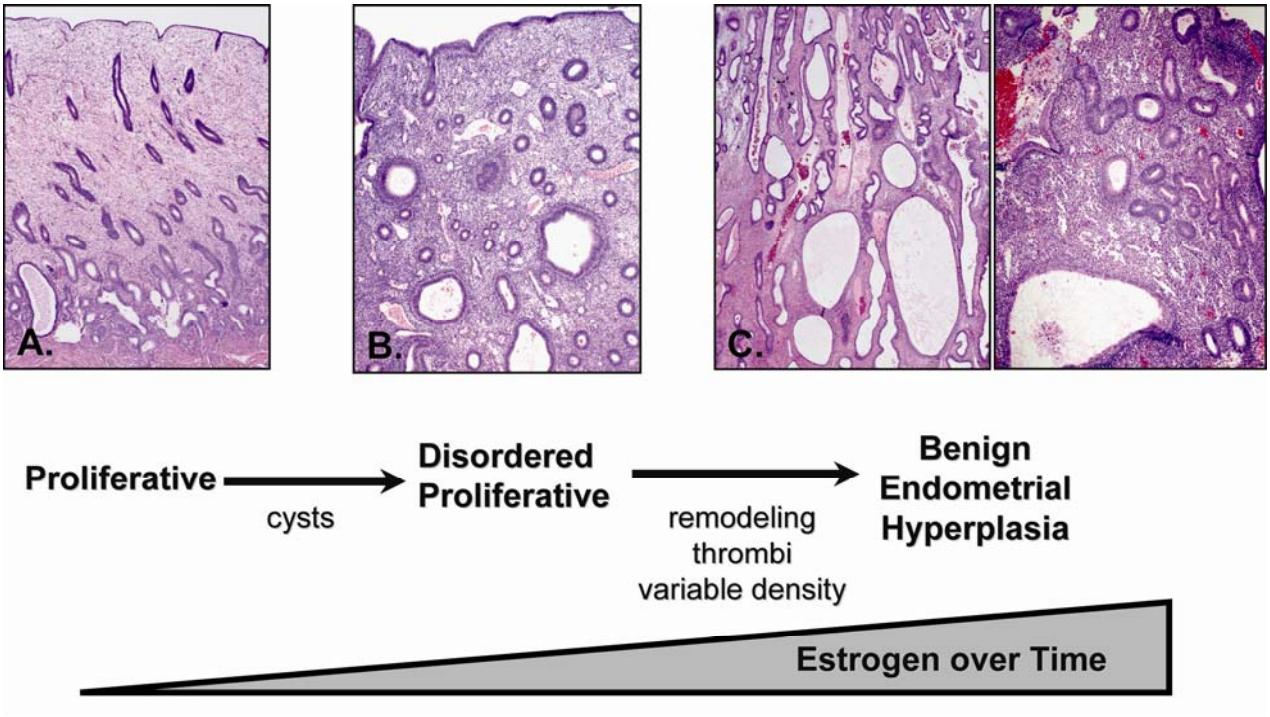


Figure 1: Progressive Effects of Unopposed Estrogens.
Early effects of unopposed estrogen are scattered cysts in an otherwise normal appearing proliferative endometrium, known as disordered proliferative endometrium. Continued exposure causes a progressive spectrum of histopathologic change (left to right) including increasing irregularity of gland density and shape, scattered alterations of cytologic appearance known as benign hyperplasia. Established benign hyperplasias demonstrate a high degree of remodeling between glands and stroma of the expanded, hyperplastic, endometrial compartment, in which the ratio of glands to stroma exceeds 1.0 in most or all of the endometrial compartment. Fibrin thrombi, stromal breakdown and associated reactive epithelial changes commonly develop, and must be carefully distinguished from neoplastic processes.

Diagnostic Features

Abundant curettings with characteristically diffuse and widespread morphologic features typify endometria altered by unopposed estrogens. The histologic changes of disordered proliferative and benign endometrial hyperplasia are conceptually and morphologically well represented as a unified disease spectrum, separate and discontinuous from EIN. The histologic hallmark of the benign hyperplasias is a generalized but non-uniform proliferation of architecturally variably shaped glands that equal or exceed the quantity of the stroma.

<u>Disordered proliferative endometrium.</u>

Disordered proliferative endometrium is an exaggeration of the normal proliferative phase without significant increase in the overall ratio of glands to stroma. The changes involve the entire endometrial compartment, and are evident at low magnification as sacculated dilations (microcysts) randomly scattered amongst tubular glands lined by mitotically active epithelial cells. The stroma is usually dense, cellular and abundant, and mitoses may also be encountered. Some background tubular glands are slightly irregular and minimal budding and branching is commonly seen. Ciliated cell change (tubal metaplasia) of endometrial glandular cells is common, reflecting estrogen's pivotal role in the process. The estrogen primed cell often has substantial cytoplasm. Characteristically, glands affected by tubal differentiation are randomly interspersed amongst proliferative glands, and they also may demonstrate tubular, branching, or cystic architecture.

Benign endometrial hyperplasia.

Benign endometrial hyperplasia develops from disordered proliferative endometrium under the continued influence of unopposed estrogens. The entire endometrial compartment contains variable gland densities caused by remodeling of stroma and glands to the extent that in some areas the gland to stroma ratio exceeds 1:1. It is the increased gland density that distinguishes benign hyperplasia from disordered proliferative endometrium. Individual glands may be tubular, cystic, or branching, and these forms are commingled throughout. On a large scale the endometrium appears uniformly affected, however, at medium magnification local admixtures of individually variable glands present quite differing appearances among separate microscopic fields. This combination of low magnification uniformity, made up of variable medium magnification fields, can be described as "regularly irregular".

A critical feature of benign hyperplasia is that the cytology does not change between architecturally crowded and uncrowded areas. This reflects the systemic hormonal etiology of the process that similarly exposes the entire endometrium, and allows its distinction from EIN. Cytologic characteristics may change over time with the evolving hormonal state of the patient, and superimposition of local factors such as breakdown and repair. During the established phase of active estrogen exposure glands are proliferative and interposed tubal metaplasia is common.

Unopposed estrogen states are the most common setting in which fibrin thrombi are seen in the intact endometrial functionalis [10]. Fibrin thrombi are rarely seen in normal late secretory endometrium, and there is little evidence that vascular thrombosis is a primary mechanism of normal menstrual shedding. Sometime after initiation of cystic gland dilatation the endothelial lining of ectatic superficial endometrial vessels becomes damaged and occlusive luminal fibrin thrombi form. Thrombi are often intimately associated with discrete areas of surrounding stromal breakdown, which has been interpreted either as a cause or effect of the vascular lesion. Whatever the sequence and mechanism of events, the two are linked in disordered proliferative endometrium and benign hyperplasias, and are responsible for patchy non-synchronous endometrial breakdown and resultant symptoms of spotting and intermenstrual bleeding. Collapse of intervening broken-down stroma may lead to close apposition of endometrial glands, degenerative epithelial changes, and dislodgement of vascular thrombi from their tissue context.

Estrogen production from persistent follicles or by peripheral conversion following the menopause is inconstant. When the estrogen level declines slowly, massive breakdown does not occur and the glands lose mitotic activity. These endometria retain the architectural features of a bulky endometrium with altered gland architecture, but the glands demonstrate a mitotically inactive and non-stratified appearance and may be karyorrhectic. With waning estrogen levels, endometrial bulk declines towards an atrophic pattern, sometimes with cysts.

Differential diagnosis of Benign Endometrial Hyperplasia

A commonly encountered pattern that may be mistaken for benign endometrial hyperplasia is composed of prominent cystically dilated glands with flimsy walls composed of scant fibrous stroma. The terms 'cystic atrophy' or 'cystic atrophic endometrium' describe these lesions, which show cuboidal or flattened and inactive cells lining the distended glands. Furthermore, the glands in cystic atrophy lack budding and infoldings.

Endometrial polyps may have many of the features of endometrial hyperplasia, but they are localized lesions with a distinctive stroma. Polyps arise as monoclonal overgrowths of genetically altered endometrial stromal cells with secondary induction of polyclonal benign glands through as yet undefined stromal-epithelial interactive mechanisms [5;11]. Thick walled blood vessels and fibrous stroma commonly seen in polyps are lacking in benign endometrial hyperplasia. Because polyps are focal lesions, specimens obtained by undirected biopsy or curettage typically contain

commingled normal endometrium with a completely different histologic pattern. This is not the case with benign endometrial hyperplasia where the entire functionalis is affected. Despite these differences, there are individual cases in which the distinction between an endometrial polyp and lesions in the benign hyperplasia sequence can be difficult, and endometrial polyp remains one of the most common causes of an incorrect diagnosis of hyperplasia.

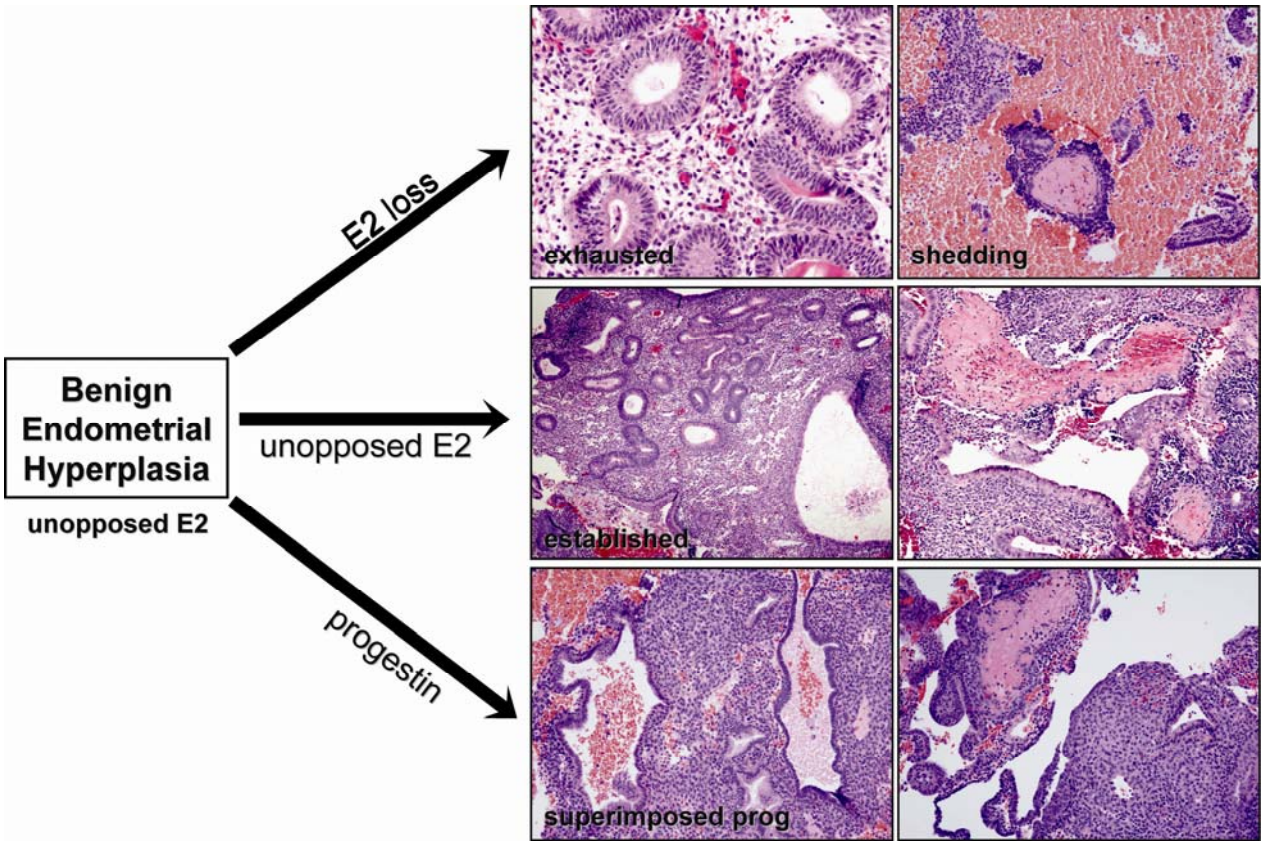


Figure 2: Sequential Modulation of Benign Endometrial Hyperplasia.
Accurate recognition of the class of changes referable to unopposed estrogen, here encompassed within the benign endometrial hyperplasia categories, is facilitated by recognition of their dynamic character and secondary modification within a sequential framework. Cessation or progesterone inhibition of prolonged estrogenic stimulation may occur at any time, at which point benign hyperplasias lose their mitotic activity and the endometrium is no longer proliferative. Architectural changes of the estrogen-driven interval are retained, so that a diagnosis of benign hyperplasia can provide indirect evidence of the prior hormonal state of unopposed estrogens.

<u>Benign endometrial hyperplasia with superimposed progestin effect</u>.

Superimposition of endogenous or exogenous progestins upon benign endometrial hyperplasia shuts down mitotic activity, and may initiate secretory change with or without subsequent stromal pre-decidualization. The most common endogenous progesterone source is delayed ovulation in a perimenopausal woman, where the corpus luteum is formed on an abnormal schedule, or otherwise is unable to elaborate normal quantities of progesterone. Similar effects can be seen in women having benign hyperplasia treated by low dose or intermittent progestins, such as are seen in many oral contraceptive formulations. High dose progestins, in contrast, usually induce pronounced stromal decidualization. The architecturally abnormal glands may persist within this background, but tend to become atrophic with time.

Withdrawal shedding following benign hyperplasia

Cessation of estrogenic stimulation, such as occurs systemically upon shutdown or exhaustion of the persistently active ovarian follicle, leads to rapid endometrial-wide stromal breakdown and heavy menses. This occurs through a direct apoptotic effect upon endometrial stromal and epithelial cells, rather than thrombosis-initiated infarction responsible for breakdown during the estrogen rich period. Evidence of secretory and predecidual change may or may not be present, depending on whether delayed ovulation occurred, and the extent of tissue preservation. Architectural features of cysts and irregular gland distribution are increasingly obscured by stromal collapse, eventually yielding a nondescript collection of individual glands with extensive reactive changes. For these reasons, it can be difficult to confirm in the late stages of shedding whether the preceding cycle was normal or abnormal, or whether a benign hyperplasia was present or not. Fibrin thrombi, which are durable sequelae of many benign hyperplasias, remain identifiable despite extensive stromal breakdown.

Part II: Endometrial Intraepithelial Neoplasia

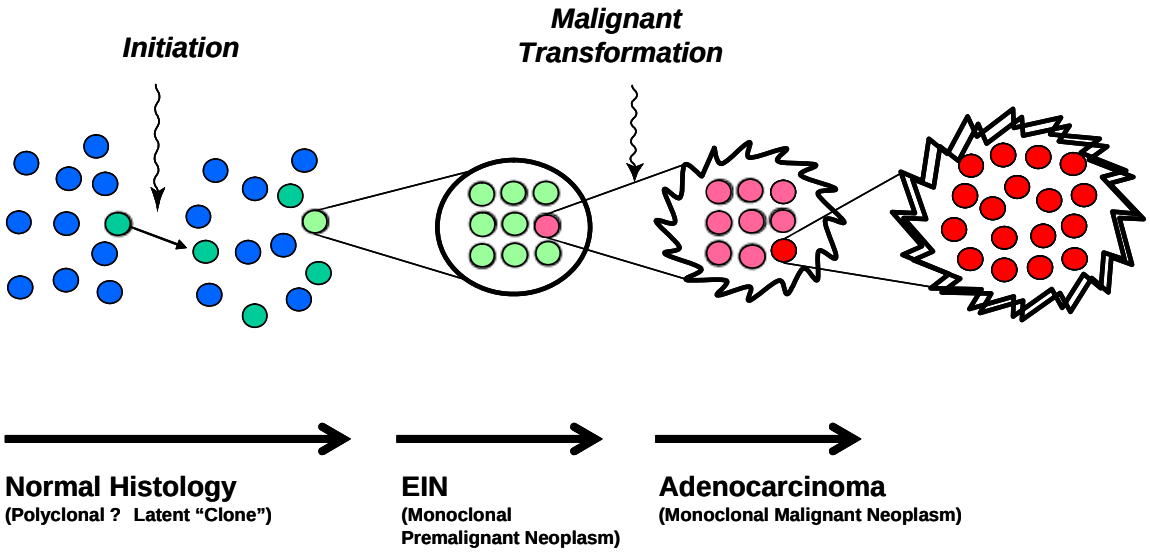
Biology of EIN: Endometrial Intraepithelial Neoplasia [26]

Endometria 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 women [29], 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 cycles [21]. 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 [24;33], 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 Group [24] 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 [9;13;20]. Divergent genotype [19].
Precancers share some, but not all features with carcinoma	Including PTEN [14;15;22], K-ras [6;25;30], and MLH1 changes [8]. Both are monoclonal [9;13;18;20]. Precancer-cancer lineage hierarchy [19].
Precancers can be diagnosed	Computerized morphometry reference standard for EIN [18]
Precancers increase risk for carcinoma	High concurrent cancer rate in EIN [2;2;7] High future cancer rate in EIN [3;4;12;27]
Epidemiologic and genetic mechanisms are linked	The PTEN gene, mutated in EIN, is subject to hormonal modulation [22;23]
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. [35]

3.WHO Hyperplasia-EIN Concordances

Concordances with EIN diagnostic system and were obtained by review of cases initially diagnosed using other endometrial hyperplasia classification schemes [12].

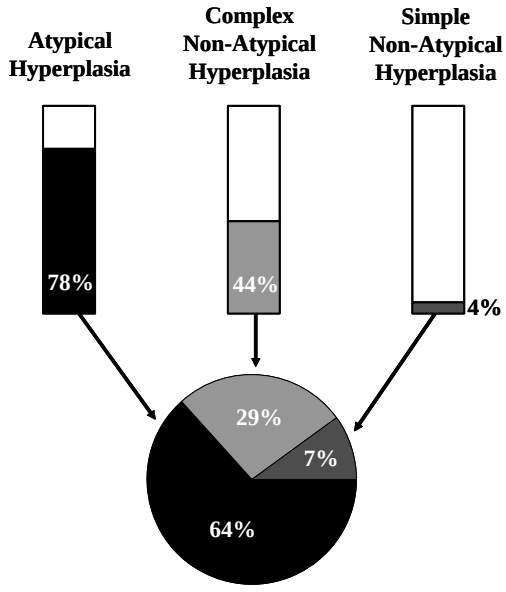


Figure 4: Correlation of WHO and EIN Diagnoses. Gray portions of Bar Graphs show approximate percentages of each WHO hyperplasia class that will be diagnosed as EIN. Remaining WHO hyperplasias not diagnostic of EIN (white) will be allocated to unopposed estrogen (anovulatory), polyp, and other categories. Pie chart shows relative contributions of each hyperplasia type to the EIN diagnostic category in a series of 97 cases with 28 EIN examples [12].

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 [4;7;27], the two studies summarized below show cancer predictive value of subjective (Figure 5) [12] and objective histomorphometric (Figures 6-8) [2] 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) schema [12]. 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.

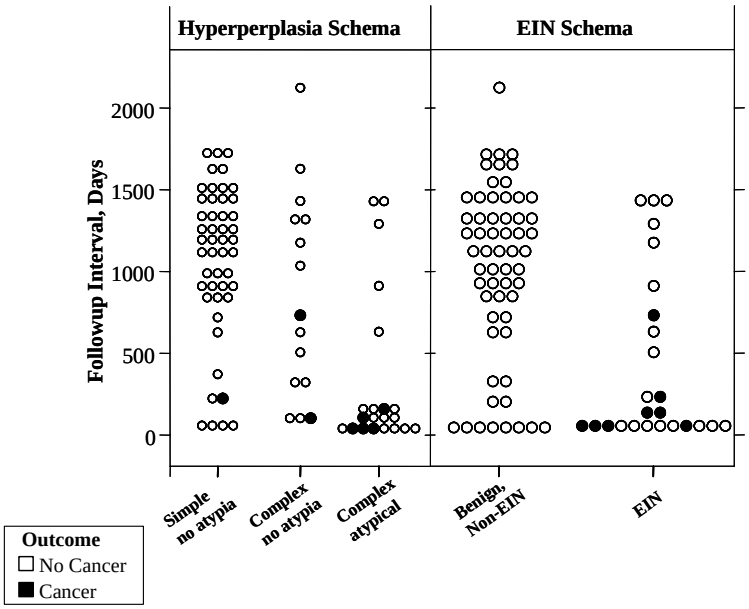


Figure 6: Overall cancer free survival of 674 patients with "endometrial hyperplasia" stratified by morphometry into EIN (D-Score <1) or benign non-EIN (D-Score>1) [2]. 65/67 cancer occurrences occurred in the EIN category. Elevated cancer risk of having an EIN lesions is 89 times that of women without 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.

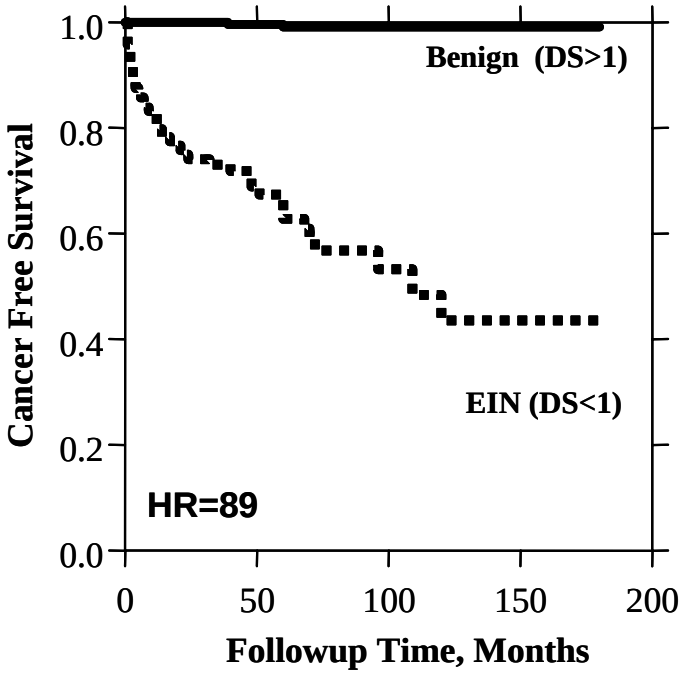


Figure 7: Concurrent Cancer in women with EIN. "Concurrent cancers," those diagnosed within 1 year of a baseline cancer-free endometrial biopsy, are more likely to be seen in women with EIN compared to women without EIN. Approximately half of patients with EIN lesions will have a cancer diagnosed in the first year. 197 Women with "endometrial hyperplasia restratified into EIN vs. non-EIN categories. 0/87 non-EIN and 43/110 EIN cases developed adenocarcinoma.

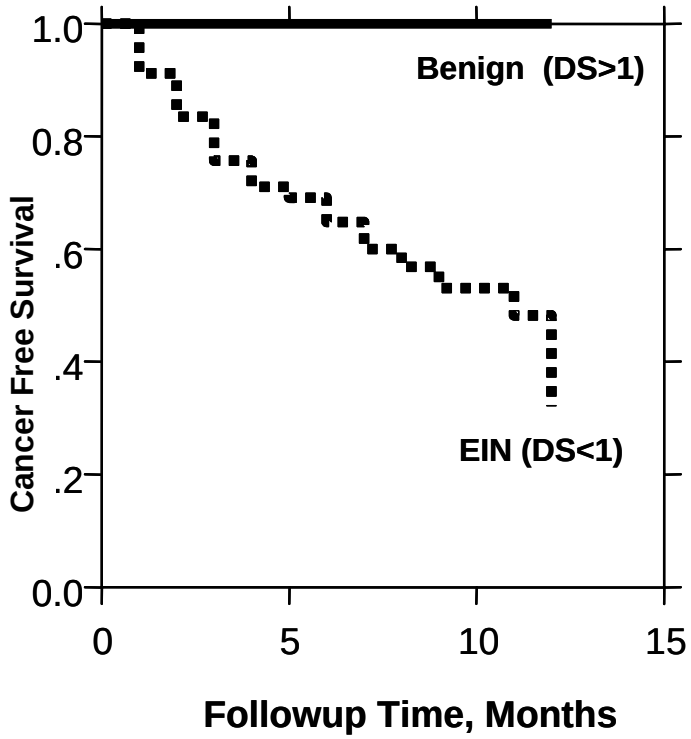
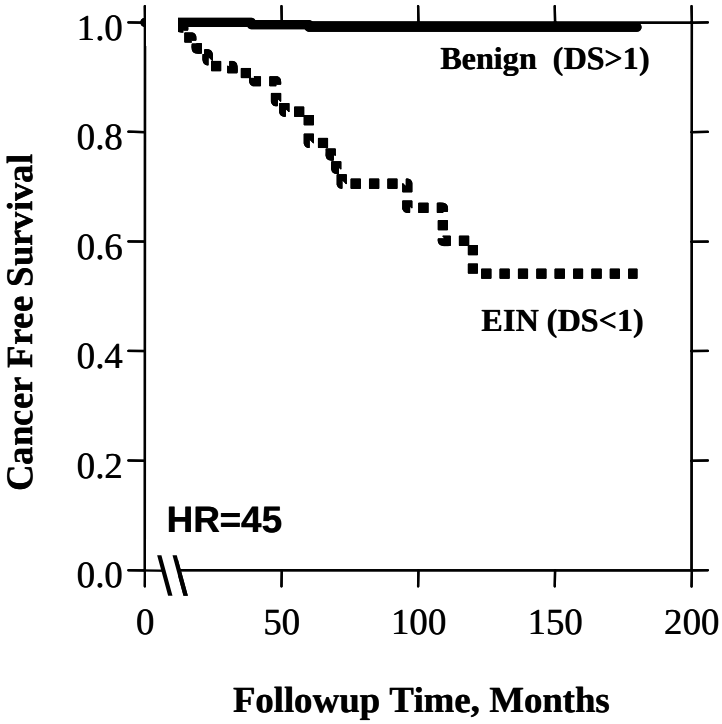


Figure 8: Long term cancer progression in women with EIN [2]. Cancer outcomes that occur more than one year after EIN diagnosis are bona-fide progression events from a premalignant to malignant phase of disease. Progression to cancer more than one year following EIN diagnosis is 45 times more likely 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 restratified 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 [16;17]. 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" proposed [1] 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 sylabus. 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 [33].

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 [2-4;7] 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 heterogenous 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 progestins [36]. 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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