Endometrial Intraepithelial Neoplasia

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- **Context.**—Developed in conjunction with molecular and progression data, the sequence classification schema for endometrial intraepithelial neoplasia (EIN)/benign hyperplasia (BH) provides an easy to adopt and reproducible method for classification of endometrial biopsies.

- **Objectives.**—To review current data supporting the use of BH/EIN to classify endometrial biopsies, and to discuss the hormone-driven endometrial sequence from anovulation/disordered proliferative endometrium through BH and EIN and their diagnostic difficulty.

- **Data Sources.**—A comprehensive review of EIN literature based on literature indexed by PubMed (National Library of Medicine) and Google Scholar.

**Conclusions.**—The BH/EIN schema is gaining wider acceptance among pathologist and clinicians. The research leading to the EIN criteria is based on molecular and progression data. The BH/EIN schema has better reproducibility among pathologists, is intuitively easy to use, and requires understanding of endometrial physiology and neoplasia.


The classification of endometrial lesions into benign hyperplasia (BH) and endometrial intraepithelial neoplasia (EIN) reliably separates the histologic features seen because of unopposed estrogen and those due to the accumulation of neoplastic mutations. The EIN classification system is gaining widespread acceptance in diagnostic surgical pathology, clinical gynecology, and basic science fields. The key to its success lies in the integration of histologic findings to the underlying genetic changes in a manner that is useful for clinical management. Simply put, EIN is the histologic manifestation of an underlying molecular progression in endometrial carcinogenesis and is a lesion that can be diagnosed for purposes of therapeutic decisions.

In comparison to the four categories (simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia) that comprise the World Health Organization (WHO) 1994 classification system, proponents of the BH/EIN classification system have shown improved reproducibility in the diagnostic setting.1–4 In addition, the EIN system accurately stratifies patients who have a high risk of developing endometrioid (type I) endometrial carcinoma.5 Issues related to intraobserver variability with the WHO classification have been widely published,6–9 with κ values for all endometrial diagnosis being 0.2 to 0.71 and 0.31 when comparing hyperplasia with, and without, atypia, respectively, which is considered a major therapeutic breakpoint. In comparison, the κ value for subjective EIN diagnosis is between 0.73 and 0.90 at the point at which patients receive treatment.1–2 In addition, the EIN classification system accurately segregates neoplastic lesions with oncogenic mutations, namely PTEN and PAX2, from those without such potential.5,10–12 Although proponents of each classification argue for the adoption of a particular scheme, knowledge about the features of the EIN system is important for understanding the features of various physiologic versus neoplastic processes of the endometrium, and it is a powerful method for classifying endometrial lesions.

Understanding the interplay of physiologic, age-related changes in the endometrium and the effects of estrogen on the endometrium is essential in separating benign endometrium from BH. Furthermore, these hormone-driven features compose the background from which EIN is thought to arise. The EIN system enables pathologists to recognize and separate truly neoplastic lesions with a high rate of progression from those that are due to hormonal imbalances.

**BRIEF HISTORY OF THE DEVELOPMENT OF EIN CRITERIA AND COMPONENTS OF THE EIN SYSTEM**

Conceptually, the EIN system is a synthesis of all new data since the 1980s into an evidence-based diagnostic schema that matches current concepts of pathogenesis. It is not a semantic sleight of hand, recasting old strategies in fresh words. Rather, it is a reduction to diagnostic practice using hematoxylin–eosin–stained slides and is based on objective correlation of computer-assisted morphometric data with molecular and clinical progression annotations. The D score is the score generated by morphometry that correlates with progression of EIN to endometrial carcinoma. Patients with biopsies with a D-score less than 1 have a high rate of conversion to endometrial carcinoma, whereas biopsies from patients with a D-score higher than 1 almost never have progression to endometrial carcinoma.13–15 The D score combines 3 variables into a mathematic formula. The...
variables were chosen for their predictive power of segregating endometrial biopsies by clinical cancer outcomes.\textsuperscript{3,13} The variables include the volume percentage of stroma (which quantifies the amount of stroma in a given area or, by extension, the number of glands); the glandular complexity, as measured by the length of the basement membrane of the endometrial gland; and the standard deviation of the shortest nuclear axis, which is a measure of pleomorphism. Although most of the original data supporting EIN was performed with objective morphometry, subjective assessment of biopsies by routine light microscopy using EIN criteria has been proven to closely correlate to morphometry, to be reproducible, and to be easy to establish in routine surgical pathology practice.\textsuperscript{14} For example, the morphometric finding that most precancerous lesions have a volume percentage of stroma of less than 50\% easily translates to “gland area exceeds that of stroma,” or more simply, “there are more glands than there are stromata.” In routine surgical pathology practice, adoption of the EIN system allows for some biopsies to be designated by their loss of genetic alterations that can lead to neoplasia and aberrant proliferation. Endometrial intraepithelial neoplasia (EIN) represents a sharp divide between those with metaplasia or lesions in a complicated polyp or atypical hyperplasia, and separates them from EIN, a precancer, and endometrial carcinoma.

**Molecular Aberrations**

Criteria used for EIN have the advantage of correlating with underlying molecular defects, which can be identified by their loss of \textit{PAX2} and \textit{PTEN} by immunohistochemical staining and appear as radially expansile, crowded foci of cytologically altered glands. By subjectively identifying EIN by light microscopy, the pathologist is identifying a clonal lesion that has a significant risk of developing into, or residing concurrently with, an endometrioid endometrial lesion that has a significant risk of developing into, or a preinvasive carcinoma. Lesions identified as EIN have been shown to be clonal cell populations with particular genetic aberrations. Mutations or alterations involving \textit{PTEN}, \textit{PAX2}, \textit{KRAS}, as well as microsatellite instability, have all been demonstrated in endometrial carcinoma.\textsuperscript{3,11,13,16} The \textit{PTEN} and \textit{PAX2} genes were the first known to be involved in the development of EIN (and in some cases of hyperplasia with and without atypia), and their loss is known to occur before a histologic lesion is evident.\textsuperscript{12,16-18} The \textit{PTEN} gene is a tumor-suppressor gene that is lost in up to 83\% of endometrioid endometrial adenocarcinomas and 63\% of EIN lesions.\textsuperscript{16} Likewise, \textit{PAX2} is lost in 77\% of endometrial carcinomas and 74\% of EINs, compared with 36\% of normal background endometrium.\textsuperscript{19} Despite their intuitive utility in delineating boundaries of clonal EIN lesions, application of \textit{PAX2} and \textit{PTEN} immunostains is to be discouraged in routine clinical practice. The immunohistochemical findings of \textit{PAX2} and \textit{PTEN} loss may be displayed before development of a clinically significant lesion; up to 43\% of normal endometrial biopsies from cycling, premenopausal women contain small foci of \textit{PTEN} or \textit{PAX2} loss.\textsuperscript{19} The loss of \textit{PTEN} and \textit{PAX2} in these cases hints at a stepwise progression of genetic alterations that can lead to neoplasia and aberrant immunostaining, which can occur before a histologically recognizable lesion is evident. In select cases, particularly those with metaplasia or lesions in a complicated polyp or secretory background, \textit{PAX2} staining may provide some assistance in separating cases of EIN from metaplasia.\textsuperscript{12,15} The \textit{PAX2} stains (nuclear) are much more robust than the \textit{PTEN} (nuclear-cytoplasmic) stains are and are easier to interpret (Figure 1).

**Clinical Significance and Diagnostic Terminology**

A new diagnosis of EIN is associated with a concurrent occult carcinoma in approximately one-third of cases defined as a cancer diagnosis within 1 year.\textsuperscript{20} For those patients who remain cancer free in the first year, they have a 45-fold risk of progression to endometrioid endometrial carcinoma compared with patients with non-EIN hyperplasias.\textsuperscript{1,2,21} Although progression rates are difficult to determine because most patients receive definitive surgery, that increased risk is at least comparable to atypical hyperplasia in the WHO nomenclature, which has been cited as having up to a 37\% to 43\% increase risk of concurrent adenocarcinoma.\textsuperscript{22,23} This contrasts to a 29\% progression rate for a diagnosis of complex atypical hyperplasia.\textsuperscript{24} Regardless of the classification system used, both schemes identify women at risk for developing carcinoma and lead to appropriate treatment. There is no direct concordance of WHO to EIN categories because the two strategies employ differing criteria that are often nonequivalent. The WHO system largely relies on relatively fixed notions of how atypical endometrial cells appear, whereas an EIN criterion combines crowded architecture and a relative change in cytology in the high-risk category.\textsuperscript{2,6} In a set of cases diagnosed using the WHO criteria, 78\% of atypical hyperplasias, 44\% of complex hyperplasias, and 4\% of simple hyperplasia were reclassified as EIN.\textsuperscript{2} The diagnosis of EIN is relatively uncommon, accounting for 1.4\% of endometrial biopsies in one series at a large academic tertiary medical center, whereas endometrioid endometrial adenocarcinoma was seen in less than 1\% of biopsies.\textsuperscript{2}

As will be discussed, BH and disordered proliferative endometrium make up a spectrum of histologic changes due to hormonal effects, whereas EIN represents a sharp transition to true neoplasia with underlying molecular mutations/alterations. Endometrial intraepithelial neoplasia greatly increases the risk of endometrioid endometrial adenocarcinoma, which shares common genetic and molecular changes. Endometrial intraepithelial neoplasia should never be confused with endometrial intraepithelial carcinoma, which refers to serous carcinoma and is driven by a \textit{p53} mutation. Awareness of these 2 entities and their histologic features is critical for avoiding misclassification.

**HYPERPLASIA: HORMONALLY-DRIVEN ENDOMETRIUM**

The endometrium may display a wide histologic spectrum that is largely dependent on the hormonal state of the patient. Estrogen, in the form of estradiol, drives proliferation of the endometrium, whereas progesterone halts proliferation and preserves the endometrium from breakdown. The relative ratio and duration of each hormone determine the histologic appearance of the endometrium from proliferative endometrium to secretory endometrium and finally withdrawal and breakdown.\textsuperscript{13} Any condition that alters the normal balance of these hormones will result in altered histology.

Most endometrial biopsies are performed following symptomatic uterine bleeding. The main clinical concern is separating women who have cancer or will develop cancer from those who are bleeding for other reasons. The latter category is composed of a diverse group of diseases including estrogen-driven hyperplasia, endometrial polyps, physical distortion of the endometrium due to submucosal leiomyomas, and atrophy. For the surgical pathologist, separating diffuse changes that are due to unopposed
estrogen from discrete premalignant lesions is the most important task and can be difficult. Unopposed estrogen may be from endogenous or exogenous sources and can occur in several clinical settings. Elevated endogenous estrogen in premenopausal or perimenopausal women commonly arises from chronic anovulation because of obesity and/or polycystic ovary disease. Women may have increased estrogen because of the peripheral conversion in adipose tissue of androstenedione to estradiol, leading to endometrial stimulation, which can occasionally result in endometrial hyperplasia and carcinoma. Exogenous estrogen may be from hormone replacement therapy or from other nonprescribed sources, such as herbal remedies. Less commonly, women with a hormonally active ovarian neoplasm present with endometrial symptoms. Regardless of source, increased estrogen not counterbalanced by progesterone can lead to a field effect of benign hyperplasia, which can be fertile soil for the development of neoplasia. 

Normally, estrogenic proliferation of the endometrial glands is offset by the effects of progesterone released by the ovary via the corpus luteum following ovulation. Anovulation results in the prolonged release of estrogen and the relative lack of progesterone resulting in disordered proliferative endometrium. Prolonged estrogenic stimulation causes the endometrial glands to continue proliferating, becoming larger and more complex. Histologically, this appears as dilated or “sacculated” endometrial glands admixed with small endometrial microcysts (Figure 2). Estrogen affects the stroma as well, and thus, the two proliferate in tandem, resulting in an altered balance of endometrial glands to stroma, which can achieve a ratio of 1:1 or higher. These architectural features are best observed at low power, where they are seen to randomly be

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**Figure 1.** Endometrial intraepithelial neoplasia (top) demonstrating loss of nuclear staining by PAX2 immunohistochemistry (original magnification ×4).

**Figure 2.** Anovulatory endometrium with microcyst formation and irregularly shaped glands. Note the presence of tubal metaplasia (inset, arrow) (hematoxylin-eosin, original magnifications ×20 [inset] and ×4).

**Figure 3.** Benign hyperplasia. An area of gland crowding is present; however, the glands are cytologically uniform. The cytologic features and regularly irregular pattern was maintained in all tissue fragments in this case (hematoxylin-eosin, original magnification ×4).

**Figure 4.** Low-power view of endometrial intraepithelial neoplasia (EIN). The glands composing the EIN can be seen spreading between normal background glands at low power within the oval. An arrow points to an example of altered cytology, visible at low power. The line denotes approximately 1 mm (hematoxylin-eosin, original magnification ×4).
The effects of unopposed estrogen from any cause may be modulated by progesterone from either physiologic or therapeutic sources. Use of low- to high-dose progesterone is common clinical practice and has a pronounced effect on the histologic appearance of the endometrium. Anovulatory endometrium may variably be followed by ovulation and progesterone production with the establishment of the corpus luteum. Depending on the duration of the corpus luteum, the effects of progesterone may be incomplete. Progesterone will result in the cessation of mitotic activity and “decidualization” of the supporting stroma. The endometrial glands become small, round, and inactive. **HISTOLOGIC CRITERIA FOR EIN**

The diagnosis of EIN must meet 5 criteria in a single fragment, including architectural gland crowding, altered cytology, minimum size of 1 mm, exclusion of carcinoma, and exclusion of mimics. The diagnosis of EIN can be summarized as a focus of clustered endometrial glands exceeding a gland to stroma ratio of 1:1, which have altered cytology from the background endometrium, and which comprise a sufficient volume of 1 mm (Table).

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<tr>
<th>Endometrial Intraepithelial Neoplasia</th>
<th>Histologic Criteria</th>
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<td>Architectural gland crowding</td>
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<td>Altered cytology relative to background glands</td>
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<td>Minimum size of 1 mm</td>
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Withdrawal of unopposed estrogen or discontinuous exposure leads to endometrial breakdown and shedding. Microthrombi may be evident in areas of hemorrhage and breakdown. Breakdown typically displays densely basophilic, stromal aggregates with a lining of benign, usually eosinophilic, endometrial epithelium. The classic features of stromal breakdown are usually seen with sudden cessation of unopposed estrogen. In situations where estrogen slowly declines, the features are more subtle. Initially, the glands cease to proliferate, and mitotic figures are rare to absent. Karyorrhectic debris may be present. The glands themselves may be sufficiently supported by the lower estrogen levels, leading to architecturally complex glands without the proliferative appearance described previously.

Continued and prolonged exposure to unopposed estrogen results in endometrial BH. The histologic break point between disordered proliferative endometrium/anovulatory endometrium and endometrial hyperplasia is indistinct because the physiologic cause is continuous. Benign hyperplasia is typically associated with higher levels of estrogen present for longer periods, when compared with anovulatory endometrium. Benign hyperplasia is largely an endometrial-wide process, and thus, the changes will be present in all fragments at low power. However, there are regional variations in hormone responsiveness, thus, leading to rare examples of “focal” BH when the entire endometrium is sampled (ie, a regularly, irregular pattern). An overall increase in the endometrial gland density, seen in most tissue present, with a lower volume percentage of stroma is the defining feature that separates disordered proliferative endometrium from BH. Although, theoretically, the changes of BH should affect the entire endometrium, individual microscopic foci will demonstrate variation at higher magnification with areas of increased glandular density; clusters of small, tubular glands; and areas of larger cystic or branching glands. Thus, at higher-power magnification, the pattern may be irregular, but the overall impression is of a uniform increase in gland density. The glands themselves are mitotically active, and large geographic clusters of crowded glands with altered cytology (cytologic demarcation) should be absent (Figure 3). Comparison of cytologic change between the crowded and uncrowded areas (when present, referred to as demarcation) is paramount in differentiating BH from EIN. As in the disordered proliferative endometrium, tubal metaplasia is common but is distributed in an interspersed, random, arrangement, unlike the cohesive nests with altered cytology required to diagnosis EIN.

Initial low-power assessment of the entire biopsy is essential in the recognition of the architectural criteria of EIN. Pathologists who begin at high power, or who do not have ready access to a very low magnification objective, are prone to miss small areas of EIN as these stand out by contrast with unaffected fragments at low power (Figure 4). Following identification of crowded glands at low power, evaluation for altered cytology (cytologic demarcation) should follow. Essentially, the crowded glands must differ cytologically from the background “normal” glands. The histologic features of the background glands are variable because they are subject to the patient’s hormonal milieu. Within the crowded glands, features of “atypia” may sometimes be seen and are classically described as an increase in nuclear size and shape, clumped or granular chromatin, loss or alteration of polarity, and stratification. Although some EINs may show these prototypic features of classic “atypia” descriptions, they are not always present in exactly this form; some EIN nuclei are elongated, and cytoplasmic differentiation may be a key part of the
cytologic changes that offset a lesion from its background (Figure 5). Hence, the use of a relative lesion-background cytologic comparison is a more robust measure of a premalignant process.

Identification of cytologic demarcation may be complicated by several factors. Longstanding or more-progressed EIN lesions may replace most of the background, leading to little to no background endometrium to evaluate. When faced with this scenario, it is important to verify there is indeed gland crowding, and, if present, a search for rare, interspersed, benign endometrial glands may be informative. If such areas cannot be found, the cytologic atypia is usually too significant to be considered benign, and a diagnosis of EIN should be made. Another complicating factor is physical separation of the lesional and background areas into different fragments. In these cases, careful comparison of the presumed precancer lesion and background material should be made, recognizing that the relevant areas may reside on completely different areas of the slide.

To qualify as EIN, the lesion meeting all architectural and cytologic criteria must measure 1 mm or more in a single linear extent. This criterion was developed and validated using fragmented biopsy and curetting specimens, so the effects of tissue breakup are already taken into account. Two separate foci may not be combined to qualify as EIN. The measurement is made from the two most-distant poles of glandular density, rather than the more-peripheral and less-dense areas of EIN. The size criterion is an essential feature of the diagnosis to prevent the overdiagnosis of EIN and subsequent hysterectomy. Often, isolated clusters of endometrial glands with altered cytology measuring less that 1 mm are found in benign endometrium.13 These foci are usually benign and may represent metaplasia or reparative change and should not be considered EIN; if concern for EIN is present, a suggestion for resampling in 3 to 6 months
may be made. The 1-mm cutoff is set to avoid overdiagnosis of benign reparative or metaplastic changes, which tend to be focal and comprise no more than 3 to 6 glands.

The exclusion of carcinoma is essential in making the correct diagnosis of EIN. Features of carcinoma include solids sheets of neoplastic cells, cribriforming, loss of intervening stroma, rambling, mazelike glandular growth, and polygonal glands with threadlike, intervening stroma. The presence of any of these findings should alert the surgical pathologist to the potential diagnosis of carcinoma, rather than EIN, regardless of size.

The exclusion of mimics can be particularly vexing because of the vast and varied appearance of the endometrium. The most common mimics are reparative endometrium, metaplasia, endometrial breakdown, secretory endometrium, the effects of unopposed estrogen, and polyps. The many benign mimics makes this criterion especially difficult, particularly for pathologists who see few endometrial biopsies.

Reparative endometrium, whether due to breakdown, infection, previous manipulation, or pregnancy, may appear crowded and atypical. The glands may contain stratified cells with loss of nuclear polarity, which, occasionally, form syncytial aggregates or pseudopapillae. Frequently, the cells may appear enlarged and polygonal with abundant eosinophilic cytoplasm (Figure 6). These features are usually limited to the superficial endometrium and should be excluded as a mimic when not identified in deeper tissue fragments.

Secretory changes overlap with EIN criteria because the nuclei of secretory glands lack polarity, are enlarged, and may be quite pleomorphic. To complicate matters further, the secretory state often leads to gland crowding, exceeding that seen in some EINs. The background stroma will typically have a predecidualized appearance. The predecidualized surface may not be present in the basalis and deep functionals. The presence of cytoplasmic vacuolization and low-power, serrated architecture may be a helpful histologic feature, even when only focally present (Figure 7). Endometrial intraepithelial neoplasia may exist within a secretory background, and low-power identification of an altered population of glands that stands out from the background is paramount. Endometrial intraepithelial neoplasia occurring alongside secretory endometrium is typically “more well differentiated” than is the surrounding background endometrium.

Polyps pose interpretive problems, and the key is to use the polyp itself as the reference background pattern, against which, an emergent, localized, cytologically altered EIN can be recognized. Polyps frequently contain altered architecture with cystically dilated glands that may be focally crowded. Indeed, fragmented polyps in endometrial biopsies can become the cause of misdiagnosed hyperplasia because of the altered, and possibly crowded, glands. Conversely, the dense, fibrous stroma of endometrial polyps may prevent the crowding of neoplastic (EIN) glands, leading to a lower level of gland crowding than would be expected in nonpolyp endometrium; however, some alteration in gland morphology is usually evident at low power. Identification of altered cytology, when compared with the background glands in the polyp, is the first step in recognizing such lesions. Occasionally, the cytology of the glands within the polyps may differ from that seen in the nonpolyp endometrium, creating the false impression of cytologic demarcation. The presence of altered cytology of the architecturally altered glands compared with the background glands in the polyp is essential in making the correct diagnosis of EIN in an endometrial polyp.

**METAPLASIA**

The evaluation of any endometrial biopsy may be complicated by the presence of metaplasia, which may have numerous appearances, including both “benign” and “malignant.” The most common types of metaplasia mistakenly diagnosed as atypia or carcinoma include ciliary (tubal), eosinophilic, squamous, mucinous, hobnail, clear cell, and papillary syncytial metaplasia. Each type of metaplasia has been associated with a risk of misdiagnosis. Accurate interpretation of the clinical significance of “metaplasia” requires an assessment of its overall topographic distribution. When present geographically in a focus of crowded glands, consideration of the possibility of EIN should be raised.

Endometrial intraepithelial neoplasia frequently coexists with various types of metaplasia, and altered cytologic differentiation is a common manifestation of the cytologic demarcation that characterizes EIN. Carlson and Mutter noted that just less than one-half of the cases diagnosed as EIN contained squamous morular metaplasia, whereas tubal secretory metaplasia was present in up to one-third. Less common are mucinous and micropapillary differentiation. Differentiation states are frequently unstable across an EIN field, so when present, this may not be a uniform characteristic of the entire lesion. Additionally, this study noted that polyps were more common in women with EIN. Additionally, the polyps themselves were associated with metaplasia and EIN. That study encouraged the use of the description of nonendometrioid, or, altered differentiation as opposed to metaplasia.

Metaplasias of various types differ in their diagnostic reproducibility because pathologists differ in their notions of the number of, and correct designations for, endometrial metaplasias. Identification of squamous morular metaplasia is the most reproducibly diagnosed metaplasia followed by mucinous metaplasia. However, squamous morular metaplasia can appear very dense and simulate EIN or adenocarcinoma as demonstrated in a study evaluating responses to an online EIN quiz, in which two-thirds of participants identified morular metaplasia as EIN or carcinoma. Squamous morules are terminally differentiated elements of proliferating glands that have lost their hormone receptors and become mitotically quiescent. They do not directly participate in progression to adenocarcinoma, so when present in an EIN lesion, the morules must be visually subtracted from assessment of the gland to stroma ratio. Additionally, the identification of other common types of metaplasia has poor agreement between pathologists. This is somewhat problematic because metaplasia is common in the endometrium and may mimic neoplasia because it appears different from the background endometrium. In such circumstances, the glandular density should remain balanced and not satisfy the architectural criteria of EIN. Squamous morular metaplasia, in particular, may cause the superficial appearance of increased gland density. However, if the morular component is mentally subtracted and the stroma is compared with the endometrial epithelium, the 1:1 ratio should be maintained.
The presence of some forms of metaplasia has been shown to be associated with neoplastic endometrial lesions such as EIN, whereas others, such as “papillary syncytial metaplasia,” are terms descriptive of degenerative effects. Therefore, the simple presence of metaplasia should be interpreted by the pathologist as being part of a broader process with clinical significance: reactive, hormonal, or neoplastic. If judged to confer increased risk to the patient, or if of unknown significance, this should be clearly mentioned in the report. Squamous morula formation, and some architectural patterns of eosinophilic, mucinous, and tubal metaplasia have been associated with a risk of developing endometrial carcinoma. Interpretation of the topographic (scattered, diffuse, local) and local (gland density) architectural context of the metaplastic glands is required to judge its clinical import. Although metaplasia is not itself neoplasia, its presence in a biopsy specimen should be met with a determined effort to more specifically reach a diagnosis that is clearly benign (reactive, hormonal, benign polyp), premalignant (EIN with altered differentiation), or malignant (adenocarcinoma with altered differentiation).

Immunohistochemistry should not play a significant role in diagnosing EIN and should not be used in routine practice because of the issues cited previously. However, the loss of PAX2 by immunohistochemistry may highlight the difference between EIN occurring in an area of confusing metaplasia. A secretory background may be confused with EIN because of its crowded glandular component and altered cytology. This may be particularly problematic if hormonally unresponsive endometrial glands are present in the background, mimicking altered cytology. A discreet focus of PAX2-null glands within a secretory background would highlight the diagnostic area of EIN, assuming it meets the criteria of EIN on routine stains.

SUBDIAGNOSTIC LESIONS

In cases where crowding of cytologically altered glands is the concern, but gland density or size are insufficient for EIN diagnosis, a descriptive diagnosis of focal crowding of cytologically altered glands with a comment suggesting follow-up and additional sampling in 3 to 6 months is appropriate. Immediate rebiopsy in the wake of a healing reactive endometrium is rarely helpful. In these cases, diligent exclusion of benign causes, such as artifact, polyp, or poorly oriented normal tissues, as well as additional levels are advised to avoid misdiagnosis. These cases are rare with a specific study citing the occurrence of 0.3% from a large number of endometrial biopsies. In that series, cases of focal gland crowding and small foci of atypical glands were noted to have an increased incidence of EIN (23%) and carcinoma (4%) on follow-up sampling.

IMPLEMENTATION

Implementation of any new classification scheme may be met with confusion and skepticism from both pathologist and clinicians. The migration from the four-tier WHO system to the 2-category EIN system (benign hyperplasia and EIN) has been successfully conducted in many practice settings. Some immediate benefits of the EIN system include improved diagnostic concordance, clearer treatment categories, and criteria-based diagnoses. Recent research and anecdotal evidence suggests that although treating clinicians have readily adopted EIN terminology, pathologists, particularly general surgical pathologists, must carry the burden of changing their own diagnostic methods while reeducating their clinical audience.

Kane and Hecht describe the adoption of EIN by a general academic surgical pathology practice. Adoption occurred in 4 phases: (1) general education of both pathologists and clinicians by gynecologic pathologist; (2) creation of sets of pathologist training slides containing EIN that had and had not been previously classified as congenital adrenal hyperplasia, endometrial polyps, and anovulation; (3) pathologist review of the training slides and a teaching seminar; and (4) implementation into clinical practice. Following their “go live” date, diagnoses of EIN, indeterminate for EIN, or any other variation requiring description were reviewed with a gynecologic pathologist. Importantly, reports during the transition included a brief description of EIN and indicated treatment similar to congenital adrenal hyperplasia. The rate of follow-up carcinoma was reported at 17% in the general surgical pathologist group, compared with 34% in the gynecologic pathologist group.

Although EIN is a departure from previous endometrial biopsy classification schema, it is easy to implement and interpret because the criteria are precisely stated and more easily communicated between pathologists when compared with “atypia.” Atypia is fundamentally ambiguous and has a high level of inherent subjectivity. Furthermore, by using features of neoplasia (ie, altered cytology, architectural crowding occurring in sufficient size), factors due to the transient hormonal state are accounted for. Anecdotally, in our experience, residents in training grasp the BH/EIN sequence rapidly and readily use this system in evaluation of endometrial biopsies. Residents have expressed greater clarification in understanding the physiology of the endometrium, in identifying EIN, and in how to handle cases where “atypia” is questionably present.

TREATMENT

One of the major strengths of the EIN system is its correlation to outcome data. As discussed, a biopsy diagnosis of EIN imparts a 45-fold increased risk of progression to carcinoma after the first year. Hysterectomy following the diagnosis of EIN is appropriate because there is a high rate of concurrent, as well as future, endometrioid endometrial carcinoma in women with EIN. In circumstances in which the patient desires fertility or is not a surgical candidate, progestin therapy is an increasingly offered alternative. Progestin regimens are not standardized, and clinical outcomes are primarily available from anecdotal series rather than controlled randomized clinical trials. A common practice following progestin administration is a follow-up biopsy every 6 months following withdrawal until a minimum of 3 negative biopsies are obtained. The purpose of the progestin withdrawal is to allow completion of a shed, which includes removal of much of the lesion. Evidence of progestin therapy includes pseudodecidualized stroma and small, round, inactive background endometrial glands. When EIN persists in the face of progestin therapy, it may display mucinous differentiation and show less crowding and complexity than in previous biopsies (Figure 8). Careful wording of the pathology report is required to convey that residual EIN is present as well as the hormonally induced changes.
CONCLUSION

The EIN classification system is gaining more-widespread acceptance as the pathology community gains more experience with the criteria. In addition to improved reproducibility, EIN classification enables a more rigorous assessment of the features of neoplasia, which takes into account architectural changes, changes in cytology, and a size cutoff set to achieve appropriate specificity and sensitivity. A diagnosis of EIN by endometrial curettage is a strong predictor of the risk of developing endometrial carcinoma. Additionally, the BH/EIN sequence accounts for a full range of histologic features encompassing prolonged hormonal stimulation and premalignant neoplastic change.

From the standpoint of diagnostic sign-out, the migration to EIN criteria should be relatively easy. The pathologist must be familiar with the overall physiology and varying histologic appearance of the endometrium due to prolonged estrogen exposure, in addition to knowing the EIN diagnostic criteria. Another essential component of adoption is communication with the managing clinician regarding the new terminology and how it translates to suggested treatment. Like any classification system, widespread adoption will reveal new difficulties that will have to be resolved. Biopsies with significant metaplasia, polyps, or progesterone-treated biopsies are areas of known diagnostic difficulty. In such cases, consultation with colleagues with significant gynecologic pathology experience or expert review would be prudent.

The EIN scheme is the result of our evolving understanding of endometrial carcinogenesis. It reflects the synthesis of molecular data with histologic changes that pathologists can readily and reproducibly identify on routine hematoxylin-eosin staining.

References