Introduction
In the past, both generalized hormonal responses and localized premalignant lesions have been lumped under the term “endometrial hyperplasia” subdivided by architectural complexity and cytologic atypia. We now know that the hormonal effects of unopposed estrogens and emergent neoplastic precancerous lesions are clinicopathologically distinct entities that can and should be diagnosed using non-overlapping terminology and discrete criteria (Table 1). 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, and is called “benign endometrial hyperplasia”. In contrast, the monoclonal subset of premalignant lesions (1) has characteristics of a non-invasive neoplasm, and is diagnosed as “endometrial intraepithelial neoplasia” (EIN) (2).

Diagnostic criteria for EIN and benign endometrial hyperplasia as presented here include several key features which were unknown at the time of development and standardization of the 1994 WHO system of atypical and non-atypical hyperplasias (3). In the case of EIN, these include minimum size of localized lesions, precise objectively defined gland crowding thresholds, and interpretation of cytologic changes by comparison with background normal glands in the same sample. For this reason entities in the EIN schema do not correlate absolutely with older WHO classes, and EIN diagnosis should be practiced as a replacement of, rather than supplement to, the 1994 WHO system.

Epidemiology and Risk Factors
Benign endometrial hyperplasia is encountered most frequently around the time of the menopause or postmenopause, 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 who may experience anovulatory cycles. Persistent estrogen production may be associated with ovarian abnormalities such as granulosa cell tumors, thecomas, polycystic ovary disease or exogenous administration of estrogens.

Epidemiologic risk factors for EIN are essentially those of endometrioid endometrial adenocarcinoma: protracted unopposed estrogen exposure and its surrogate markers of obesity, and diabetes. EIN is a rare lesion, being present in only 1.4% of endometrial biopsies in a busy practice environment (4). The average age of women with EIN is 53 years (5), which is about nine years earlier than the average of 62 for endometrial adenocarcinoma (6). Fully 37% of women with EIN in an endometrial biopsy will have adenocarcinoma detected at hysterectomy (7). These can be specified as occult concurrent carcinomas not appreciated at biopsy. The interval for progression from EIN to adenocarcinoma can be estimated in individual patients who undergo protracted surveillance following an EIN diagnosis. Once patients with concurrent adenocarcinoma are excluded (defined as cancer found within the first year of follow-up), the average interval to diagnosis of adenocarcinoma is 4 years (8).

Screening
Because there are no systematic endometrial screening programs, and the PAP smear is ineffective for screening, benign endometrial hyperplasia and EIN are detected almost always within the context of an endometrial biopsy performed in response to patient symptoms or incidental to workup of an unrelated disorder or when monitoring women receiving hormone replacement therapy. Thoroughness of sampling

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Cancer Risk</th>
<th>Topography</th>
<th>Functional Category</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Benign Endometrial Hyperplasia</td>
<td>1-5x</td>
<td>Diffuse</td>
<td>Prolonged Estrogen Effect, polyclonal field changes</td>
<td>Hormonal therapy, Symptomatic</td>
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<tr>
<td>Endometrial Intraepithelial Neoplasia (EIN)</td>
<td>45x</td>
<td>Focal progressing to diffuse</td>
<td>Precancerous monoclonal neoplasm</td>
<td>Hormonal or surgical</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma, endometrioid type, well differentiated</td>
<td>--</td>
<td>Focal progressing to diffuse</td>
<td>Malignant monoclonal neoplasm</td>
<td>Surgical stage-based</td>
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is a key element in successful detection of EIN lesions, especially those that are physically small and localized at the time of diagnosis. Because only some EIN lesions are grossly evident, the practitioner should always perform random sampling of the endometrium, even when a visible lesion is evident at hysteroscopy (9,10). Use of hysteroscopic sampling devices that yield crushed, cauterized, or very small samples should be avoided as these can be difficult for the pathologist to interpret. Endometrial biopsy (including by Pipelle) and dilation and curettage are both sensitive in EIN detection, so the choice is largely a clinical one (11-13).

Symptoms
Most patients with benign endometrial hyperplasia eventually become symptomatic and present with abnormal vaginal bleeding. This is easily recognized in the postmenopausal woman. In a woman of childbearing age there is characteristically prolonged or excessive bleeding at intervals that are initially longer than normal, or infertility. As the endometrial bulk increases through proliferation, the bleeding may become more frequent and almost continuous.

The most common (84%) presenting symptom of EIN is abnormal bleeding (5), but some patients have no symptoms and the abnormality only becomes apparent when diagnosed incidentally at biopsy or the lesion has progressed to carcinoma.

Diagnosis and Histopathology
Distinction between benign endometrial hyperplasia and EIN is critical because the former will result in symptomatic hormonal management, and the latter aggressive attempts at lesion ablation by surgery or high dose progestin therapy. Benign endometrial hyperplasia is essentially a normal endometrial field responding to an abnormal hormonal environment, whereas the cells of an EIN lesion are intrinsically abnormal in having clonal mutations that confer a growth advantage over adjacent tissues (Figure 1). This difference in biology is reflected in their respective cancer risks of 1-5 fold and 45 fold.

Benign endometrial hyperplasia is a functional class of diffuse estrogen induced lesions characterized by irregular remodeling of glands, and variably accompanied by vascular thrombi, stromal breakdown and randomly scattered cytologic changes. 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. Early effects of unopposed estrogen are scattered cysts in an otherwise normal appearing proliferative endometrium, known as disordered proliferative endometrium. These are usually considered as deviations from the normal endometrial cycle, and are rarely confused with premalignant (EIN) lesions. Continued exposure causes a progressive spectrum of pan-endometrial histopathologic change including increasing irregularity of gland density and shape, scattered alterations of cytologic appearance known as benign hyperplasia (Figure 2). Stromal breakdown and associated reactive epithelial changes commonly develop, and must be carefully distinguished from neoplastic processes.

Localized origin of EIN, caused by clonal outgrowth of genetically altered endometrial glands was not recognized until 2000 (1). They are true neoplasms, albeit nonmalignant ones, bearing monoclonal inactivation of the PTEN tumor suppressor or PAX2 nuclear transcription factor in 44% and 71% of cases, respectively (14). There are no reliable biomarkers for their routine recognition in clinical practice, nor are previously validated objective computer aided diagnostic

Figure 2. Histopathology of Benign Endometrial Hyperplasia. The endometrial compartment is uniformly altered by systemic estrogens, causing a regularly irregular pattern of gland dilation and packing. Estrogen induced changes become progressively more complex with exposure dose and duration, beginning with scattered cysts known as “disordered proliferative” or “anovulatory endometrium” and eventually “benign endometrial hyperplasia.” Benign endometrial hyperplasia is effectively a functionally normal endometrium responding to an abnormal endometrial environment.
treatment targets removal of the lesion itself.

is a primary neoplastic process of the endometrial tissues in which
(45-fold elevated) endometrioid endometrial adenocarcinoma. It
importance is a high risk of concurrent occult (about 40%) or future
background, characterizes these clonal precancers whose clinical

cytology, within the crowded gland focus relative to that of the
background similar to that seen in Figure 2. A discrete change in
There is a localizing EIN (arrows) emerging from an estrogen altered
endometrium, thereby removing the convenient lesion-to-
time, EIN lesions may completely overrun the background
background from which they have emerged (Figure 3). Over
approaches (8) generally available. Diagnosis is thus by a
trained pathologist examining routinely stained (hematoxylin
and eosin) tissues. Early EIN lesions are easily diagnosed
by their contrast in architecture and cytology with the
background from which they have emerged (Figure 3). Over
time, EIN lesions may completely overrerrn the background
endometrium, thereby removing the convenient lesion-to-
background contrast which is so useful in their recognition.
EIN diagnostic criteria include architectural, cytologic, and
size diagnostic features, in addition to exclusion of benign
mimics and carcinoma. All five EIN diagnostic criteria (Table
2) must be met in every case to maintain a high level of
diagnostic specificity and clinical predictive value. EIN lesions
have gland crowding such that the area of glands exceeds that
of intervening stroma, and these crowded foci are made up of
glands which have a cytology different from the background in
the same patient (“cytologic demarcation”). Areas with these
features occupying a contiguous geographic area of 1mm or
greater in a single tissue fragment can be diagnosed as EIN.

Solid growth patterns, folded epithelial sheets that form maze
like structures, or cribiform architecture are indicative of
cancer. Non-endometrioid differentiation such as mucinous,
A diagnosis is very high, at 99% (8).

May include change in nuclear polarity, nuclear
pleomorphism, or altered cytoplasmic different-
tation state.

size diagnostic features occupying a contiguous geographic area of 1mm or
greater in a single tissue fragment can be diagnosed as EIN. Solid growth patterns, folded epithelial sheets that form maze
like structures, or cribiform architecture are indicative of
cancer. Non-endometrioid differentiation such as mucinous,
squamous morular, or tubal type is at least partially present
in 47% of cases (4). Most common are squamous morules
(22%), which when present, require specialized diagnostic
criteria to distinguish EIN from carcinoma (15). Full diagnostic
details are available online (16), in published reviews (17),
and in standard textbooks (18,19).

Where have all the (WHO) hyperplasias gone? Practical
identification of some hyperplasia categories, like atypical
endometrial hyperplasia, have always been elusive in
everyday practice because of interpretive difficulties in the
traditional definition of “atypia” in this tissue (20). All lesions
need to be individually diagnosed using new criteria that were
never part of the WHO schema, such as lesion size, and
relative (lesion vs background) rather than absolute (“atypia”)
definitions of significant cytologic alteration. As a result,
there is no direct or absolute concordance between WHO
hyperplasia and EIN schema diagnoses. 79% of atypical
hyperplasia, 44% of complex non-atypical hyperplasias, and
5% of simple non-atypical hyperplasias, are classifiable as
premalignant EIN lesions. After removing EIN lesions from the
WHO hyperplasia pantheon, remaining lesions are reassigned
largely into specific categories such as endometrial polyp,
disordered proliferative endometrium, benign endometrial
hyperplasia, and a variety of normal structures such as
endometrial basalis and lower uterine segment.

Benign endometrial hyperplasia management should
address underlying mechanisms for elaboration of unopposed

Table 2. Diagnostic features of EIN (All must be met in a single
area).

<table>
<thead>
<tr>
<th>EIN Criterion</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Architecture</td>
<td>Area of Glands exceeds that of Stroma (Glands/ Stroma &gt; 1). Lesion composed of individual glands which may branch slightly and vary in shape.</td>
</tr>
<tr>
<td>Cytology</td>
<td>Nuclear and/or cytoplasmic features of epithelial glands and normal background glands. May include change in nuclear polarity, nuclear pleomorphism, or altered cytoplasmic differentiation state. If no normal glands present, highly abnormal cytology.</td>
</tr>
<tr>
<td>Size</td>
<td>Maximum linear dimension exceeds 1mm in a single fragment.</td>
</tr>
<tr>
<td>Exclude mimics</td>
<td>Benign conditions with overlapping criteria: Disordered proliferative, basalis, secretory, polyps, repair, etc..</td>
</tr>
<tr>
<td>Exclude Cancer</td>
<td>Carcinoma if maze like glands, solid areas, or significant cribriorming</td>
</tr>
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Evaluation and Treatment

The EIN diagnostic schema has proven to discriminate better
between benign and premalignant conditions than the WHO
classification in general usage since 1994. A clinical outcome
study incorporating 477 endometrial “hyperplasia” patients
who had no concomitant cancer within the 1st year of followup
and restratified into EIN and benign hyperplasia categories
showed that the EIN group had an overall 45-fold increased
frequency of endometrial cancer (8). One third of women with
a new diagnosis of EIN who undergo clinical surveillance by
repeat biopsy and/or hysterectomy will be diagnosed with
adenocarcinoma within one year (8). In contrast, the negative
cancer predictive value of a representative endometrial biopsy
showing benign endometrial hyperplasia but which lacks EIN
is very high, at 99% (8).
Benign Endometrial Hyperplasia and Endometrial Intraepithelial Neoplasia (EIN)

estrogens and, and provide symptomatic relief. Endocrine evaluation in the young and perimenopausal patient includes failed or delayed ovulation. Most women experience occasional anovulatory or delayed ovulatory menstrual cycles during the perimenopausal years with onset of erratic ovarian responsiveness to gonadotropins. The symptom of irregular bleeding in these patients can to a certain extent be treated by progestins, which when withdrawn causes shedding of the overstimulated endometrium. A benign endometrial hyperplasia in the postmenopausal woman without a history of exogenous (pharmacologic) estrogen use requires explanation. Elaboration of estrogenic compounds by hormonally active ovarian tumors should be considered especially in this group, but may also occur in the younger patient. If the clinician is confident of sampling adequacy, and the pathologist has not indicated some particular problem in interpretation of the specimen, observational follow-up with symptom management can be justified for a diagnosis of benign endometrial hyperplasia. Not all cases are so straightforward, however, as there will be individual cases where there is lingering concern of sampling adequacy, discordance between the clinical presentation and pathologic diagnosis rendered, or interpretive uncertainty by the pathologist. In these instances the diagnostic process should be considered incomplete, and repeat sampling indicated.

Management of women with a diagnosis of EIN centers on two objectives: 1) exclusion of a coexisting carcinoma, management of which would supersede that of the EIN itself, and 2) ablation of EIN as a cancer preventative strategy. Hysterectomy fulfills both goals by simultaneously removing the EIN lesion itself while providing a definitive pathology specimen for exclusion of adenocarcinoma. Although current practice favors hysterectomy for EIN in women past childbearing age, there is an active interest in developing uterus-sparing alternatives for younger women and those who present unfavorable surgical risks. Progestin-based hormonal therapies capable of ablating EIN lesions offer the best alternative to surgery, but the optimal regimens, expected clinical response, and attendant risks remain to be defined. Topical endometrial ablation by thermal or cautery mediated devices applied directly to the endometrial lining are not recommended as a treatment option because they may leave residual islands of lesional tissue behind, and create intrauterine adhesions which hinders post-treatment surveillance by biopsy.

Follow Up

Clinical evaluation of the risk for cancer will determine the appropriate follow-up and need for endometrial biopsy following a diagnosis of benign endometrial hyperplasia. Women with intractable chronic anovulation, such as that caused by polycystic ovarian syndrome or associated with obesity, may be exposed to unopposed estrogen for years and thus have a slightly elevated endometrial cancer risk.

If managed nonsurgically, hormonally treated EIN must be followed by multiple surveillance biopsies to assess treatment efficacy and possible progression to carcinoma. A problem is that there are no accepted criteria for assessing premalignant endometrial lesions while under the influence of progestins (21). High dose progestins alter the appearance of the EIN itself, often making it non-diagnostic. Glands are pushed apart by stromal pseudo decidualization, and nuclei become smaller and less mitotically active (22). “Improvement” in cytology or lessening of gland crowding cannot necessarily be viewed as evidence of clearance of an EIN lesion when the follow-up biopsy is taken in the presence of active progesterational agent. Furthermore, rebiopsy of a hormonally treated EIN while still on progestins may be a premature endpoint to assess lesion involution, as the patient has not yet had the benefit of withdrawal shedding, a significant component of the ablative process.

The best way to resolve any diagnostic uncertainty introduced by hormonal therapy is to rebiopsy 2-4 weeks following a withdrawal bleed. The hormonal effects will no longer be present, thereby permitting accurate assessment of the presence or absence of residual EIN. The clinical context, and intent of the managing physician must be understood before invoking this option. Withdrawal may not be feasible in women with subcutaneous or intrauterine devices impregnated with hormone.

Ongoing Debates

Best Treatment Regimen for Hormonal Management of EIN

Progestin treatment offers the potential for fertility-sparing management of younger women with EIN, or even endometrial adenocarcinoma (23). Although EIN treated with progestins is associated with up to a 75-80% response rate (24,25), and post-treatment pregnancies may be achieved (26), an effective formulation, dose, and schedule for progesterational therapy has not been standardized, nor is it possible to predict a response in advance from individual lesion or patient demographic features. The induction of apoptosis has been found to be an important component in the therapeutic effect of progestins, and this effect is much greater upon progesterone withdrawal compared to continuous exposure (27). This has led to the untested suggestion that intermittent, rather than continuous, progestin treatment may be more effective clinically for the treatment of EIN.

Desired Therapeutic Outcome of EIN Hormonal Therapy

There are two different therapeutic intents for progestin therapy of premalignant endometrial disease, which apply to separate subsets of patients. The first is that circulating progestins can stabilize a premalignant (or even well differentiated malignant) lesion, preventing its progression as long as the hormonal exposure is maintained. In this model, continuous uninterrupted high dose delivery to the endometrium for an indefinite period is desired. Progestin-impregnated intrauterine devices capable of locally delivering supraphysiologic quantities of hormone at low systemic levels are a new treatment option. More studies are needed to define
efficacy, pathologic endpoints, and long term outcomes. A different therapeutic goal is achieving permanent ablation of premalignant lesions by transient progestin therapy, resulting in a disease free endometrium that does not require ongoing progestin therapy. In this scenario, the maximal therapeutic effect of apoptosis, and synchronized shedding of lesion-bearing endometrial tissues occurs through repeated, cyclical, withdrawal of hormone following a priming interval. For all patients treated hormonally, close follow-up is mandatory and repeated sampling strongly recommended.

References