Lecture: Clinical Aspects of EIN
Speaker: George L. Mutter, MD

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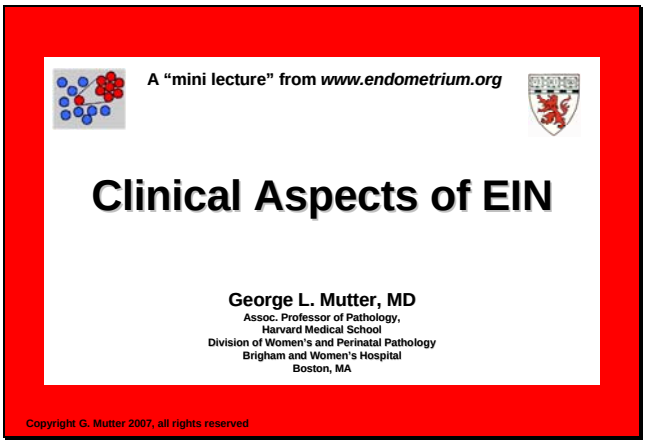

Introduction

This is George Mutter, I am a gynecologic pathologist at Brigham and Women's Hospital in Boston, and today we are talking about the clinical aspects of Endometrial Intraepithelial Neoplasia (EIN).

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EIN Diagnostic Classes

EIN Nomenclature	Topography	Functional Category	Treatment
Benign endometrial hyperplasia Sequence (Unopposed Estrogen effect)	Diffuse	Estrogen Effect	Hormonal therapy
EIN Endometrial Intraepithelial Neoplasia	Focal progressing to diffuse	Precancer	Hormonal or surgical
Carcinoma	Focal progressing to diffuse	Cancer	Surgical stage-based

Diagnostic Classes

The other talks in this series have provided a biological foundation and diagnostic strategy for EIN. Here you see an overview of the broad diagnostic classes as they relate to each other. One class of estrogen-driven changes diffusely affect the endometrial compartment. This is the benign endometrial hyperplasia sequence. Patients with these abnormalities are candidates for hormonal therapeutic intervention. In contrast, endometrial intraepithelial neoplasia is a monoclonal precancer which begins at a point in space within the endometrium, enlarging over time. These are premalignant lesions. The therapeutic goal with EIN is ablation of the lesion through surgical or hormonal means. EIN lesions are distinguished from well-differentiated endometrial adenocarcinoma, as management of patients with adenocarcinoma is based upon surgical staging.

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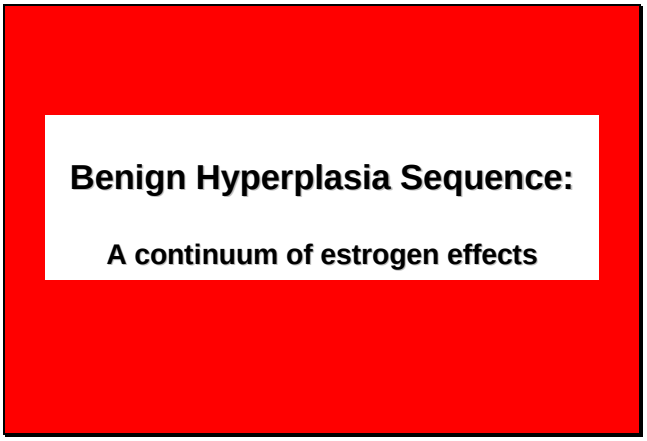

Benign Endometrial Hyperplasia

The EIN diagnostic schema replaces the World Health Organization (WHO) hyperplasia schema. WHO hyperplasias are reclassified into two broad categories of benign hyperplasia and EIN. Benign endometrial hyperplasia is a diffuse endometrial effect caused by circulating unopposed estrogens.

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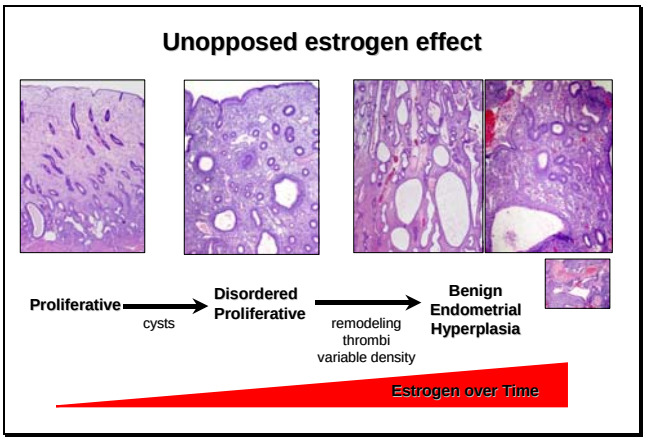

Estrogen Effects= Benign Hyperplasia

With increasing duration and dose of estrogen exposure, endometrial glands become progressively irregular in distribution in a diffuse and random fashion. The pathologic endometrial changes may be considered diagnostic of the underlying hormonal state. The patient's future cancer risk is primarily driven by persistence of unopposed estrogens and therapy is therefore directed at the hormonal environment rather than ablation of any specific endometrial lesion.

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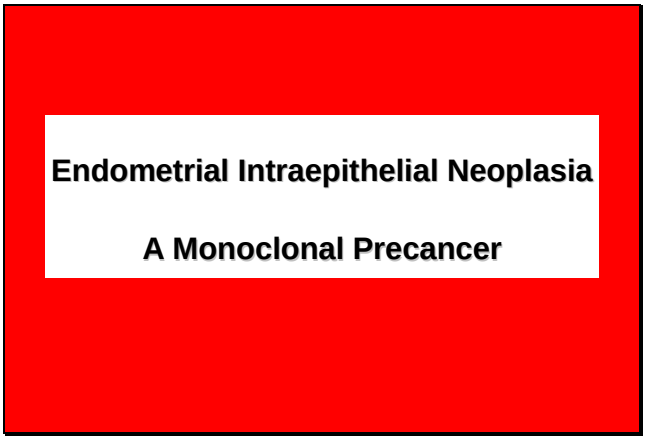

EIN

EIN, or endometrial intraepithelial neoplasia, is a precursor lesion to the endometrioid type of endometrial adenocarcinoma. This is the type of carcinoma often preceded by estrogen exposure and distinguished from papillary serous adenocarcinoma of the endometrium. There is a pre-invasive form of serous carcinomas, often called serous endometrial intraepithelial carcinoma, or serous EIC, which should not be confused with EIN.

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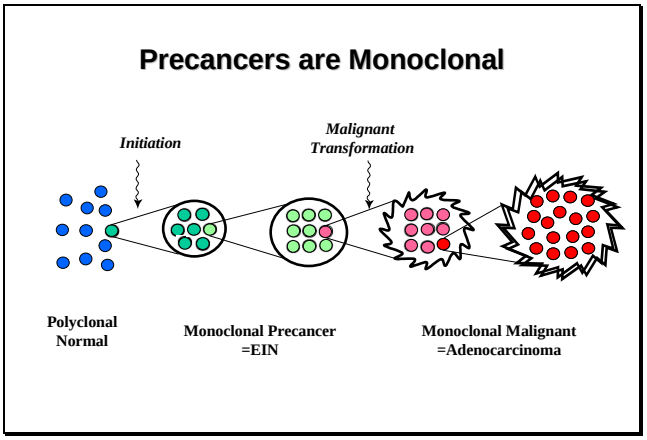

EIN=Monoclonal Precancer

This cartoon shows initiation of an EIN lesion through mutation and clonal expansion. Clusters of adjacent mutated glands comprise the EIN lesion. The cells of the EIN lesion are prone to malignant transformation. Emergence of EIN through mutation occurs within a localized area of the endometrium, and differs from those polyclonal estrogen-induced changes we now know as benign endometrial hyperplasia. The histology of EIN lesions is discontinuous from those of hormonally-driven benign endometrial hyperplasias.

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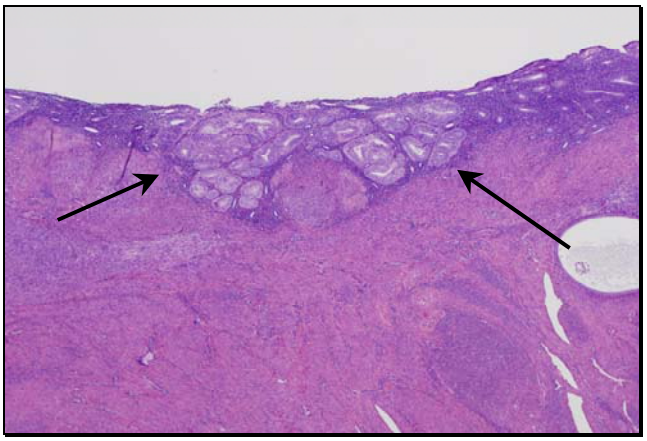

Localized EIN

Here we see a localized EIN lesion, marked by the arrows, arising within an otherwise unremarkable endometrium. These lesions may be diagnosed even in fragmented biopsy specimens obtained using a number of devices. EIN diagnostic criteria and their clinical outcome predictive value have been developed and validated using a variety of tissue sampling formats including Pipelle biopsies and endometrial curettages.

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EIN
Endometrial Intraepithelial Neoplasia

- Endometrioid Precancer (45-fold cancer risk)
- No Subdivisions (Grades)
- Goal is Ablation
  Hormonal
  Surgical

EIN Endometrial Intraepithelial Neoplasia

EIN is a premalignant lesion which confers approximately a 45-fold increased risk of future endometrioid carcinoma. This entity is diagnosed in a singular fashion, without sub-division or stratification into differing grades. Once diagnosed, the clinical therapeutic goal is ablation of the endometrial tissue involved by EIN using hormonal or surgical approaches.

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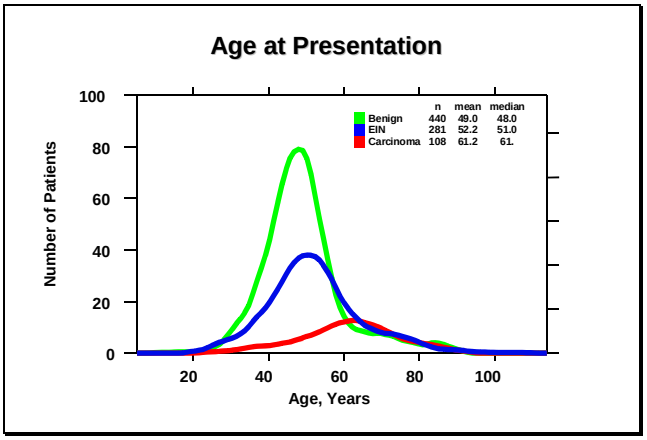

Age of EIN

As one might expect for a precursor lesion, the average age of presentation with EIN is younger than that of presentation with endometrial adenocarcinoma. This graph shows age of initial diagnosis with benign endometrial hyperplasia in green, EIN in blue, and adenocarcinoma in red. The patient numbers within each group are not proportional to each other, having been compiled through diagnostic searches rather than sequential presentation. Note that EIN is predominately a perimenopausal lesion, whereas adenocarcinoma is primarily postmenopausal. There is, however, substantial overlap in the ages of presentation of EIN and adenocarcinoma. Frequently, these are diagnosed concurrently at initial presentation.

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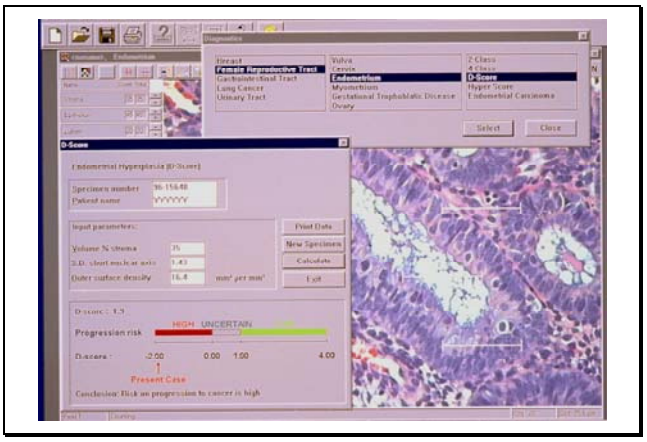

Computer EIN Diagnosis

There are several ways to diagnose EIN. One of the research tools that was used to define the histologic characteristics of premalignant lesions was computerized histomorphometry. These were applied to H&E-stained routine histologic sections, and diagnosed using a mathematical algorithm. I refer you to the other mini lectures on the subject of EIN diagnosis for further details. Even though computerized morphometry was a major tool for EIN discovery, computers are not required today for its diagnosis. In a minute, we will talk about subjective, routine diagnosis of EIN at a microscope by pathologists with no special equipment.

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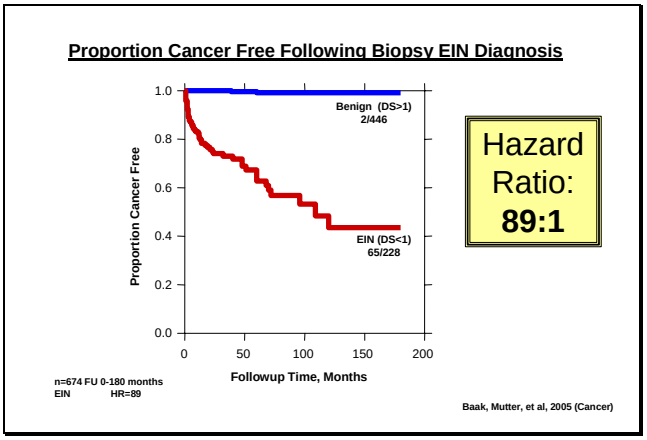

EIN Leads to Cancer

The largest clinical follow-up studies of patients with endometrial premalignant disease have been done using computerized morphometric approaches. A study published in 2005 in the journal ***Cancer*** [1] included 674 women with a variety of endometrial hyperplasias diagnosed by the WHO hyperplasia system. These were stratified by computerized morphometry into EIN and non-EIN lesions. These plots show the fraction or proportion of patients which remain cancer free during clinical follow-up. The average follow-up interval exceeded 5 years. What you see, in the blue line, are only 2 cancer occurrences occurring out of 446 women who were EIN-free. In contrast, of the 228 women with EIN, 65 developed carcinoma during clinical follow-up. The risk of getting cancer was 89 times greater in those women who had an EIN lesion compared to those without. If you look closely at the red curve, there are two different components. Within the first 12 months or so, about 15-20% of patients are diagnosed with adenocarcinoma. Many of these patients probably had their cancers at the time of intake, which were somehow missed. These can be considered concurrent cancers rather than true progression events. Notice however, that accumulation of cancers continues at a steady rate after the first year and for several years thereafter. Almost half of women with an EIN diagnosis will develop adenocarcinoma over time if their uterus remains.

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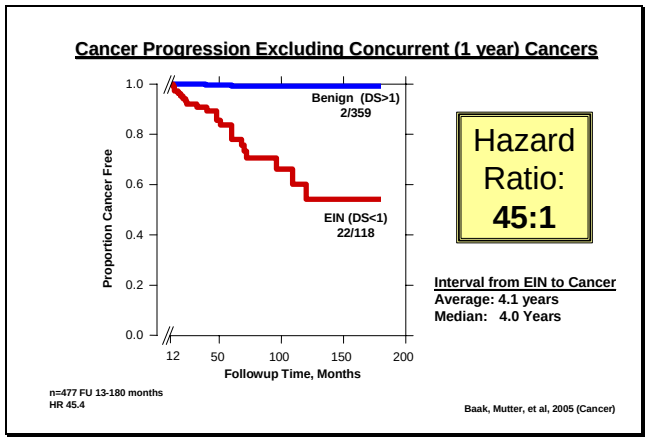

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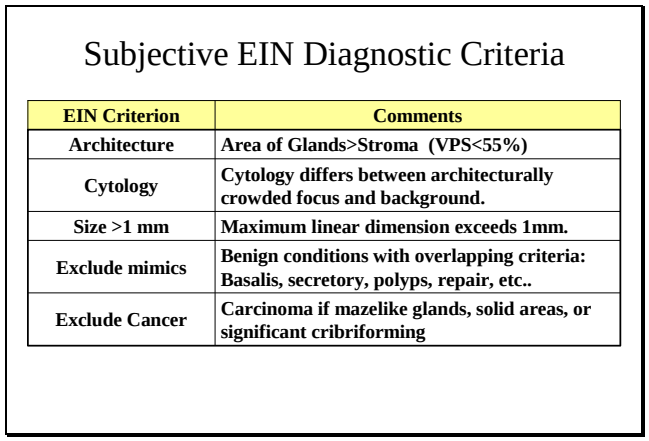

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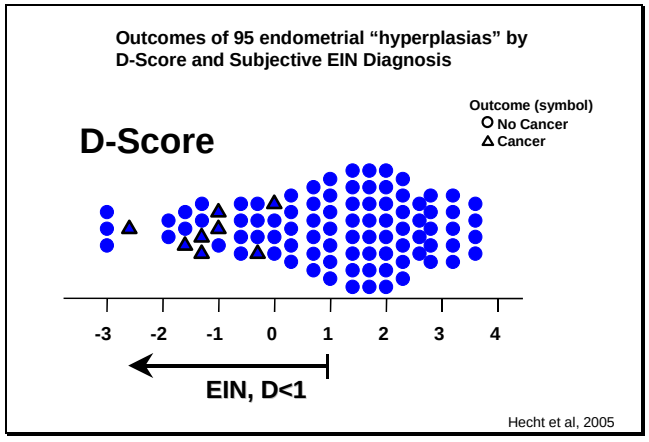

45-Fold EIN Progression Risk

Let us now exclude those women who are found to have cancer within the first 12 months. By excluding those with "concurrent" cancer, we may more purely represent the dynamics of true lesion progression from EIN to adenocarcinoma. Here you see a subset of the prior data, corrected to exclude all patients who developed carcinoma within the first 12 months. For patients who remain cancer-free in the first year, they have a 45-fold increased risk of long-term cancer development. This number is probably close to the risk for true progression events. Within this group of patients, the median interval from EIN to cancer is about 4 years.

Subjective EIN Dx

The computerized morphometry approach is not a practical modality of diagnosis in many areas. It has contributed, however, insight into newly recognized features which are important components in recognition of premalignant disease. These have been delimited in a series of diagnostic criteria which may be applied by a pathologist without reference to computerized morphometry. All 5 of the diagnostic criteria shown here must be met in each case. How does application of such criteria relate to computerized recognition of lesions?

95 Cases: D Score

This next study addresses that question [2]. Here you see 95 patients, each represented by a symbol. All were diagnosed as having some form of endometrial hyperplasia by the WHO system. This scattergram shows their morphometric D-score values used for EIN diagnosis. D-score values of <1 correlate with EIN. Triangular symbols show those patients who developed carcinoma during clinical follow up. Notice that the triangular symbols are skewed to the left, included within the group of EIN lesions. Morphometric EIN diagnosis has captured all of the cancer occurrences during follow up.

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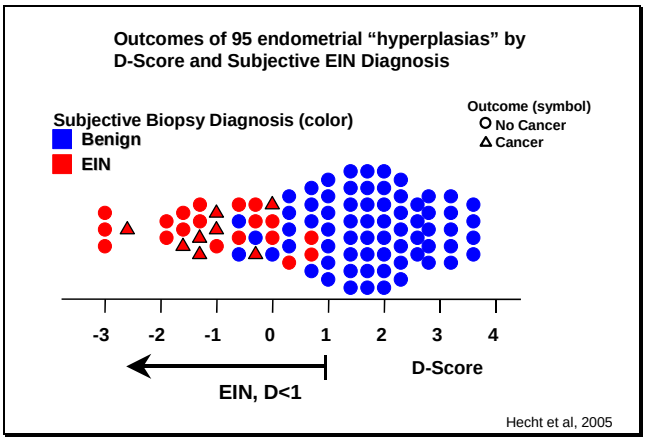

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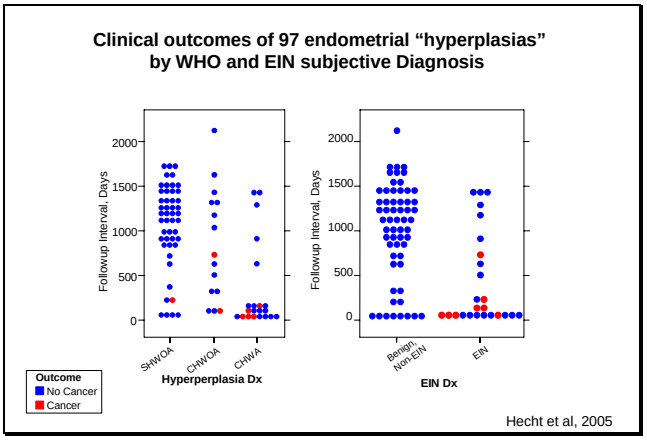

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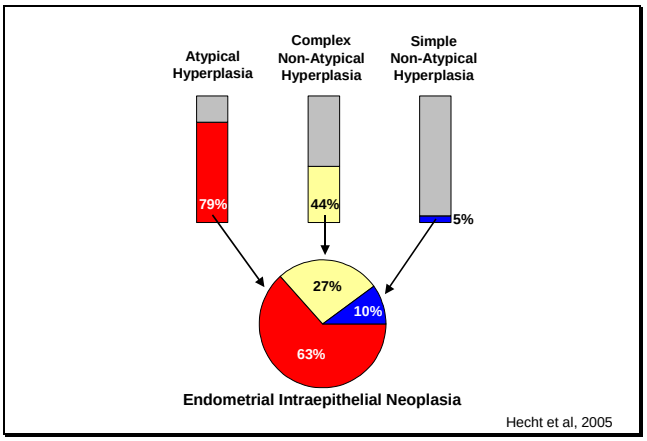

95 Cases: Subjective

We now can take the same cases and show you in red those examples which were diagnosed subjectively by a pathologist as EIN. Notice that all of the pathologist-diagnosed EIN lesions had D-scores <1. All of the cancer occurrences were diagnosed as EIN by both the pathologist and the computer. If anything, the pathologist has an advantage. There are many histologic mimics of EIN which the computer is unable to distinguish. Many of the blue symbols which appear at a D-score level <1 represent cases of secretory endometrium, or endometrial polyps; conditions which confound a morphometric approach. The pathologist, however, is capable of distinguishing these as benign or premalignant.

WHO vs. EIN Outcome

In the left panel you see cancer outcomes in red for three groups of WHO hyperplasias. From left to right, simple hyperplasia without atypia, complex hyperplasia without atypia, and complex hyperplasia with atypia. Notice that 3 out of the 8 cancers take place in non-atypical varieties of endometrial hyperplasia. In the right panel, the same cases were diagnosed as non-EIN benign, or EIN. Re-diagnosis using EIN criteria places all 8 of the red cancer occurrences in the high-risk category. Significantly, the number of cases diagnosed as EIN is approximately the same as the number of cases diagnosed as atypical hyperplasia. Changing diagnostic strategy from hyperplasia to EIN does not significantly increase the number of patients identified as high-risk.

WHO-EIN Discordance

EIN diagnosis utilizes discrete histologic criteria which have never been part of the WHO hyperplasia schema. For example, EIN diagnosis includes architectural features of gland crowding and lesion size, neither of which is well represented in the distinction between atypical and non-atypical hyperplasia. Because the criteria are so different for EIN diagnosis compared to WHO hyperplasia diagnosis, there is no fixed or direct correlation. Rather, each case must be completely reevaluated using entirely new criteria for classification. The three bars in the top show proportions of each WHO hyperplasia category which are re-diagnosed as EIN. You will notice that the EIN lesions emerge from all of these categories, but at differing likelihoods. We all know, however, that the frequency of different types of hyperplasias is non-equivalent, so they disproportionately contribute to the final EIN pool. The pie chart in the bottom represents all diagnosed EIN lesions. 63% come from the atypical hyperplasia category; 27% from the complex non-atypical hyperplasias, and 10% from simple non-atypical WHO hyperplasias.

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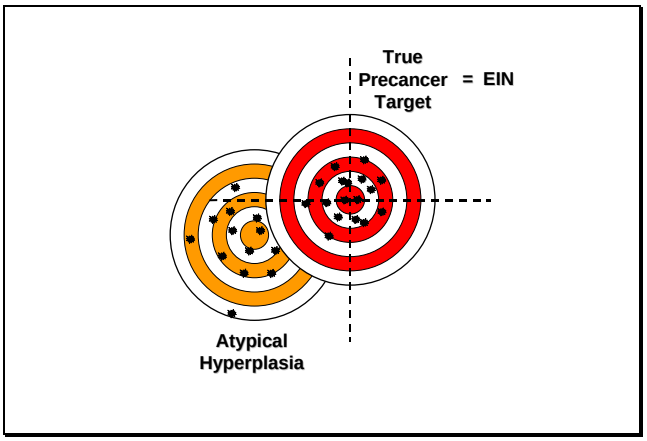

Precision vs. Accuracy

If you think of the diagnostic objective of recognizing a true precancer, it is clear that atypical hyperplasias, our putative precursor of the past, is somewhat off the mark. Criteria for precancer recognition are incomplete in the WHO atypical hyperplasia diagnosis. This problem is not one of precision or reproducibility. Rather, the problem is one of accuracy, where atypical hyperplasia has failed to define the proper target. In contrast, those features which define EIN lesions have been verified as being quite close to lesions which behave in a premalignant fashion. Even if the reproducibility of EIN diagnosis was no better than that of atypical hyperplasia, clinical prediction would be increased. As it turns out, diagnostic reproducibility for EIN recognition is also improved compared to that for atypical hyperplasia. The net effect is improved segregation of high from low risk patients.

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Clinical Management Issues

- EIN is managed as a premalignant lesion (much as atypical hyperplasia has been)
- Occult concurrent carcinoma rates as high as 40%
- Surgery: Hysterectomy is diagnostic and therapeutic
- Progestin therapy: systemic continuous vs. interrupted. Needs careful followup.
- Progestin IUD increasingly used.

Clinical Management Issues

What happens once an EIN lesion is diagnosed? EIN should be managed as a premalignant lesion. For those of you who have considered atypical endometrial hyperplasia to be a premalignant lesion, your management of EIN should resemble that you have previously applied to patients diagnosed with atypical hyperplasia. It is important to recognize that many of these women have concurrent carcinomas. As many as 40% of women with an EIN diagnosis will have an occult concurrent carcinoma that will be diagnosed within one year. Today in the United States, hysterectomy is the most common therapeutic treatment for premalignant endometrial disease. This is perhaps the most reliable way to definitively evaluate the presence or absence of concurrent carcinoma. If no concurrent carcinoma is identified, hysterectomy is curative.

There is clinical interest in hormonal therapy of premalignant endometrial disease, although efficacy and therapeutic response have not been defined in a formal randomized clinical trial. Some women with EIN will undergo complete lesion regression after a course of progestins, but it is not possible to predict in advance which women will and will not respond. There are different modalities for administration of progestins, including continuous or interrupted systemic administration through oral or subcutaneous roots. Commercially available progestin-impregnated intrauterine devices are of high clinical interest because of diminished systemic side effects while maintaining high local delivery. A decision to treat with progestins also comes with a requirement for careful informed consent, and clinical follow-up to confirm ablation of the lesion and exclude a co-existing carcinoma.

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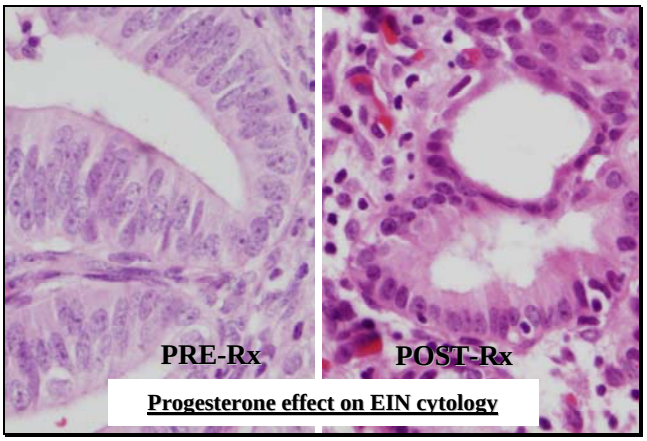

Progestin Changes Cytology

I would like to say a few things about the follow up of patients who are being treated with progestins. The first is that progestins, whether synthetic or natural, cause dramatic changes in the cytology of EIN glands. In these two photomicrographs taken at the same magnification, you see one patient's lesion before and after 3 months of progestin therapy. Notice how the round nuclei have become much smaller after progestin therapy. Nuclear cytology changes with hormonal environment, and even persistent lesions may have a different appearance if sampled while on active progestins.

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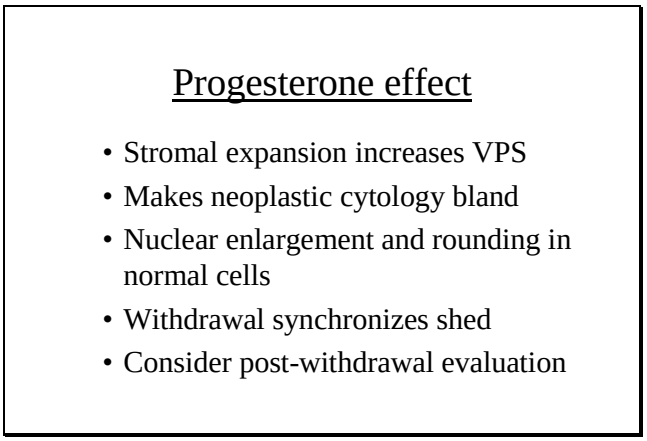

EIN Progestin Effect

In addition to the problems of change in cytology, circulating progestins expand the stromal compartment through predecidualization. This has the effect of decreasing gland density, a characteristic that may make it more difficult to recognize EIN lesions. For these reasons, the pathologist may have difficulties in interpreting an endometrial biopsy taken from a woman with an EIN lesion under active progestational therapy. There are other problems with evaluating therapeutic efficacy while still on progestins. A substantial component of the therapeutic effect occurs through a synchronized shedding of the endometrium which takes place after withdrawal of the progestational agent. Patients who have not undergone a withdrawal shedding have not realized the full benefit of therapy. There is an advantage, for all of these reasons, to evaluate therapeutic efficacy by rebiopsy after hormonal agents have been withdrawn and the patient has completed a withdrawal bleed.

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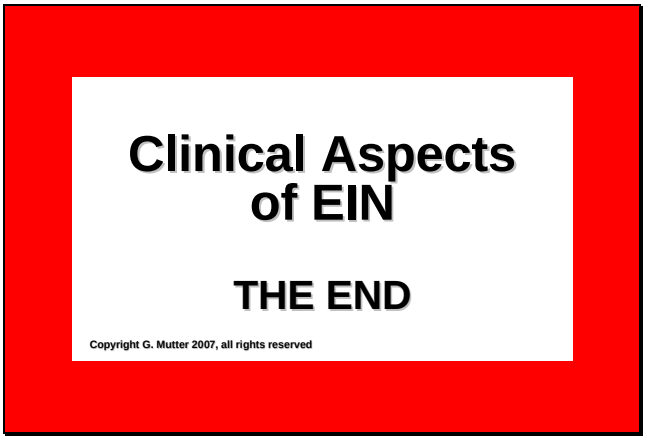

Summary

That ends this mini lecture on the subject of clinical aspects of EIN. This is George Mutter signing off from www.endometrium.org in Boston.