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## ENDOMETRIAL HYPERPLASIA – WHAT IS NEW?

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**ABSTRACT:** The diagnosis and classification of endometrial hyperplasia is still one of the rare areas in histopathology that is still purely based on morphology without the use of ancillary techniques. The two popular systems used for classification of endometrial hyperplasia are the WHO system and the newer still not so popular EIN system proposed by the Endometrial Collaborative Group. Herein we discuss these two systems of classification and the implications for management of patients thus classified with emphasis on pitfalls in the assessment of follow up biopsies of patients managed conservatively.

**KEYWORDS:** Endometrial hyperplasia, Endometrial Intraepithelial Neoplasia (EIN), atypical endometrial hyperplasia, progestin therapy.

**INTRODUCTION:** When a gynecologist performs endometrial curettage in a peri or postmenopausal woman complaining of abnormal uterine bleeding, the most important information that he or she expects from the pathologist is whether there is an endometrial hyperplasia or malignancy in the biopsy. Considering the wide variation in the interpretation of endometrial biopsies showing hyperplasia like changes between pathologists,<sup>1,2</sup> evaluation of such biopsies is no easy task. A pathologist needs to be fully aware of all the pitfalls that arise in the evaluation of endometrial biopsies, particularly since the diagnosis and classification of endometrial hyperplasia is purely based on histomorphological basis and there are no ancillary techniques presently available to aid in this. In this article it is our effort to bring out some of the basic concepts of this endometrial pathology along with discussion on some recent developments in this difficult yet important area in the field of gynecologic pathology.

**DISCUSSION:** In broad terms, endometrial hyperplasia relates to a diffuse process of excessive proliferation of endometrial tissue, where an increase of glands to stromal ratio is seen at greater than 1:1. The term 'disordered proliferative endometrium' is used when this process is focal or when the proliferation is evident but not enough to qualify as hyperplasia by the previously mentioned criteria. The endometrial hyperplasia is further classified according to International Society of Gynecological Pathologists (ISGP), International Federation of Gynecology and Obstetrics (FIGO), and World Health Organization (WHO) classifications (which are identical) as simple or complex with or without atypia<sup>3</sup> (table). The pitfalls that need to be distinguished from hyperplasia include cystic atrophy, endometrial polyps, artifactual crowding of glands due to stromal collapse disordered proliferative endometrium and sometimes chronic endometritis.

### Is there an adenocarcinoma in situ?:

It is common to expect an 'in situ carcinoma' that is in between complex atypical hyperplasia and well differentiated adenocarcinoma in the neoplastic sequence just like in the

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other sites like cervix and gastrointestinal tract. Professor Harold Fox gives the best refusal to this concept when he says "A true adenocarcinoma in situ of the endometrium is one in which the glands have undergone neoplastic change but in which there is no invasion of the endometrial stroma. It is doubtful if any adenocarcinoma of this type exists or if it could be recognized even if it did exist".<sup>4</sup> Because of similar objections this term does not exist in the WHO classification of endometrial neoplasia and preneoplasia.<sup>5</sup>

## **What is Endometrial Intraepithelial Neoplasia (EIN)?**

Endometrial intraepithelial neoplasia is a clonal proliferation of pre neoplastic endometrial glands that are architecturally and cytologically altered and which are prone to malignant transformation upon acquisition of additional genetic damage. This term was proposed by the Endometrial Collaborative Group<sup>6</sup> to accommodate changing concepts of endometrial pre neoplastic disease. It should be noted that EIN is pre neoplastic stage of endometrioid adenocarcinoma (Type I) of endometrium and should not be confused with unrelated serous Endometrioid Intraepithelial Carcinoma (serous EIC) which is an early phase of (Type II) papillary serous adenocarcinoma of endometrium.

Criteria for diagnosis of EIN includes all of the following, that is, area of glands greater than stroma, cytology of the glands differs between architecturally crowded focus and the background, maximum linear dimension exceeds 1mm and benign mimics like polyp, basaloid and repair has to be excluded.

Proponents of the EIN classification system have argued that it predicts disease progression in endometrial hyperplasia more accurately than WHO classification system.<sup>7</sup> In one study<sup>8</sup> up to 44% of complex non atypical hyperplasias and 4% of simple non atypical hyperplasias were diagnosed as EIN using the above mentioned diagnostic criteria. These cases which had higher risk of malignancy would not have been aggressively managed had they not been diagnosed as EIN. However in a more recent study women observed for at least 1 year after biopsy based diagnosis of endometrial hyperplasia, EIN, and atypical hyperplasia were found to have similarly increased risk of progression to adenocarcinoma.<sup>9</sup> Therefore EIN appears to have added more confusion than clarity and advantage into the classification system of endometrial hyperplasia.

## **Interpretation of follow up biopsies:**

Total hysterectomy is curative for atypical endometrial hyperplasia (AEH) or EIN and provides definitive standard for assessment of concurrent carcinoma.<sup>10</sup> Treatment with progestin therapy may provide safe alternative to hysterectomy patients who wish to preserve fertility or those for whom surgery is not a viable option.<sup>10</sup> Follow up of such patients is through repeated endometrial biopsies. In this context it is important for pathologist to be aware of the changes that appear in the progestin treated AEH/ EIN.

In their study of 44 patients of AEH/ well differentiated carcinoma treated with progestin, Wheeler, Bristow and Kurman<sup>11</sup> found that progestin induced regressive changes in the form of decrease in extent of lesion, decrease in cellularity of glands with decrease or absence of nuclear atypia. Other changes like cystic dilatation, secretory effect and squamous, mucinous or

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eosinophilic metaplasia were also seen. However some architectural abnormalities like cribriform and papillary patterns appeared or became more pronounced mimicking progression of the disease. Hence only cytologic atypia was best predictor of progression of disease. These points are important in evaluating a biopsy showing progesterin effect; especially the first time biopsy should never be diagnosed as malignant when focal cribriform or papillary patterns are seen without cytologic atypia when the background shows progesterin effect. A repeat biopsy should be recommended after discontinuation of treatment for proper evaluation of the endometrium in such instance. In follow up biopsies, these architectural changes should not be interpreted as progression of disease unless there is cytologic atypia accompanying them.

**CONCLUSION:** Presently the two popular ways of classifying endometrial pre cancers are the WHO classification system and the EIN system advocated by the Endometrial Collaborative Group. Whatever way they are classified as the management of AEH/ EIN is similar in that total hysterectomy is curative and in those who wish to retain fertility or in whom surgery is not possible, progesterin therapy may be tried. The follow up biopsies of such progesterin treated patients should be carefully interpreted as some architectural features like papillae formation and cribriform pattern may give false impression of progression to malignancy. Cytologic atypia is the best criteria to assess progression of the disease in these follow up biopsies.

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WHO CLASSIFICATION	ENDOMETRIAL COLLABORATIVE GROUP
SIMPLE HYPERPLASIA	ENDOMETRIAL HYPERPLASIA
COMPLEX HYPERPLASIA	ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA
SIMPLE HYPERPLASIA WITH ATYPIA	
COMPLEX HYPERPLASIA WITH ATYPIA	

Table 1

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