# Endometrial Hyperplasia: Different Classification systems and Advantages of WHO 2014 Classification System.

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**Abstract**

**Background:** Endometrial hyperplasia (EH) is a pathological condition which occurs due to unopposed estrogenic effect. It is usually manifest by abnormal uterine bleeding affecting women in 5th and 6th decades of life. Some cases of endometrial hyperplasia especially those with atypical cytological features may progress to endometrial adenocarcinoma, while others follow an indolent course. Several classification systems have been developed over years. Early classifications were based on structural and cytological features. However, the recently developed classification system by WHO in 2014 was based mainly on the cytological atypical features as the architectural features have been proved to be clinically irrelevant. Cellular morphology was also included in this classification system.

**Conclusions:**WHO 2014 classification system described both cellular morphology and nuclear atypia as some newly described variants like atypical mucinous glandular proliferation was proved to be precancerous despite of its minimal cytological atypia. Glandular architectural features were proved to be clinically irrelevant, so they were excluded from this classification.

**Keywords:**Endometrial hyperplasia, Abnormal uterine bleeding, Endometrial carcinoma,Endometrial intraepithelial neoplasia, WHO.

## Introduction

Endometrial hyperplasia (EH) is a pathological condition which occurs mainly in perimenopausal and postmenopausal women due to high level of estrogen. It is characterized by hyperplastic changes affecting both endometrial glands and stroma with increase in gland-to-stroma ratio(**Armstrong et al., 2012**).EH is one of the most frequent causes of abnormal uterine bleeding (AUB). Most cases occur in 5th or 6th decades of life. EH if left untreated, it may progress to endometrial adenocarcinoma. A considerable number of hysterectomy specimens done due to AUB as a result of EH as diagnosed in curettage biopsies, revealed hidden foci of endometrial carcinomas(**Lacey et al., 2009**). All cases of EH are characterized by glandular crowding and architectural irregularities. However, not all cases of EH show cytological atypia.EH with atypical cytological features is considered as a precancerous lesion as it may progress to endometrial adenocarcinoma. On the other hand, EH without atypical cytological features usually does not progress to malignancy. This necessitates an accurate classification system for EH in order to recognize the precancerous lesions and subsequently prevent the development of endometrial adenocarcinoma and at the same time, to avoid over management of EH with bland cytological features(**Allison et al., 2008**).

**WHO 1994 classification system:**

Over years; different classification systems were adopted for EH. In 1994, the World Health Organization (WHO) adopted a classification system for EH, based on both glandular architectural features and cytological atypia to produce a four-tired classification system for EH; simple EH, complex EH, simple EH with atypia and complex EH with atypia(**Allison et al., 2008) (Figure 1).**Despite being the most widely used classification system for EH, WHO 1994 classification system showed marked inter and intra-observed variations. In addition, the term endometrial intraepithelial neoplasia (EIN), which is of great benefit in clinical management, wasn't included in this classification system**(Baak et al., 2005).**

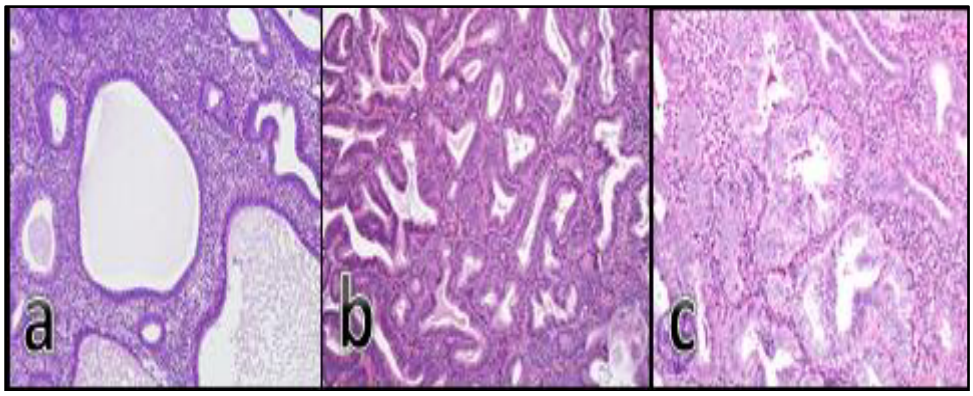


**Figure 1. H&E stained sections of endometrial tissue. a; Simple endometrial hyperplasia, the glands are lined by single layer of bland looking epithelial cells. b; Complex endometrial hyperplasia, the glands are crowded, irregularly branched but without atypical features. c; complex endometrial hyperplasia with rounded and pleomorphic nuclei, (Allison et al., 2008).**

**European working group (EWG) classification system**

In 1999, the European working group (EWG) proposed a classification system for endometrial hyperplasia. This classification included only two diagnostic categories; benign hyperplasia and endometroid neoplasia. Simple EH and complex EH without atypia were included in benign hyperplasia category. Atypical EH and well differentiated endometrial adenocarcinoma were included in endometroid neoplasia category. This classification system didn't gain a wide agreement; this is because it was applied only on endometrial curettage specimens**(Bergeron et al., 1999).**

**Endometroid Intraepithelial Neoplasia (EIN)**

The term endometroid intraepithelial neoplasia (EIN) was first described by Mutter in 2001. This lesion is completely identical to complex EH with atypia; formed of crowding, irregularly-branching glands with cytological atypia. Because of its great similarity to atypical EH, the term EIN wasn't widely accepted**(Baak et al., 2005).**

**WHO 2014 Classification System for Endometrial Hyperplasia**

In 2014, WHO recommended a classification system for EH. It was based mainly on the cytological features of the hyperplastic endometrial glands, rather than the glandular architectural complexity as such architectural features were proved to have no clinical significance**(Kurman et al., 2014)**

**Endometrial hyperplasia without atypia**

This variant occurs due to unopposed estrogenic effect on the endometrium. It is histologically similar to disordered proliferative endometrium as regards to the crowded and irregularly branched glands. However, when glands predominate over the stroma; the diagnosis of endometrial hyperplasia without atypia is appropriate. The risk of progression to endometrial carcinoma from this variant is low, not exceeding 1-3%**(Kurman et al., 1985).**

**Endometrial hyperplasia with atypia**

Glandular crowding and complexity in addition to cytological atypia are the main features of this variant**(Figure 1c).** The epithelial lining of the hyperplastic endometrial glands is characterized by nuclear enlargement, rounding, pleomorphism and conspicuous nuclei. Endometrial hyperplasia with atypia is considered as a precancerous lesion for low grade endometroid adenocarcinoma. The incidence of malignant progression is about 15% in some literatures and reaching up to 30% in other literatures**(Mutter, 2001).** Sever architectural complexity and cytological atypia in an endometrial biopsy raise the suspicion of a well differentiated endometrial adenocarcinoma over atypical endometrial hyperplasia. However, the presence of fused glands without intervening stroma, papillary or villoglandular architectural patterns are features supporting the diagnosis of well differentiated endometrial adenocarcinoma**(Dijkhuizen et al., 2009).**

**Atypical mucinous glandular proliferation**

As mentioned before, the classification system adopted by WHO in 2014 was based on cytological atypia in addition to cytological morphology of the lining glandular epithelial cells. In this variant, the endometrial glands show crowding, complexity and irregularity. The lining glandular epithelium show prominent mucinous metaplasia. A minimal degree of cytological atypia may be occasionally encountered. This type of endometrial hyperplasia may be easily misdiagnosed as normal endocervical tissues. Atypical mucinous glandular proliferationis considered as a premalignant lesion. The incidence of adenocarcinoma in hysterectomy specimens performed after the diagnosis of Atypical mucinous glandular proliferation is about 45%. Therefore; hysterectomy is considered as the ideal treatment in Atypical mucinous glandular proliferation **(Rawish et al., 2017).**

**Papillary proliferation of the endometrium**

It was first described by Lehman and Hart in 2001. There is a prominent papillary architectural pattern. The papillae are covered by a single layer of epithelial cells that may be ciliated. The cytoplasm is pale eosinophilic or mucinous. Absence of marked cytological atypia differentiates papillary proliferation of endometrium from endometrial carcinoma**(Lehman et al., 2001).** Papillary proliferation of the endometrium is subdivided into simple and complex subtypes. The simple subtype is characterized by short papillae with predominant non-branching stalks

that involve one or two foci not exceeding 50% of the examined specimen. On the other hand, complex Papillary proliferation of the endometrium is composed of complex papillae with secondary branching. The complex subtype involves more than 50 % of the examined specimen. Simple Papillary proliferation of the endometrium is considered clinically equivalent to endometrial hyperplasia without atypia, while complex subtype resembles atypical hyperplasia in its clinical behavior**(Ip et al., 2013).**

**Atypical secretory hyperplasia**

This variant is characterized by glandular architectural abnormalities and atypical cytological features within secretory endometrium. This histological picture resembles those seen in endometrial tissue in $16^{th}$ or $17^{th}$ day of normal menstrual cycle. Despite being not fully understood, atypical secretory hyperplasia usually shows involution especially when the surrounding unaffected endometrial tissue shows secretory changes**(Parra-Herran et al., 2013).**

**Conclusion**

Endometrial hyperplasia is a pathological condition affecting mainly perimenopausal and postmenopausal women due to hyperestrogenic state. Different classification systems have been introduced over years in order to avoid over or under management. Initial classification systems were dependent mainly on both architectural and cytological features. However, the architectural criteria proved to be clinically irrelevant. In 2014, WHO recommended a classification system based mainly on cytological features as cellular morphology and nuclear atypia.

**Disclosure**

Authors report no conflict of interest.

**References**

**Allison KI, Reed SD, Voigt LF, Jordan CD, Newton KM, Garcia RL. (2008).** Diagnosis of endometrial hyperplasia: why is it difficult to agreed. Am J SurgPathol, 32:691-698.

**Armstrong AJ, Hurd WW, Elguero S, Barker NM, Zanotti KM. (2012).**Diagnosis and management of endometrial hyperplasia. J Minim Invasive Gynecol, 19:562-571.

**Baak JP, Mutter GL, (2005).**EIN and WHO94. J ClinPathol, 58;1-6.

**Baak JPA, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. ( 2005).** The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than 1994 World Health Organization Classification System. Cancer, 103: 2304-2312.

**Bergeron C, Nogales FF, MasseroliM,Abeler V, Duvillard P, Muller-Holzner E, et al. (1999).**A multicentric European study testing the reproducibility of the WHO classification of endometrial hyperplasia and curettage specimens. Am J SurgPathol, 23: 1102-1108.

**Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. (2009).** The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and

hyperplasia: a meta-analysis. Cancer, 89:1765-1772.

**Ip PP, Irving JA, McCluggag WG, Clement PB, Young RH. (2013).**Papillary proliferation of the endometrium: a clinicopathologic study of 59 cases of simple and complex papillae without cytologic atypia. Am J SurgPathol, 37:167-177.

**Kurman RJ, Carcangiu ML, Herrington CS, Young R. (2014).**WHO Classification of Tumors of the Female Reproductive Organs. Lyon: IARC.

**Kurman RJ, Kaminski PF, Norris HJ. (1985).** The behavior of endometrial hyperplasia: A long-term study of "untreated" hyperplasia in 170 patients. Cancer, 56:403-412.

**Lacey JV, Chia VM.(2009).** Endometrial hyperplasia and the risk of progression to carcinoma.Maturitas, 20:39-44.

**Lehman MB, Hart WR. (2001).** Simple and complex hyperplastic papillary proliferations of the endometrium: a clinicopathologic study of nine cases of apparently localized papillary lesions with fibrovascular stromal cores and epithelial metaplasia. Am J SurgPathol, 25:1347-1354.

**Mutter GL. (2001).**Histopathology of genetically defined endometrial precancers.Int J GynecolPathol, 19:301-309.\

**Parra-Herran CE, Monte NM, Mutter GL. (2013).**Endomtrial intraepithelial neoplasia with secretory differentiation: diagnostic features and underlying mechanisms. Mod Pathol, 26:68. 73.

**Rawish KR, Desouki MM, Fadare O. (2017).** Atypical mucinous glandular proliferations in endometrial sampling: follow-up and other clinicopathologic findings in 41 cases. Hum Pathol, 63:53-62.