

# The endometrial hyperplasias revisited

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**Abstract** The proliferating lesions in the endometrium form a morphological continuum extending from benign to malignant, through a transitional pre-invasive stage. Within this spectrum, several classifications of endometrial hyperplasia have been developed over the years in which the precancerous lesions gained a substantial distinction, although not without inconsistencies in definitions and terminology. The revised WHO 1994 classification explicitly recognizes cytological atypia as the defining feature for distinguishing genuine hyperplastic lesions (simple and complex endometrial hyperplasia) from those that are potentially precancerous (simple and complex atypical endometrial hyperplasia) and puts an end to the verbal anarchy by adopting a common language of communication. This taxonomy, however, was criticized for complexity and low level of reproducibility. Thus, in the name of improved reproducibility a new classification was recently proposed which (a) combines simple and complex endometrial hyperplasia within one diagnostic category known as endometrial hyperplasia and (b) defines new criteria for recognising the precancerous lesions: a monoclonal growth, known as endometrial intraepithelial neoplasia (EIN), comprising clusters of crowded glands, greater than 1 mm in diameter, having a cytologically altered epithelium. The EIN concept was challenged of not being independently tested and received with great enthusiasm by some scholars and relative skepticism by others.

**Keywords** Endometrial hyperplasia · Precancerous lesions · WHO · EIN

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## Introduction

Hyperplasia is, in general terms, an increase in the size of an organ or tissue as a result of an increase in the number of its constituent cells per unit volume. In the endometrium, there are several forms of hyperplasia, some of which progress to carcinoma. Indeed, the most common type of endometrial carcinoma, endometrioid adenocarcinoma, frequently develops from pre-existing areas of hyperplasia—a concept originally described by Thomas Cullen in 1900 [1]. In addition, the morphological continuum endometrial hyperplasia/endometrioid adenocarcinoma shares in common many genotypic alterations, including microsatellite instability, PTEN and K-ras gene mutations [2–8]. As a consequence, the form of hyperplasia which is related to endometrial adenocarcinoma (EA) with unusual frequency is considered precancerous and should be treated accordingly. It is mandatory, therefore, to distinguish the endometrial hyperplasias into those that progress into malignancy and those that do not.

## Classification schemes of endometrial hyperplasia: from anarchy to WHO

Several classification schemes of endometrial hyperplasia have been introduced over the years. These were essentially biased by inadequate long-term follow up data and inconsistency in definitions and terminology. As Gore (1973) characteristically stated, “not only are different names applied to the same lesion, but the same name is applied to different lesions, presumably of different malignant potential” [9].

Thus, many scholars in the field employed the term “atypical” hyperplasia for all hyperplastic lesions of the endometrium with a presumed malignant potential [10–12].

Others used the designation “adenomatous” hyperplasia in a similar way [13–19], and still others used the two terms interchangeably [20, 21]. Interestingly, morphological distinction between “atypical” and “adenomatous” hyperplasia was exercised by a number of investigators [22–26], but they did not all use the same criteria. Beutler et al. recognized two distinct forms of hyperplasia with some malignant potential: one with atypical glandular proliferation, the other with atypical epithelial proliferation [27]. Scully and Blaustein (1980) applied the term “complex” hyperplasia [28, 29] and Hall “irregular” hyperplasia to include every form of non-invasive proliferating lesion of the endometrium other than “simple” endometrial hyperplasia [30]. Earlier workers made no attempt to differentiate endometrial hyperplasia into any form [31–33].

This era of communication failure was succeeded by the 1975 WHO (World Health Organization) classification which recognized three main forms of endometrial hyperplasia: the cystic, the adenomatous and the atypical hyperplasia [34]. In this taxonomy, cystic endometrial hyperplasia corresponds to diffuse proliferation of both glands and stroma, most commonly with cystically dilated glands. Adenomatous hyperplasia represents focal glandular proliferation with crowding and complexity. Atypical endometrial hyperplasia reflects conspicuous proliferation of glands with apparent cytological atypia.

Kurman and associates found progression to carcinoma in fewer than 3% of cases of hyperplasia without atypia (cystic and adenomatous), compared with 22% of patients with atypia (atypical hyperplasia) [35]. Comparable results reported by Ferenczy and Gelfand with progression to carcinoma was 0% versus 25% for endometrial hyperplasias lacking cytological atypia and those having this feature, respectively [36].

The aforementioned classical studies demonstrated quite clearly that the absolute criterion for differentiating the genuine hyperplastic endometrial lesions from those that are potentially precancerous is the presence of cytological atypia. In view of this development, the revised WHO94 classification provided a scheme primarily dividing hyperplasias into those with and those without cytological atypia, while the degree of glandular crowding (simple versus complex) received secondary importance (Table 1) [37]. The ambiguous term “adenomatous” was abolished since a lesion cannot be neoplastic and hyperplastic at the same time.

In the new classification, simple endometrial hyperplasia indicates lesions formerly designated as cystic hyperplasia; complex endometrial hyperplasia refers to lesions with marked glandular complexity, usually with glandular crowding [38]. Cytological atypia is characterized by nuclear changes (see under “The WHO94 criteria”).

Lacey et al., classifying endometrial hyperplasia according to nuclear atypia and the severity of glandular crowding,

**Table 1** The WHO75 and WHO94 classifications

WHO 1975 classification	WHO 1994 classification
Cystic glandular hyperplasia	Endometrial hyperplasia
Adenomatous hyperplasia	Simple
Atypical endometrial hyperplasia	Complex
	Atypical endometrial hyperplasia
	Simple
	Complex

predicted the subsequent relative risk for developing endometrial adenocarcinoma [39]. They reported progression risks RR=2.0 for simple endometrial hyperplasia, RR=2.8 for complex endometrial hyperplasia and RR=14 to 48 for atypical hyperplasia. The study included 138 cases initially diagnosed as endometrial hyperplasia and subsequently evolved to carcinoma (1970–2003). Using the same classification scheme, Horn et al. found that 2% of the cases with complex endometrial hyperplasia (eight of 390) progressed into carcinoma as compared to 52% of the atypical hyperplasia cases (58 of 112) [40]. There were also a percentage of cases (10.5%) which from complex endometrial hyperplasia transformed into atypical hyperplasia.

### The WHO94 classification: criticism and simplification

The WHO94 classification scheme, however, based on Kurman and Norris’ earlier suggestions [35, 41], was criticized for complexity and low level of reproducibility [42–44]. There were indeed several challenging reports. Thus, Skov et al. found considerable intra- and inter-observer variation using both the WHO1975 and the WHO1994 classifications of endometrial hyperplasia [42]. Bergeron et al. centered on the revised WHO94 taxonomy and reported comparable results [43]. There is also the recent report of the Gynecologic Oncology Group on 306 women who were diagnosed with atypical endometrial hyperplasia (AEH) and referred for further treatment (the study was initiated to assess the efficacy of hormonal therapy); however, after re-examination of the slides by a panel of three gynecologic pathologists who used WHO criteria, significant discrepancies were identified between review and original diagnoses in 62% of the cases [44].

Skov et al. improved reproducibility of the WHO classifications by reducing the four categories to two with clinical importance: atypical endometrial hyperplasia versus others—1975 classification, and atypical endometrial hyperplasia (complex) versus others—1994 classification [42]. Bergeron et al. succeeded in increasing the reproducibility of the WHO94 classification by introducing a combined category for simple and complex hyperplasia,

called “hyperplasia”, and a combined category for atypical hyperplasia and well-differentiated adenocarcinoma, called “endometrioid neoplasia” (EN) [43]. Mutter and the Endometrial Collaborative Group (ECG) in a series of articles argued for the simplification of the WHO classification by entertaining two, rather than four, categories—“benign endometrial hyperplasia” (replacing simple and complex hyperplasia) and “endometrial intraepithelial neoplasia” (EIN), representing the immediate precursor of endometrioid adenocarcinoma with a 45-fold increased cancer risk [45–50].

### The EIN classification

#### The EIN criteria

According to Mutter’s group [46], an EIN lesion, presumed to be distinct from atypical endometrial hyperplasia, should only be diagnosed if it fulfils the following molecular, morphometric and morphological criteria: (a) monoclonal growth; (b) size greater than 1 mm in diameter or more than ten glands; (c) closely packed glands with a gland area (combined epithelium and lumens) greater than stroma area (volume percentage stroma <55%); (d) cytological change that is always different from that of the adjacent normal endometrium. There should be exclusion of cancer and a variety of benign conditions with overlapping features, including basal, secretory and menstrual endometrium, polyps and cystic endometrial atrophy [45, 47, 50–52]. The above diagnostic criteria should be met in their entirety.

Some pathologists subscribed enthusiastically to these views [53]. However, before a new classification system is adopted into clinical practice, it is expected to satisfy two basic requirements: reliability and reproducibility. In this context, it is worth investigating whether or not these conditions are fulfilled in the EIN taxonomy.

#### Reliability of EIN

*Monoclonality and neoplastic growth* How strong is such an association in the endometrium? Yilmaz et al. have shown that six out of 17 (35.3%) simple endometrial hyperplasias and four out of six (66.6%) complex endometrial hyperplasias were monoclonal in the absence of cytological atypia [54]. In contrast, three of 12 (25.0%) atypical hyperplasias (complex) were polyclonal. Similarly, Sun et al. have demonstrated monoclonality in 17 of 31 (55%) complex endometrial hyperplasias without atypia, whereas two of 15 (13%) cases of endometrial hyperplasia with atypia were polyclonal [55]. In the small sample of the study by Mutter et al., another troublesome matter emerged; only two of the four atypical endometrial hyperplasias were positive, whilst the remaining two were inconclusive [56].

In the study by Jovanovic et al., a polyclonal process was noted in two of nine (22.2%) atypical hyperplasias but also in seven of 22 (31.8%) endometrial adenocarcinomas [2]. These data indicate that clonality, a major feature of the EIN lesion [2, 45], is suggestive but not conclusive of endometrial neoplasia. It is of some interest that monoclonality has also been recorded in endometrial polyps [2] and endometriotic cysts [57, 58].

*Lesion size and volume percentage stroma* Clusters of crowded glands confined to an area of less than 1 mm<sup>2</sup> in diameter (fewer than ten glands) are not suitable for evaluation. Yet, such lesions of only microscopic size may well represent the earliest stage of endometrial carcinogenesis.

If, however, the lesion is greater than 1 mm in size, as indeed most are, the gland area should exceed that of stroma (volume percentage stroma <55%) in order to qualify as a precancerous endometrial lesion. There has been an overriding importance attached to this criterion, for as Prat [59], quoting the classical paper by Kurman et al. [35], pointed out that complex non-atypical endometrial hyperplasias often contain greater than 45% glandular component, despite their proven benign nature. Besides, many well-differentiated endometrial adenocarcinomas do not conform to this criterion and display an exceedingly high volume percentage stroma without being detracted from the diagnosis of malignancy [60].

*The altered epithelium* This is an important criterion which is expected from any precancerous lesion. It is vaguely defined by the Endometrial Collaborative Group as an epithelium “different from that of the adjacent normal endometrium”. Such a definition does not preclude a morphological similarity of the EIN epithelium with that of atypical hyperplasia (WHO94). Cytological atypia is, of course, not peculiar to WHO94 classification and may be found in any EIN lesion. According to ECG [61], 78% of the endometrial biopsies which were originally diagnosed as atypical hyperplasia were reclassified as EIN.

*Exclusion of conditions with overlapping features* This is self evident and should be always exercised in any classification system.

#### Reproducibility of EIN

Within the last few years, a considerable number of studies have been reported on the subject of endometrial hyperplasia describing an “apparent” advantage of the EIN taxonomy over the WHO94 classification (these are listed in the references). However, it should be noted that many reviews and reproducibility studies that can be cited in support of the EIN concept were designed and performed by collaborating

and not independent research groups [44, 47, 50, 51, 61–63]. No exception to that is the absence of an independent assessment of the gland-to-stroma ratio by routine light microscopy [59]. Furthermore, by advocating a computerized morphometric analysis, the so-called D-score, rigidity was introduced into the EIN system. The D-score (volume percentage stroma, standard deviation of the shortest nuclear axis and gland outer surface density) needs special equipment and specifically trained personnel [63], and it is not, at present, applicable to everyday laboratory practice. Equally impractical for routine clinical work is the application of molecular assays for clonal analysis [47].

At present, there are no adequate follow up data to indicate whether the presence of clonality or the quantitative evaluation of the gland–stroma ratio is associated with short- or long-term development of invasive carcinoma [59].

### Reliability of the study of Bergeron et al.

It is worth mentioning here that the study of Bergeron et al. [43], while criticizing the WHO94 classification for low level of reproducibility, suffered itself from a number of flaws [59, 64]. In particular, the study was based on 16 cases of well-differentiated endometrioid adenocarcinoma and only six cases of atypical hyperplasia. An inadequately documented methodology was preferred [59] with omissions in regard to the cases used; were they consecutive or cases with perceived diagnostic difficulties [64]? There were no photomicrographs or adequate histological descriptions.

The lack of any justification for combining the four existing categories of endometrial hyperplasia into the proposed two are presented in some detail under the “need not” subtitles (“Simple endometrial hyperplasia need not be combined with complex endometrial hyperplasia”; “AEH need not be combined with EA”; see below).

### The WHO94 classification at a second look

#### The WHO94 criteria

These are, in essence, two: atypia and complexity. The former refers to cytology (hyperplasia with and without cytological atypia), the latter refers to architectural abnormality, that is, the degree of glandular crowding (simple versus complex hyperplasia; Table 1) [35, 37]. These features have been described in the preceding section “Classification schemes of endometrial hyperplasia: from anarchy to WHO”, and are discussed further under the “need not” subtitles (see below: “Simple endometrial hyperplasia need not be combined with complex endome-

trial hyperplasia” and “AEH need not be combined with EA). Here it will suffice to comment on the criterion of cytological atypia.

*Cytological atypia* In the WHO94 classification, the diagnosis of a precancerous endometrial lesion is resting principally upon the presence of cytological atypia: round and, often, enlarged nuclei, prominent nucleoli, chromatin clearing or clumping, and a tendency for epithelial stratification with a loss of nuclear polarity [38, 65–67]. Despite claims to the contrary, these morphological features could be recognized and reproduced with a fair degree of precision by several independent groups of workers [35, 36, 39, 40, 68].

#### Reliability and reproducibility of WHO

Kendall et al., examining endometrial biopsy specimens, found a satisfactory reproducibility for the diagnoses of hyperplasia (both simple and complex), atypical hyperplasia and well-differentiated adenocarcinoma [68]. Further support for this conclusion was obtained by Horn et al. [40] who, after using the WHO94 classification, reached an overall (interobserver) correlation of 90% which is far better than the overall interobserver agreement of the study of Bergeron et al. (70–82%) [40]. Kurman et al. [35], Ferenczy and Gelfand [36] and Lacey et al. [39] reported comparable results, as these have been analysed in “Classification schemes of endometrial hyperplasia: from anarchy to WHO”.

### “Complexity” or is there a need for simplification?

Simple endometrial hyperplasia need not be combined with complex endometrial hyperplasia

There is no apparent justification for amalgamating simple and complex hyperplasia into a single diagnostic category, as suggested by the EIN proponents [45–50], Skov et al. [42] and Bergeron et al. [43]. For, indeed, simple hyperplasia is unique among the endometrial hyperplasias in involving diffusely both glands and stroma, with mitoses in both endometrial components. These features, by depriving pathologists of any morphological alternatives, make the diagnosis of simple endometrial hyperplasia straightforward.

Complex endometrial hyperplasia, on the other hand, as a focal lesion affecting, exclusively, glands, shows glandular complexity and glandular crowding. As a consequence, complex endometrial hyperplasia should be differentiated from a normal late proliferative endometrium, irregular

proliferative endometrium or anovulatory endometrium [65, 69–71]. It could be also confused with atypical endometrial hyperplasia if it was not for the presence of cytological atypia, but definitely, complex endometrial hyperplasia can not be mistaken with simple endometrial hyperplasia.

AEH need not be combined with EA

In contrast to Bergeron et al. views [43], Kendall and his colleagues indicated that the major problem in the differential diagnosis of proliferating endometrial lesions was the distinction between complex hyperplasia and atypical hyperplasia and not between atypical hyperplasia and well-differentiated adenocarcinoma [68]. It is true that the two lesions often co-exist [72–74] and share common genetic alterations, including microsatellite instability, PTEN and K-ras mutations, beta-catenin and MLH1 changes [6, 75–78], which may offer an explanation for the increased risk of progression from atypical hyperplasia to endometrial adenocarcinoma [35, 36, 79–82]. Yet, the two lesions should clearly be distinguished from each other for a hypothetical acceptance of the endometrioid neoplasia concept [43] will lead to overtreatment.

Atypical endometrial hyperplasia, very much like complex endometrial hyperplasia, is restricted to the glandular component of the endometrium, and it is usually focal rather than multifocal or diffuse [38]. The lesion usually, though not invariably, shows crowding and architectural complexity of the glands, but above all, it shows the features of nuclear and cytological atypia. These tend to be exuberant in atypical hyperplasia and less so in endometrial adenocarcinoma, whilst crowding and irregularity of glands is the dominant feature in adenocarcinomas and not in precancerous lesions [83, 84]. Furthermore, endometrial adenocarcinomas are commonly diffuse lesions and may show stromal fibrosis (stromatogenesis), stromal necrosis or stromal infiltration by polymorphonuclear leucocytes—features which are indicative of stromal invasion [38, 83, 85] and are particularly useful in curettage specimens [86, 87].

There has been one study which gives another dimension to the issue. Jacques et al. [88] found that determination of certain histopathological features of the endometrial adenocarcinoma, such as the histological type of the tumour and the degree of tumour differentiation, was a greater problem than differentiating adenocarcinoma from atypical hyperplasia.

### Where do we stand?

The aforementioned studies, with all their discrepancies and shortcomings, demonstrate quite clearly that the endometrial hyperplasias form a spectrum of proliferating diseases

ranging from benign (simple and complex hyperplasia) to malignant (well-differentiated adenocarcinoma) through a transitional pre-invasive stage. This has been designated as simple and complex atypical endometrial hyperplasia or, more recently, endometrial intraepithelial neoplasia without necessarily having the same meaning.

Irrespective of nomenclature, these lesions can be considered precancerous and should be definitely recognized as such, for they progress to malignancy with an unusual frequency and often coexist with well-differentiated endometrial adenocarcinoma with which they share common genetic abnormalities.

In the name of improved reproducibility, there is a tendency for combining subcategories of endometrial hyperplasia in generic groupings: the European Group combined simple and complex hyperplasia into endometrial hyperplasia, and atypical hyperplasia and well differentiated adenocarcinoma into endometrioid neoplasia [43]; the Endometrial Collaborative Group followed a similar approach with regard to simple and complex hyperplasia but differentiated endometrial adenocarcinomas from the precancerous endometrial lesions, which they call EIN, as distinct, though not convincingly so, from atypical hyperplasia [45, 46].

By combining diagnostic groups, the objective could be reached to a certain extent, but it would compromise the evolution of the scientific knowledge [64]. Such a contraction of the number of diagnostic choices seems simplistic rather than simple and bring us back to the early 1930s when no attempt was made to differentiate endometrial hyperplasia into any form [31, 32]. Certainly, a combined EH and EN category would improve reproducibility even further at the expense of the patient care [59]. Equally, the proposed EIN lesion, despite its molecular and morphometric basis, is not adequately supported by reproducible histological criteria, and the EIN concept, as a whole, has not been independently tested. Besides, it would be impracticable for everyday use in pathology labs.

There is no compelling evidence that the WHO94 classification is less reproducible than other classification systems, although the occasional equivocal case may cause difficulties; these should be faced by improving the young pathologists' diagnostic skills [64]. Thus, cytological atypia, the histologic feature most commonly in diagnostic dispute [89], should be endorsed when large epithelial cells with large rounded nuclei, either dense or vacuolated, and abundant cytoplasm, often with a tendency to stratification, are seen in the context of disorganized endometrial glands.

Finally, if there was some phrasal complexity in the WHO94 classification, this would ease by introducing the descriptive terms “atypical hyperplasia with glandular crowding” and “atypical hyperplasia without glandular

crowding”, instead of complex and simple atypical hyperplasia, respectively, and retain the time-honoured terms “simple” and “complex” for the genuine endometrial hyperplasias.

## Treatment

Several factors are taken into account in order to determine the best course of treatment for the woman with endometrial hyperplasia. The two most commonly considered are the specific type of hyperplasia and the patient’s reproductive status.

Simple and complex endometrial hyperplasia can safely be treated with progestins [40, 90–92]. Lindahl and Willen presented the 5-year follow-up of 82 patients with endometrial hyperplasia without cytological atypia treated with 500 mg medroxyprogesterone acetate (MPA) i.m. twice weekly for 3 months [93]. No carcinoma developed, although bleeding problems often led to surgery (13 cases).

Atypical endometrial hyperplasia is traditionally treated by hysterectomy [40, 90, 92]. Yet, medical treatment (high-dose MPA) may be offered to patients with a contraindication to surgery and to young women who wish to retain fertility [92, 94, 95]. In this case, treatment should be continued for no less than 6 months [96]. The main obstacles to this object, of course, remain the lack of large prospective randomized trials, the poor standardization of dose and the frequent coexistence of an occult endometrial adenocarcinoma. Jobo et al. reported the clinical outcome of 53 women with atypical hyperplasia after receiving different treatments [97]. Thirty of 53 patients with atypical hyperplasia of the endometrium were treated by hysterectomy, and 20 of 53 were treated with MPA alone as a primary therapy: two of the 12 patients who were treated with low-dose MPA progressed to endometrial adenocarcinoma. Three of the eight patients treated with high-dose MPA conceived after treatment, having three healthy infants. The authors concluded that primary treatment with high-dose MPA is a safe and effective therapy for women with atypical hyperplasia who wish to preserve their fertility [97]. This benefit would have been lost, resulting in overtreatment, had Bergeron’s concept of endometrioid neoplasia [43] been accepted.

## Conclusions

Cytological atypia remains the defining feature in differentiating precancerous from genuine hyperplastic endometrial lesions. This, in a way, stands true not only for the WHO94 classification but also for the recently proposed EIN classification which, among other criteria, requires a

“cytologically altered epithelium” for detecting precursors to endometrial adenocarcinoma. It is, therefore, necessary for the students of endometrial pathology to recognize cellular atypia.

The endometrial hyperplasias have been the subject of many proffered classifications over the years; the EIN classification is the latest. After a critical review of the literature on the topic, it appeared to us that the EIN concept is impractical and not adequately supported by reliable and reproducible criteria and that the WHO94 classification is reasonably good and has a considerable merit in the everyday routine practice. This, of course, should not discourage research on the various forms of endometrial hyperplasia, particularly in relation to molecular pathology, for as Scully [98], and Fox and Langley [99] stated, “it is our belief that the greater our understanding of the true nature of a lesion the greater, essentially, will be the possibility of a rational therapy”.

**Conflict of interest statement** We declare that we have no conflict of interest.

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