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REVIEW PAPER

New classification system of endometrial hyperplasia WHO 2014 and its clinical implications

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Abstract

Endometrial hyperplasia (EH) is a pathological condition characterised by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity. Endometrial hyperplasia, particularly with atypia, is a significant clinical concern because it can be a precursor of endometrial cancer. Accurate diagnosis of precancerous lesions of the endometrium and exclusion of coexisting endometrial carcinomas are absolutely required for the optimal management of patients. The classification of endometrial hyperplasia has had numerous terminology. According to the classification of WHO94, based on glandular complexity and nuclear atypia, EH is divided into four groups: non-atypical endometrial hyperplasia (simple, complex) and atypical endometrial hyperplasia (simple, complex). Estimated risk of progression of atypical hyperplasia to endometrial cancer is 8-29%. The American College of Obstetricians and Gynaecologists and the Society of Gynaecological Oncology states that endometrial intraepithelial neoplasia (EIN) classification is superior to the World Health Organisation (WHO 94) classification for histology of endometrial hyperplasia. However, the WHO classification system remains the most commonly used and reported in existing literature.

The new classification, WHO 2014, accepted by the International Society of Gynaecological Pathologists, divided hyperplasia into two groups: benign hyperplasia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN). The WHO 2014 schema is more likely to successfully identify precancerous lesions than the WHO94 classification.

Key words: WHO2014, EIN, EWG classifications system, endometrial intraepithelial neoplasia (EIN), endometrioid neoplasia (EN), endometrial hyperplasia, benign endometrial hyperplasia, atypical endometrial hyperplasia.

Introduction

Endometrial hyperplasia (EH) is a pathological condition characterised by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity [1]. Most cases of EH result from high levels of oestrogens, combined with insufficient levels of progesterone [2, 3]. Unopposed oestrogenic stimulation of the endometrium causes proliferative glandular epithelial changes, including glandular remodelling, resulting in variably shaped, irregularly distributed glands. Risk factors for the development of EC include obesity, unbalanced oestrogen therapy, tamoxifen treatment, PCOs, and nulliparity [4].

Endometrial hyperplasia is common in women aged 50-54 years with body mass index (BMI) over 30 [5]. The average age for EH is 52 years, which is nine years lower than the average age for EC. The increased risk of endometrial cancer among overweight (BMI > 25) and obese persons appears to be greater in postmenopausal than in younger women [6]. Accordingly, the growing epidemic of obesity in Poland, in conjunction with an ageing cohort, has the potential to result in a significant increase in EC and its precursors.

Endometrial hyperplasia is one of the most frequent causes of abnormal uterine bleeding, which leads to EC if left untreated. In 10% of premenopausal women with abnormal uterine bleeding, histological findings show endometrial hyperplasia, and in 6% of postmenopausal women with uterine bleeding EC is found [4]. The primary role of endometrial sampling in patients with AUB is to determine whether carcinomatous or premalignant lesions are present by evaluating histological samples [7, 8]. A study conducted by the Gynaecological Oncology Group on biopsy-based diagnosis of atypical hyperplasia found 42.6% of concurrent endometrial carcinoma in hysterectomy specimens [9]. The most

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useful tool to assess endometrium and make preliminary diagnosis is ultrasound imaging (USG TV). Tissue sampling should be performed in women with risk factors of EC, who present symptoms of abnormal vaginal bleeding or pathological vaginal discharge.

Correct clinical evaluation of endometrial hyperplasia is made more complicated by the different classification systems still in use. Pathological diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish clinicopathological entities that are to be managed differently. Many attempts to reclassify retrospectively collected data have resulted in an extensive lexicon for endometrial cancer precursors [10, 11]. Traditional histopathological classification systems for EH exhibit wide and variable degrees of diagnostic reproducibility. As a consequence, developing standardised patient management procedures can be challenging. The risk of coexisting cancer in women with a diagnosis of EH in endometrial biopsy/curettage specimen evaluation is due to limitations in both endometrial sampling and diagnostic grading differences among pathologists. There are some technical issues limiting diagnosis of endometrial curettage samples. Some of these factors comprise insufficient clinical data, curettage performed in the wrong cycle phase, inadequate sampling, technical problems such as unsuitable fixation and insufficient staining quality, and lack of pathologist experience in evaluating endometrium tissue. Some studies have reported that insufficient material is the foremost cause of misdiagnosis [12].

For correct EH diagnosis the criteria of differential diagnosis should be determined. Many of the diagnostic features for atypia (nuclear irregularity, loss of polarity, prominent nucleolus, chromatin coarsening) can also be observed in hormonal irregularities, regeneration, and metaplastic changes. Endometrial hyperplasia is one of most commonly misdiagnosed lesions (overdiagnosed) [13]. Endometrial polyps are often diagnosed as hyperplasia due to comprised fixation problems, misconduction of sections, and excessively bleeding curettages [14].

Atypical hyperplasia/EIN is a precancerous lesion and requires a different approach in treatment than other types of hyperplasia and adenocarcinomas. In contrast, development of invasive carcinomas is very rare in cases of hyperplasia without atypia (< 5%) [15].

Hyperplasia without atypia responds well to progestins. Hyperplasia with atypia requires definitive treatment with hysterectomy due to the high rate of concurrent endometrial cancer.

WHO 94 classifications of endometrial hyperplasia

The classification system currently most widely used is based on the Kurman *et al.* schema, which uses architectural features and cytological atypia (glandular complexity and nuclear atypia) to identify precursor lesions, termed atypical endometrial hyperplasia (AEH) [10]. Parallel use of the older classification system of WHO 1994 led to confusion among clinicians.

World Health Organisation 1994 (WHO94) classification:

1. simple hyperplasia,
2. complex hyperplasia,
3. simple hyperplasia with atypia,
4. complex hyperplasia with atypia.

The categories of WHO 94 division are descriptive and their interpretation does not suggest any specific management algorithms. Various studies indicate poor reproducibility of individual case classification [16]. Diagnoses often overlap because of the different classification systems in current use. As a consequence, there are too may hysterectomies performed for hyperplasia without atypia or gestagen treatment administered for atypical hyperplasia. Pathologists also experience difficulties in comprising predetermined classifications. A vast amount of terminology is not standardised and not defined, and diagnostic criteria are not reproducible. It is barely possible to compare and retrospectively interpret published studies regarding endometrial precancerous conditions [17-19]. The WHO94 schema is the one most commonly used by pathologists, but transitioning to the endometrial intraepithelial neoplasia (EIN) nomenclature would be of greater benefit to clinical management [1, 12, 16].

Alternate classifications of endometrial hyperplasia: EWG and EIN

Due to the poor reproducibility of diagnoses, gynaecological pathologists have proposed two alternative, simple grading systems of endometrial hyperplasia (EH), but they are (currently) not widely used [17, 20, 21]. Both consist of two categories (as opposed to four found in the WHO classification):

- The European Working Group of Experts – EWG (Bergeron, 1999),
- The International Endometrial Collaborative Group – EIN (Mutter, 2000).

In 1999 Bergeron and the European Working Group (EWG) [20] proposed a simplified categorisation of endometrial hyperplasia, to overcome poor reproducibility of the WHO system. The EWG classification, established for use only on endometrial biopsy/curettage specimens, has two diagnostic categories: hyperplasia and endometrioid neoplasia. The authors combined atypical hyperplasia and well-differentiated adenocarcinoma in one category – endometrioid neoplasia (EN), and simple and complex hyperplasia without atypia into benign hyperplasia.

European group of experts – EWG classification (1999):

1. endometrial hyperplasia/benign hyperplasia,
2. endometrioid neoplasia (EN).

EIN classification of endometrial hyperplasia

In 2000, another group of pathologists (the International Endometrial Collaborative Group) proposed a new classification system based on a constellation of quantitative morphological measures associated with clonality assessment. It uses the term endometrial intraepithelial neoplasia (EIN). Endometrial intraepithelial neoplasia is a premalignant lesion, characterised by increased volume of glandular crowding (greater than the stromal volume), the presence of cytological alterations, size of lesion larger than 1 mm, and exclusion of mimics or carcinoma [17, 21, 22].

Endometrial collaborative group – EIN classification (2000):

1. endometrial hyperplasia,
2. endometrial intraepithelial neoplasia (EIN).

EIN classification included three categories: benign (benign endometrial hyperplasia), premalignant (endometrial intraepithelial neoplasia), and malignant (well-differentiated endometrial adenocarcinoma). EIN diagnostic criteria have been developed based on histopathological correlation with clinical outcome, molecular changes, and objective computerised histomorphometry [16]. It has been confirmed as a prognostic factor in several studies [16, 22, 23].

In 2003 the WHO accepted the EIN system as an alternative to the WHO 1994 classification. EIN is tailored mostly for this objective by incorporating modified pathological criteria based upon evidence that have become available since the creation of the more widely used WHO94 [24, 25]. Despite its values, the EIN system seems to be too demanding to take the place of the WHO94 classification. The EIN diagnosis requires either a qualified pathologist or computer analysis performed by expensive devices (D score).

Ordi *et al*. [11] compared the reproducibility of histological findings, respectively, to three hyperplasia current classifications: WHO, EIN, and EWG. This study confirms that all classifications of endometrial hyperplasia are associated with marked inter-observer variability, even among expert gynaecological pathologists. Compliance of diagnosis among pathologists re-evaluating hyperplasia samples in accordance with current classifications is 28% for the WHO system, 39% for EIN, and 59% for EWG. With only two diagnostic categories, full agreement among all pathologists increased to 70% in the WHO classification, 69% in the EIN classification, and 72% in the EWG classification (Table 1). What is important, reproducible studies in support of the EIN concept were designed and performed with collaboration of a qualified gynaecological pathologist, not in groups of beginners.

In 2014 the WHO published a new, simplified WHO classification of endometrial hyperplasia, which con-

Table 1. Reproducibility of histological findings in EIN, EWG, and WHO systems regarding complexity of divisions into categories

<table>
<tr><th>WHO classification
6 categories</th><th>WHO classification
2 categories</th><th>EIN classification
4 categories</th><th>EIN classification
2 categories</th><th>EWG
classification
3 categories</th><th>EWG classification
2 categories</th></tr>
<tr><td>Benign</td><td rowspan="3">Benign
and hyperplasia
without atypia</td><td>Cycling endometrium, benign</td><td rowspan="3">Benign and benign hyperplasia</td><td>Benign</td><td rowspan="3">Benign
And hyperplasia</td></tr>
<tr><td>Simple hyperplasia without atypia</td><td rowspan="2">Benign hyperplasia</td><td rowspan="2">Hyperplasia</td></tr>
<tr><td>Complex hyperplasia without atypia</td></tr>
<tr><td>Simple hyperplasia with atypia</td><td rowspan="3">Atypical
hyperplasia
and carcinoma</td><td rowspan="2">Ein</td><td rowspan="3">Ein and carcinoma</td><td rowspan="3">Endometrioid neoplasia</td><td rowspan="3">Endometrioid neoplasia</td></tr>
<tr><td>Complex hyperplasia with atypia</td></tr>
<tr><td>Carcinoma</td><td>Carcinoma</td></tr>
<tr><td>Consistency of diagnosis
28%</td><td>Consistency of diagnosis
70%</td><td>Consistency of diagnosis
39%</td><td>Consistency of diagnosis
69%</td><td>Consistency of diagnosis
59%</td><td>Consistency of diagnosis
72%</td></tr>
</table>

sists of only two categories of hyperplasia: with and without atypia, as opposed to four found in the WHO94 classification [26, 27]. This reduction to two categories was due to the need to do away with the confusing multitude of terms currently in use.

New WHO 2014 classification of endometrial hyperplasias [27]:

1. non-atypical endometrial hyperplasia (benign hyperplasia),
2. atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia (EIN)/well differentiated carcinoma.

Differential diagnosis between benign uterine lesions and atypical hyperplasia/EIN is based mainly on morphological criteria but may be supported by additional immunohistochemical markers and molecular alterations in problematic cases [16]. Atypical hyperplasia and EIN had similar sensitivity and negative predictive values for coexisting endometrial cancer [28]. Others found the EIN classification to be better at predicting progression to cancer [16, 17, 19]. ACOG and SGO Committee Opinion recommend use of the EIN schema for more clear terminology to distinguish premalignant lesions [29, 30].

In 2016 the joint guidelines of two committees were published: the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE), regarding hyperplasia treatment and classification [31]. They recommended the WHO2014 classification, which divides endometrial hyperplasia into two groups: hyperplasia without atypia and atypical hyperplasia. The guidelines also state the algorithms for managing endometrial hyperplasia. They detail the treatment options that are preferred and give advice on the time for endometrial biopsy for patients after conservative treatment. Clinical management of atypical hyperplasia and EIN is the same.

Conclusions

The WHO classification system remains the most commonly used and reported in existing literature. The new WHO 2014 schema consist of only two categories of hyperplasia and is tailored most closely to the objective of incorporating modified pathological criteria of diagnosing premalignant lesions. The WHO 2014 schema improves the reproducibility and clearly distinguishes between clinic-pathologic entities that are managed differently. Thereby, it should be considered for the diagnosis of endometrial biopsy/curettage specimens. According to ACOG guidelines published in year 2015, the preferred terminology is "endometrial intraepithelial neoplasia" (rather than "atypical endometrial hyperplasia"). 2016 RCOG guidelines recommend the WHO 2014 classification and present clear algorithms for hyperplasia (with or without atypia) treatment and, what is also significant, the preferred time of endometrial follow-up biopsy after pharmacological treatment. We are awaiting similar guidelines to be incorporated by PTG. Setting precise indications for endometrial biopsy due to abnormal uterine bleeding in premenopausal women would decrease the number of D&Cs performed and the number of unnecessary hysterectomies (overtreatment cases). Distinguishing between hyperplasia and true precancerous lesions has significant clinical implications because distinct endometrial precancerous conditions require appropriate intervention.

Disclosure

Authors report no conflict of interest.

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