Original Article

An Audit of Endometrial Hyperplasias at the Lagos University Teaching Hospital

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Abstract

Introduction: There has been much controversy and confusion surrounding the endometrial hyperplasias stemming from the use of a wide variety of terminologies and also from the pathophysiologic mechanisms underlying the various entities. The current classification by the World Health Organization (WHO) published in 2014 clarifies these issues. **Objective:** The aim of this study, therefore, was to audit and standardize cases of endometrial hyperplasia diagnosed in our institution from 2007 to 2011. **Materials and Methods:** The slides and request forms of cases diagnosed as endometrial hyperplasias at the Department of Anatomic and Molecular Pathology from January 1, 2007, to December 31, 2011 were retrieved, reviewed, and reported according to the WHO 2014 classification scheme. **Results:** Hyperplasia without atypia accounted for the vast majority of cases (95.5%) and was the most common in the 5th decade. Concordance rates of 74.5% and 100% were found between endometrial hyperplasias without atypia and atypical hyperplasias with their previous diagnoses, respectively. **Conclusion:** The WHO classification scheme standardizes and simplifies the terminology used in the diagnosis of endometrial hyperplasias, while reflecting, at the same time, the current understanding of genetic changes that provide information necessary for prognostication and treatment.

Keywords: *Atypical, complex, endometrial, hyperplasia, nonatypical, simple*

Date of Acceptance:
14-Aug-2017

Introduction

Various terminologies have been employed in a highly subjective manner to characterize endometrial hyperplasias, some with no discernible prognostic import. In 1994, the classification of the World Health Organization (WHO) into four categories[1] considerably reduced the widespread confusion in the diagnosis of endometrial hyperplasias and was also found useful for predicting clinical behavior. In the latest classification, the WHO now only differentiates between hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia. This scheme, although apparently simple, reflects the new understanding of molecular genetic changes.[2] This study aims to audit and standardize endometrial hyperplasia diagnosed in our institution.

Materials and Methods

The study was a retrospective histopathological review of slides and request forms of cases received in our institution between January 1, 2007, and December 31, 2011, which were reported as endometrial hyperplasia or other related nomenclature. The slides were retrieved and reviewed. New sections were cut from archival formalin-fixed paraffin-embedded tissue blocks and stained routinely with hematoxylin and eosin (H and E) for cases where slides were damaged or otherwise unavailable. Cases with an inconclusive clinical indication or missing biodata on histopathological forms were excluded from the study. Low-grade endometrial hyperplasia, cystic glandular hyperplasia, and simple endometrial hyperplasia were all considered to be simple endometrial hyperplasia, while high-grade endometrial hyperplasia and complex endometrial hyperplasia were

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_274_16

How to cite this article: Dawodu OO, Ikeri NZ, Banjo AA. An audit of endometrial hyperplasias at the Lagos University Teaching Hospital. Niger J Clin Pract 2017;20:1074-8.

considered to be complex endometrial hyperplasia. All cases were reported according to the WHO classification scheme for endometrial hyperplasias.

The Epi Info version 7.1.4.0 statistical software was used for data entry and validation. Frequency distributions were generated for all categorical variables, for example, type of lesion, histological diagnosis, mean, and age range. The Chi-square was used for determining the association between qualitative variables.

Results

A total of 288 cases of endometrial hyperplasia were reviewed. After the audit and standardization, we reported 275 hyperplasias without atypia (254 with simple architecture and 21 with complex architecture), and 13 atypical hyperplasias (six with simple architecture and seven with complex architecture). Figure 1 shows the distribution of these cases.

The majority of cases (83.7%) were seen between 31 and 60 years. The 41–50 years age bracket was the peak age for both the atypical and nonatypical endometrial hyperplasias accounting for 41.8% and 30.8% of cases, respectively. Figure 2 shows the age distribution of the various hyperplasias.

There was a 74.5% concordance between endometrial hyperplasia without atypia, and the previous diagnoses, 56 (20.4%) were observed to coexist with endometrial polyps, and 14 (5.1%) had associated chronic nonspecific

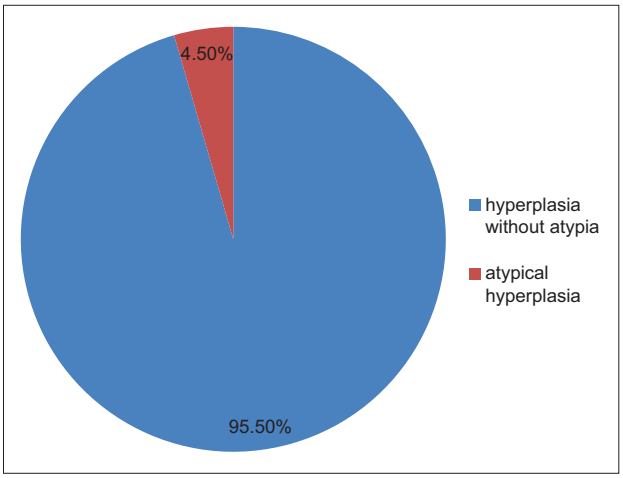

Figure 1: Distribution of endometrial hyperplasias

Table 1: Audit of endometrial hyperplasias

Previous diagnosis	Current diagnosis
Simple endometrial hyperplasia without atypia (initially reported as low-grade endometrial hyperplasia, cystic glandular hyperplasia, and simple endometrial hyperplasia) and complex endometrial hyperplasia without atypia (reported as high-grade endometrial hyperplasia or complex endometrial hyperplasia without atypia) (*n*=275)	Endometrial hyperplasia without atypia, (frequency [%]=205 [74.5])
	Endometrial hyperplasia without atypia and endometrial polyp (frequency [%]=56 [20.4])
	Endometrial hyperplasia without atypia and chronic endometritis (frequency [%]=14 [5.1])
Simple endometrial hyperplasia with atypia and complex endometrial hyperplasia with atypia (reported as high-grade endometrial hyperplasia or complex endometrial hyperplasia with atypia) (*n*=13)	Atypical endometrial hyperplasia with atypia (frequency [%]=13 [100])

Table 2: Biologic behavior of endometrial hyperplasia (Kurman *et al*.)

Histologic type	Regressed (%)	Persisted (%)	Progressed to cancer (%)
Simple hyperplasia without atypia	80	19	1
Complex hyperplasia without atypia	80	17	3
Simple hyperplasia with atypia	69	23	8
Complex hyperplasia with atypia	57	14	29

Actual data for the figures

	Hyperplasia without atypia	Atypical hyperplasia
Percentage	95.5	4.5

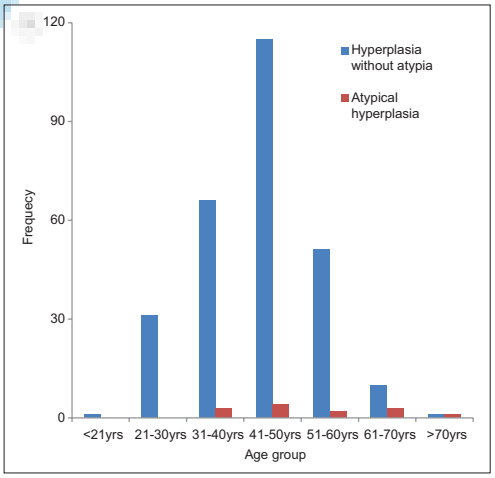

Figure 2: Age distribution of the endometrial hyperplasias

Age group (years)	Hyperplasia without atypia	Atypical hyperplasia
<21	1	0
21-30	31	0
31-40	66	3
41-50	115	4
51-60	51	2
61-70	10	3
>70	1	1

endometritis. There was a 100% concordance between the diagnosis of atypical endometrial hyperplasia and their previous diagnoses. These values are shown in Table 1.

Discussion

Endometrial hyperplasias have been reported to be among the most commonly overdiagnosed lesions in surgical pathology.[3] This has been attributed to the under recognition of benign mimics which includes: artifacts, cystic atrophy, lower uterine segment endometrium, Arias-Stella effect, benign papillary proliferations, endometritis, and polyps. All these conditions are often characterized by increased gland-to-stroma ratio and must be ruled out before a diagnosis of endometrial hyperplasia is made.[3,4]

Endometrial hyperplasia may occur at any age from puberty to menopause with the highest incidence being in the premenopausal period.[5] The peak age of involvement in our study was the 5th decade. This is similar to reports by Reed *et al*., and this age distribution has remained the same over the last decade in Lagos.[6-8]

The current study observed lack of uniformity in the histopathological terminology used in making a diagnosis of hyperplasia such as benign cystic hyperplasia, low-grade endometrial hyperplasia, and high-grade endometrial hyperplasia. It was also observed that few reviewers included whether atypia was present or absent in the diagnosis, which would have helped identify cases needing close monitoring due to the associated increased risk for malignancy.

Both the International Society of Gynecological Pathologists and the WHO in 1994 classified endometrial hyperplasia into four categories, namely, simple hyperplasia without atypia, simple hyperplasia with atypia, complex hyperplasia without atypia, and complex hyperplasia with atypia. This internationally agreed classification considerably reduced the widespread confusion in the diagnosis of hyperplasia.[1,3,4]

Simple hyperplasia without atypia was reported to be the most common histologic form. The proliferative activity involved both glands and stroma, resulting in an increase in the endometrial volume with a gland-to-stroma ratio that was normal or slightly increased. There was usually great variability in size and shape of the proliferating glands, many of which appeared large and cystically dilated with some epithelial budding, while others were small and had a smooth round outline. The cells lining the glands were pseudostratified and columnar with oval, basally located bland nuclei, smooth and uniform nuclear contours, and amphophilic cytoplasm. There was an increase in the number of estrogenized epithelial cells (clear cells). The stromal cells were more dense than in proliferative endometrium. These cells remained spindle-shaped but appeared plump with enlarged nuclei and indistinct cytoplasm. Mitoses were seen in both epithelial and stromal cells. In complex hyperplasia without atypia, the proliferation was limited to the glands leading to crowding and architectural complexity. The lining epithelium by definition lacked atypia.[3,4,9]

In the atypical forms of endometrial hyperplasia, essential cytologic features included the presence of large nuclei, almost twice the normal size, which are rounded, instead of elongated; the nuclei were vesicular rather than hyperchromatic, usually with one or more prominent nucleoli; loss of the normal nuclear polarity; loss of cell-to-cell and cell to basement membrane cohesion; abundant cytoplasm, with indistinct cell borders, and intense eosinophilia; and no evidence of stromal invasion.[10,11]

This classification scheme was extensively studied and found to be useful for predicting the biological behavior of the various histological subtypes. The table below [Table 2] shows the result between of a prospective follow-up study of 170 patients with endometrial hyperplasia conducted by Kurman *et al*.[12]

Baak *et al*. published similar findings. In their study, 0%, 17%, 7%, and 45% of cases with simple hyperplasia, complex hyperplasia, simple atypical, and complex atypical hyperplasias, respectively, progressed to endometrial cancer.[13] Complex hyperplasia with atypia therefore had the highest risk of progression. Silverberg, in a review of four cases series, showed that risk of progression could be associated more with complex architecture than with the presence of cytologic atypia.[3] Simple hyperplasia with atypia was, however, the least common type, as was the case in our study.

Although this classification scheme reduced the confusion associated with the diagnoses of endometrial hyperplasia, it was nonetheless fraught with its own difficulties. Confusion among the clinicians resulted in an inadequate diagnosis resulting in hysterectomies performed for hyperplasias without atypia or progestogens administered in hormone replacement therapy dosages for atypical hyperplasia. Pathologists also experienced difficulties with categorization. This, with the coexistent use of the endometrial intraepithelial neoplasia (EIN) classification scheme, added to the confusion.[14]

The Endometrial Collaborative Group proposed the EIN classification system for precursors to endometrioid endometrial adenocarcinoma in 2000, as an alternative to the WHO system.[4] Mutter in this scheme proposed the terms endometrial hyperplasia, EIN and adenocarcinoma

to define distinctive subgroups that were functionally relevant to the management of the patients with endometrial diseases. All endometrial precancers in this scheme are designated EIN in recognition of their monoclonality.[15] Although initially defined using morphometry and molecular studies, these diagnoses can actually be made on routine histopathologic assessment with H and E.[4,15-17] All of the following must be met to make a diagnosis of EIN; the area of glands must be greater than the stroma, the cytology must differ between architecturally crowded focus and the background or must be clearly abnormal, the maximum linear dimension must exceed 1 mm, benign mimics (e.g., polyps) must be excluded and cancer must be excluded by recognizing maze-like glands, areas of polyclonal "mosaic-like" glands, myoinvasion, or significant cribriform.[18] In this classification scheme, a few cases of nonatypical hyperplasias and all cases of atypical hyperplasias were categorized as EIN. Both the WHO and EIN classification schemes were found to have equally satisfactory reproducibility and expected the risk of progression to endometrial adenocarcinoma.[9] Some, however, pointed out that the implementation of the EIN scheme would require retraining pathologists and clinicians who would be confused by yet another classification of endometrial hyperplasia.[4] Others questioned the validity of the EIN scheme, stating that monoclonality, which was the bedrock of the scheme, was only suggestive of endometrial neoplasia and not conclusive since it also occurred in endometrial polyps, endometriotic cysts, and in complex endometrial hyperplasia without atypia.[9] McCluggage recommended that pathologists and clinicians stick to the 1994 WHO classification scheme until further evidence emerged regarding reproducibility, practicalities and prognostic implications of the EIN system.[4]

In the latest classification published in 2014, the WHO now distinguishes only between two categories: hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia.[2] Simple and complex hyperplasias without atypia are now categorized simply as hyperplasia without atypia.[2,14] They have no significant genetic changes and will regress after the endocrine milieu has normalized. However, if the endocrine disorder persists for a long time, they can progress to adenocarcinoma. They are therefore treated conservatively; preventive hysterectomy being considered only in exceptional cases.[14]

Atypical hyperplasias now include the previously designated simple hyperplasia with atypia, complex hyperplasia with atypia, and EIN.[2] These, in contrast to nonatypical hyperplasia, exhibit the genetic aberrations characteristic of endometrioid endometrial carcinoma.[2,14] They are at extremely high risk for developing invasive adenocarcinoma and are treated by total hysterectomy.[2,14] Some have recommended that until the new classification comes into general use, histologic findings should be reported using the new and previous WHO classification schemes.[14]

Conclusion

Endometrial hyperplasias should be reported according to the WHO classification scheme, as it removes all ambiguities with respect to the terminology and explains the genetic mechanisms of each category.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Scully RE, Bonfiglio JA, Kurman RV, Silverberg SG, Wilkinson EJ. Histological typing of female genital tract tumors. In: World Health Organization. International Histological Classification of Tumors. Vol. 92. New York: Springer-Verlag; 2001. p. 2578-84.
2. Zaino R, Carinelli SG, Ellenson LH. Tumors of the Uterine Corpus: Epithelial Tumors and Precursors. Lyon: WHO Press; 2014.
3. Silverberg SG. Problems in the differential diagnosis of endometrial hyperplasia and carcinoma. Mod Pathol 2000;13:309-27.
4. McCluggage WG. My approach to the interpretation of endometrial biopsies and curettings. J Clin Pathol 2006;59:801-12.
5. Foster LN, Montgomery R. Endometrial carcinoma: A review of prior biopsies. Am J Clin Pathol 1965;43:26-35.
6. Culson WF. Surgical Pathology. 2nd ed. New York: Gower Medical Publishing; 1988.
7. Ikop UE. Histologic Survey of Uterine Curettings in Lagos University Teaching Hospital, Lagos: A One Year Prospective Study from June 2002 – May 2003. Dissertation for Part II National Postgraduate Medical College of Nigeria; 2004.
8. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, *et al.* Incidence of endometrial hyperplasia. Am J Obstet Gynecol 2009;200:678.e1-6.
9. Sivridis E, Giatromanolaki A. Demystifying endometrial hyperplasia. Diagn Histopathol 2013;19:223-30.
10. Buckley H, Fox H. Biopsy Pathology of the Endometrium. 19th ed. Edinburg: Churchill Livingstone; 1989.
11. Rosai J. Female Reproductive System, uterus-corpus. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 9th ed. New York: Mosley; 2004. p. 1581-94.
12. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer 1985;56:403-12.
13. Baak JP, Wisse-Brekelmans EC, Fleege JC, van der Putten HW, Bezemer PD. Assessment of the risk on endometrial cancer in hyperplasia, by means of morphological and morphometrical features. Pathol Res Pract 1992;188:856-9.

14. Emons G, Beckmann MW, Schmidt D, Mallmann P. Uterus Commission of the Gynecological Oncology Working Group (AGO). New WHO classification of endometrial hyperplasias. Geburtshilfe Frauenheilkd 2015;75:135-6.
15. Mutter GL. Endometrial intraepithelial neoplasia: A new standard for precancer diagnosis. Am Obstet Gynaecol 2001;46:92-8.
16. Mutter GL. Histopathology of genetically defined endometrial precancers. Int J Gynecol Pathol 2000;19:301-9.
17. Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL, *et al.* Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. Mod Pathol 2005;18:324-30.
18. Silverberg SG, Mutter GL, Kurman RJ, Kubik-Huch RA, Nogales F, Tavassoli FA. Tumors of the uterine corpus, epithelial tumors and related lesions. In: Tavassoli FA, Stratton MR, editors. WHO Classification of Tumors: Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon, France: IARC Press; 2003. p. 221-32.