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Endometrial Hyperplasia - Changing Concept

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ABSTRACT

Introduction: The World Health Organization (WHO) (1994) classification of endometrial hyperplasia is plagued by poor diagnostic reproducibility and suboptimal prognostic prediction. In 1998 Drs, Mutter and Baak provide newer data to diagnose endometrial hyperplasia. Aim: To reclassify endometrial hyperplsia into two broad categories, Endometrial intraepithelial hyperplasia (EIN) and benign hyperplasia (non-EIN) and compare this with WHO hyperplasia classification. Material and method: The present study consists of 201 cases of endometrial hyperplasia lesions.After processing all the endometrial material received was subjected to haematoxylin and eosin stain. All the lesions were classified by five independent observers using WHO (1994) classification and again reclassified by applying EIN criteria.Results: In the present study out of 201 cases of WHO classified endometrial hyperplasias 91 were reclassified as EIN lesion and rest 110 diagnosed as non-EIN lesion. Variance of WHO endometrial hyperplasia classification is16.3,10,16.3 and 50.5 for simple typical, complex typical, simple atypical and complex atypical hyperplasia respectively whereas variance for EIN is 1.299. Conclusion: EIN classification system has good reproducibility. It is valuable to reclassify WHO hyperplasia classification by EIN criteria as unnecessary hysterectomies, its surgical complications and high cost of treatment can be prevented by applying EIN criteria.

KEYWORDS : WORLD HEALTH ORGANISATION (WHO), ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA, ENDOMETRIAL HYPERPLASIA.

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital tract and its most frequent subtype; endometriod carcinoma is often preceded by histologically evident precursor lesion. Accurate and sensitive recognition of these precursors have great clinical value as an early warning of heightened cancer risk and a potential target of preventive treatment[1]. WHO (1994) classification of endometrial hyperplasia is plagued by poor diagnostic reproducibility and suboptimal prognostic prediction, particularly with regard to presence or absence of cytological atypia. The endometrial collaborative group an international group of 19 pathologists including Mutter and Baak began discussion in 1998 to consider the diagnostic implications of newly emerging data on the biopsy of endometrial precancers.

According to this system we reclassify endometrial hyperplsia into two broad categories, endometrial intraepithelial neoplasia (EIN) and non-EIN and compare this with WHO hyperplasia classification.

MATERIAL AND METHOD

The present study consists of 201 cases of endometrial hyperplastic lesion. The patients were admitted in Guru Gobind Singh General Hospital affiliated to Shiri M.P. Shah Medical College, Jamnagar from the period between Jan 2012 to Dec. 2013. Chief complaint was mainly abnormal vaginal bleeding. The histopathological material consisted of Dilatation and Curettage, Endometrial Biopsy and Hysterectomy specimens. After processing all the material received was subjected to haematoxylin and eosin stain.

Patient those on therapeutic hormones; the diagnosis tissue sample was obtained 4 weeks after stopping exogenous hormones. All the cases were diagnosed using WHO (1994) classification and again by applying following EIN criteria by 5 independent observers:

(A) Architecture: Gland area exceeds stromal area [2]:
A cardinal architectural feature of endometrial precancers is glandular crowding, with a threshold quantitative cutoff is more than 55%. Areas with large dominant cysts should always be avoided in making this assessment.

(B) Cytology of architecturally crowded area is different than background, or clearly abnormal[2]:
There is no absolute standard for cytologic features of EIN lesions, but the cytology of EIN is clearly demarcated as divergent from that of co-existing benign endometrial tissues in the same patient.

(C) Size >1mm in maximum dimension [2]:
Accurate EIN diagnosis requires a contiguous field of glands sufficiently large to enable reliable assessment of architecture. A minimum lesion size of 1 mm maximum dimension is required to diagnose EIN.

(D) Exclusion of Benign Mimics [2]
Benign Mimics like reactive changes caused by infection, physical disruption, recent pregnancy or recent instrumentation should be carefully excluded before identifying EIN. Benign entities such as Persistent Estrogen Effect secretory endometrium and endometrial polyps are carefully excluded.

(E) Exclusion of Carcinoma [2]

OBSERVATION AND RESULT

We find that age group commonly involve in WHO classification is 3rd and 4th decade and minimum number are in 7th decade. Maximum number of patients with EIN lesion is in 4th decade and minimum number were in 2nd and 7th decade.

Table no.1 showing inter observer variability in WHO and EIN classification

	Simple typical hyperplasia	Complex typical hyperplasia	Simple atypical hyperplasia	Complex atypical hyperplasia	EIN
Observer 1	54	55	46	46	91
Observer 2	50	59	41	51	89
Observer 3	58	52	50	41	90
Observer 4	59	53	49	40	91
Observer 5	51	51	42	57	92
VARIABILITY	50-59	51-59	41-50	40-57	89-92
Variance*	16.3	10	16.3	50.5	1.299

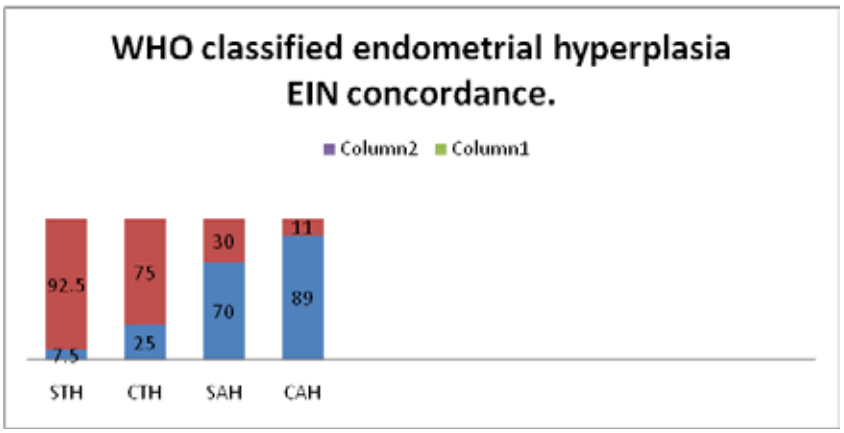
*** Formula used to calculate variance is**

$$s^2 = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2$$

where n is the sample size and x-bar is the sample mean.

Variance of WHO endometrial hyperplasia classification is 16.3, 10, 16.3 and 50.5 for simple typical, complex typical, simple atypical and complex atypical hyperplasia respectively whereas variance for EIN is 1.299.This suggestive of EIN classification has good reproducibility among pathologist.

Chart Showing WHO classified endometrial hyperplasia EIN concordance.



	No. of cases of WHO Hyperplasia	No. of EIN cases	No. of Non-EIN cases
Simple Typical Hyperplasia (STH)	54	4(7.5%)	50(92.5%)
Complex Typical Hyperplasia (CTH)	55	14(25%)	41(75%)
Simple Atypical Hyperplasia (SAH)	46	32(70%)	14(30%)
Complex Atypical Hyperplasia (CAH)	46	41(89%)	5(11%)
TOTAL	201	91((45.3%)	110(54.7%)

With above results it is clear that EIN classification is not simple conversion of WHO (1994) classification into EIN system. Cases classified earlier as highly premalignant (complex atypical hyperplasia) also turned out as Non-EIN lesions and vice versa.

DISCUSSION

The WHO 1994 classification system originally proposed by Kurman and Norris [5] subdivided hyperplasias by architectural complexity and cytologic atypia into four groups. Overall reproducibility of atypical hyperplasia diagnosis is poor [3, 4].

A Proposal to use the EIN [4, 5]:

Precancers should be placed in a single diagnostic category distinguishing by terms which will not be confused with benign hormonal effects. The endometrial collaborative group an international group of 19 pathologists including Mutter and Baak began discussion in 1998 to consider the diagnostic implications of newly emerging data on the biopsy of endometrial precancers.

Computerized morphometric analysis with the help software incorporated into the digitized light-microscope has developed in this respect. It is used on delineated regions on H&E stained sections. Improved image analysis incorporates computer-measure architectural as well as cytological features into a cancer predictive formula (D-Score).

D-score = 0.6229 + (0.0439 × VPS) – [3.9934 × Ln (SDSNA)] – (0.1592 × outSD)

Where VPS is Volume Percentage of Stroma, Ln (SDSNA) is Standard Deviation of Shortest Nuclear Axis, which reflects nuclear pleomorphism and (out SD) is Gland Outer Surface Density.

Morphometric EIN diagnosis has advantage of totally objective D-score which eliminates intra and inter observer variations but in country like india cost of machine and availability is limiting factor. On the other hand semi objective criteria applied in this study are easy to use and provide good reproducibility. Hecht et al [10] concluded that subjective application of EIN criteria correlates well with objective morphometry and successfully segregates patients into high and low cancer risk subgroups with high reproducibility.

In the present study, majority of specimen were Dilatation and Curettage which is similar to study done by Kaplan et al [6] and Dunton et al [7].

In the present study, 36(36%) hysterectomy samples were taken which is relatively close to hysterectomy specimens i.e. 30(35.3%) taken by Dunton et al [7] where as hysterectomy specimens taken by Kaplan et al[6] were much higher i.e.90(46.8%).

Similar to Kurman et al [10] and Mutter et al [4] we also found that majority of cases of endometrial hyperplasias were in 4th decade (46%) of life.

In the present study 91 cases of EIN were rediagnosed from 201 cases of WHO classified endometrial hyperplasia and 110 cases were in Non – EIN category.

Baak et al[9] had done the study on 132 patients with endometrial hyperplasias and redefined EIN in 26 cases based on morphometric D – score.

Baak et al [11] carried out multicentric study on 477 cases of endometrial hyperplasias and on the basis of morphometric D – score redefined 118 cases of EIN.

Hecht et al [8] studied 97 cases of endometrial hyperplasia subjectively and redefined 28 cases of EIN.

The finding in the present study are relatively similar to Hecht et al[8] but finding of the present study are not consistent with study of Baak et al[9, 11].

Table no. 2: Showing comparison of WHO Hyperplasia – EIN concordance in different studies

	Baak et al [9] EIN percentage	Hecht et al[10] EIN percentage	Baak et al[11] EIN percentage	Present study EIN percentage
Simple typical Hyperplasia	13	3.5	12	7.5
Complex typical Hyperplasia	34	45	43	25
Atypical Hyperplasia	58	78	47	79.3

In the present study out of 54 Simple typical hyperplasias, 4 cases were redefined as EIN (7.5%).

In study of Baak et al [9], 65 simple typical hyperplasias were found out of which 9 cases were redefined as EIN (13%).

Baak et al [11] studied 289 simple typical hyperplasias out of which 37 cases were redefined as EIN (12.8%).

The subjective study of Hecht et al [10] found 2 cases of EIN (3.5%) from 56 Simple typical hyperplasia cases.

In the present study 14 out of 55 (25.5%) Complex typical hyperplasia cases were redefined as EIN lesions.

In study of Baak et al [9]; 2 cases of EIN (34%) were redefined out of 6 cases of complex typical hyperplasias.

Baak et al [11] redefined 29 cases of EIN (43%) out of 67 cases of Complex typical hyperplasias.

Hecht et al [10] redefined 8 cases of EIN (45%) out of 18 cases of Complex typical hyperplasia. The findings of present study are relatively similar with the study of Baak et al [9].

In present study 73 EIN lesions (79.3%) were rediagnosed from 92 cases of atypical hyperplasia.

Baak et al [9] redefined 35 cases of EIN (58%) from 61 cases of atypical hyperplasia.

Hecht et al [10] studied 23 atypical hyperplasia out of which 18 cases were rediagnosed as EIN subjectively (78%).

Baak et al [11] redefined 58 cases of EIN (47%) out of 123 cases of atypical hyperplasias based on morphometric D- score.

The present study correlates with study done by Hecht et al. [10]

Although present study has its own limitations but it is valuable to reclassify WHO hyperplasia classification based on EIN criteria as unnecessary hysterectomies, its surgical complications and high cost of treatment can be prevented by applying EIN criteria. [10]

Finally we conclude that WHO 1994 classification has many inadequacies as its reproducibility varies among pathologist worldwide. The EIN classification based on new criteria has better reproducibility and prognostic value. The majority of WHO classified endometrial hyperplasia are reclassified as EIN (79.3%). The majority of WHO classified typical hyperplasia belongs to non-EIN category, but few cases of simple typical hyperplasia are reclassified as EIN.

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