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Pathology

COMPARISON OF ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA & WHO CLASSIFIED ENDOMETRIAL HYPERPLASIA IN PREDICTING THE RISK OF PROGRESSION TO ENDOMETRIAL CARCINOMA

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ABSTRACT

Background: Endometrial hyperplasia is the precursor lesion of most endometrial cancers of endometrioid type. The most commonly used classification system for endometrial hyperplasia is WHO 1994 classification system in which architecture disruption and cytological atypia are used to identify four types of endometrial hyperplasia including simple or complex hyperplasia with or without atypia. Newer EIN diagnosis by cytological atypia is of great consideration for the progression to endometrial cancer.

Material And Methods: The study consists of 100 cases of WHO classified endometrial hyperplasia for period of 4 yrs from 2015 to 2019. Type of sampling procedures- dilation & curettage, endometrial biopsy and fractional curettage.

Objective:

1. To discuss revised criteria for recognition of endometrial intraepithelial neoplasia (EIN).
2. To find out the sensitivity of endometrial intraepithelial neoplasia (EIN) classification in predicting the risk of malignancy.

Results: This study consists of 100 cases of endometrial hyperplasia. Patients were mostly postmenopausal & presented with abnormal vaginal bleeding. From WHO classified endometrial lesions, 2 out of 35 cases of simple typical hyperplasia, 10 out of 14 cases of complex typical hyperplasia,12 out of 20 cases of simple atypical hyperplasia and 20 out of 21 cases of complex atypical hyperplasia were reclassified as EIN.

Conclusion: To estimate the risk of progression to carcinoma and guide clinical management, the histo-pathologic diagnosis of endometrial hyperplastic lesion is very important, specially the diagnosis of EIN lesions. EIN carries a much greater risk of progression to endometrial cancer than other WHO classified endometrial hyperplasia.

KEYWORDS : Endometrial, hyperplasia, EIN, endometriod, carcinoma

INTRODUCTION:

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries.[1] Endometrioid type adenocarcinoma accounts for 75 to 80% of cases, and is associated with long-term unopposed estrogenic stimulation of the endometrium.[2] This estrogenic stimulation results in endometrial hyperplasia (EH) which is the precursor lesion of most endometrial cancers of Endometrioid type.[3] Endometrial hyperplasia is characterized by non-physiological proliferation of endometrium that results in glands with irregular shapes and varying sizes.[4] The most commonly used classification system for endometrial hyperplasia is the World Health Organization (WHO) 1994 classification system, in which architectural disruption and cytological atypia are used to identify four types of EH, including simple or complex hyperplasia with or without atypia.[5] Especially, cytological atypia is of great consideration, not only for the progression to endometrial cancer, but also for the risk of a coexistent endometrial cancer in women with endometrial hyperplasia.[6,7] Therefore, the correct identification of endometrial hyperplasia type has great clinical value as an early warning of heightened cancer risk and a potential target of preventive treatment.[8]

On the other hand, there is considerable inter-observer and intra observer variation in the diagnosis and typing of endometrial hyperplasia, because the diagnostic criteria of the WHO classification are largely subjective. [9,10,11] Endometrial hyperplasia deserves special mention because of its relationship to endometrial carcinoma. It is classified as lower grade hyperplasia. Lower grade include simple hyperplasia (cystic or mild hyperplasia) and complex hyperplasia (Adenomatous hyperplasia without atypia). Higher grade includes atypical hyperplasia (Adenomatous hyperplasia with atypia).[12]

For this reason, an endometrial intraepithelial neoplasia (EIN) classification based on molecular genetics and computerized morphometric analysis was introduced to identify patients at risk of having real precancer or cancer, and to facilitate proper and more uniform patient management.[13] During routine practice, the diagnosis of EIN is achieved by using hematoxylin-eosin stained sections. The diagnostic criteria include the presence of cytological demarcation, crowded gland architecture, minimum size of 1 mm, careful exclusion of mimics and cancers.[14]

Endometrial precancers are collectively termed EIN in recognition of their monoclonal growth. Implication of this proposal will bring diagnostic terminology into agreement with current concepts of endometrial premalignant disease and facilitate more uniform patient management.

AIMS AND OBJECTIVES:

1. To correlate WHO classified hyperplasia with newer entity EIN.
2. To discuss revised criteria for recognition of endometrial intraepithelial neoplasia (EIN).
3. To find out the sensitivity of EIN classification in predicting the risk of malignancy.
4. To guide the clinician/gynecologist about the mode of therapy in various endometrial hyperplasia & EIN.

MATERIAL AND METHOD:

The present study consists of 100 cases of endometrial hyperplasia for a period of 2 years between august 2018 to July 2020.

Sampling Procedures:

The histopathological material was received in the histopathology section of pathology department which consisted of Dilation and Curettage specimens, Endometrial Biopsy material and fractional curettage specimens. Information regarding age, chief complains, associated complains, menopausal status, any other relevant clinical or past history and method of sampling were recorded in requisition form.

Processing & Staining Method:

The material was fixed in 10% formalin and processed in graded alcohol and xylene and then embedded in paraffin wax to make a block. The blocks were cut at 4 to 5 um in thickness and thin sections were taken up on properly pre-labeled slides. Sections were deparaffinized in xylene and brought to water through descending grades of alcohol. The hydrated sections were than subjected to Hematoxylin and Eosin staining. Among the routine H & E stained slides, most representative sections were selected and were examined applying WHO classified endometrial hyperplasia terminology including descriptions of both architecture (complex or simple) and cytology (atypical or non-atypical).

Slides were then reviewed and reclassified into EIN Lesion or Non-EIN Lesion using the following EIN criteria.

The EIN Criteria applied were as follows:

1) Glandular crowding i.e. Area of Glands > Stroma.

Glandular crowding with Volume percentage stroma i.e. VPS < 55%.

***2)* Cytological Demarcation**

EIN Lesions have an abnormal cytology within the crowded glands

comprising ad EIN focus, relative to the background endometrium within the same patient.

***3)* Size > 1 mm**
Maximum linear dimensions exceed 1mm. Supportive morphometry and clonal analysis applies EIN to a lesion with a largest diameter measuring at least 1mm.

4) Exclude confounding benign processes like secretory endometrium, polyps, repair etc.

***5)* Exclude Cancer**
Carcinoma if mazelike glands, solid areas or significant cribriforming present.

Cases were followed for the development of endometrial carcinoma either by repeat D & C, endometrial biopsy or hysterectomy (only of follow up cases). Then comparison was done between EIN and WHO classified endometrial hyperplasia in predicting the risk of progression to endometrial carcinoma.

Inclusion Criteria:
a) Any female above the age of 25 years.
b) Females with high body mass index (>30-35).
c) Females with PCOD, estrogen secreting ovarian tumor.
d) Females on tamoxifen drug for treatment of breast cancer.
e) Infertile females and Elderly females with H/O diabetes.

Exclusion Criteria:
a) Patients younger than 25 years of age.
b) Patients having reactive changes caused by infection, recent pregnancy or recent instrumentation.

RESULTS:
Total 100 patients were studied at a tertiary care centre. Most common procedure done was dilation & curettage (71%) followed by endometrial biopsy (16%) & least was fractional curettage (13%).

Most common chief complaint was post menopausal bleeding (36%) followed by metrorrhagia (21%), menorrhagia (17%), abnormal vaginal discharge (10%) mid cycle spotting (9%) polymenorrhea (6%) & oligomenorrhoea (1%) in decreasing order of frequency.

Endometrial hyperplasia was most common in postmenopausal women (37%) closely followed by premenopausal women(35%) & perimenopausal women (28%).

Table 1: Subcategories Of Endometrial Hyperplasia According To The Age Distribution (n=100)

Endometrial Hyperplasia	Simple typical hyperplasia	Simple atypical hyperplasia	Complex typical hyperplasia	Complex atypical hyperplasia	Total
25-29	3	0	1	1	5
30-39	14	7	6	3	30
40-49	12	6	14	8	40
50-59	6	4	3	5	18
>60 yrs	2	1	0	4	7
Total	37	18	24	21	100

Simple typical hyperplasia was most common in 3rd decade of life whereas simple atypical hyperplasia, complex typical hyperplasia and complex atypical hyperplasia were more common in 4th decade of life.

Table 2: Distribution Of Cases In Endometrial Hyperplastic Group According To The WHO Classification Showing Cytological Feature And Architectural Pattern (n=100)

Histological Diagnosis	Cytological Atypia	Architectural pattern	No of case
Simple typical Hyperplasia	Absent	Regular	37
Complex typical Hyperplasia	Absent	Irregular	24
Simple atypical Hyperplasia	Present	Regular	18
Complex atypical Hyperplasia	Present	Irregular	21
Total			100

Commonest hyperplasia was simple typical type with regular architectural pattern & absent cytological atypia (37%)

Table 3: W.H.O. Classified Endometrial Hyperplasia & EIN Concordance (n=100)

WHO hyperplasia diagnosis	No of cases of WHO hyperplasia	No of case with EIN	Non EIN
Simple Typical Hyperplasia	37	2(5.40%)	35
Simple Atypical Hyperplasia	18	6(33.33%)	12
Complex Typical Hyperplasia	24	10(41.66%)	14
Complex Atypical Hyperplasia	21	20(95.23%)	01
TOTAL	100	38	62

Out of 37 patients with simple typical hyperplasia 2 patients were reclassified as EIN, while out of 18 patients with simple atypical hyperplasia 6 patients were reclassified as EIN. Out of 24 patients with complex typical hyperplasia 10 patients were reclassified as EIN while out of 21 patients with complex atypical hyperplasia 20 patients were reclassified as EIN.(fig:1)

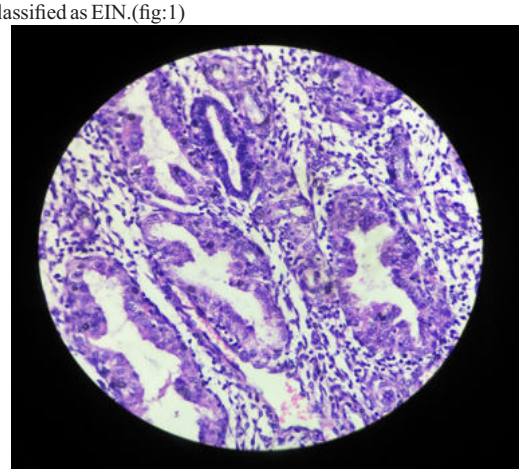

Figure 1: Endometrial Intraepithelial Neoplasia (E.I.N) (H & E, 40X)

Table 4: Progression To Endometriod Type Endometrial Carcinoma Among WHO Classified Endometrial Hyperplasia Group (n=100)

WHO hyperplasia diagnosis	Endometrial Carcinoma	Total cases
Simple Typical Hyperplasia	1(3.03%)	33
Simple Atypical Hyperplasia	1(5.88%)	17
Complex Typical Hyperplasia	2(8.69%)	23
Complex Atypical Hyperplasia	12(57.14%)	21
No follow up	-	06
TOTAL	16	100

Patient with complex atypical hyperplasia had the highest chances of progression to endometrioid endometrial carcinoma.(fig:2)

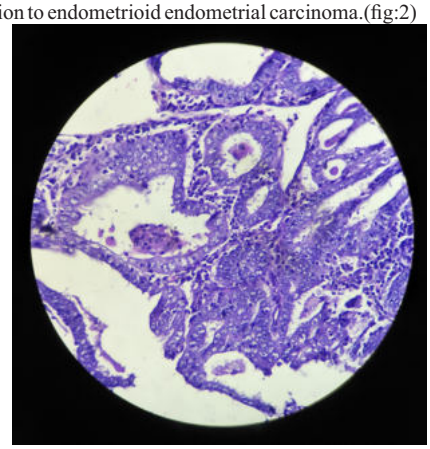

Figure 2: Well differentiated Endometrioid endometrial carcinoma type I, FIGO grade I (H & E, 40X)

We compared our results of EIN (38%) with other authors & they showed correlation with Khanna R et al 2010[15] (39%), Bake et al 2001[16](34.84%), Hechet et al 2005[17] (29%) & Sandeepa et al 2014[18] (26.47%).

DISCUSSION:

Endometrial carcinoma is the most commonly diagnosed gynaecological malignancy with approximately 150 000 cases annually worldwide. Approximately 90% of cases are sporadic, and the remaining 10% are hereditary. [19] The incidence has increased with lifestyle and environmental changes.

Classification of EH is a long-standing issue. Endometrial hyperplasia (EH) is an irregular proliferation of endometrial glands, which can progress to endometrial cancer (EC) .[20,21]The risk of progression of EH to EC depends on the nature of the lesion, which can be a benign reaction to an unopposed action of estrogen, or a neoplastic premalignant process. [12, 21] These two conditions require two different therapeutic approaches: benign EH may be managed with observation alone, with progestin reserved to symptomatic case. [22] On the other hand, premalignant EH should be treated with hysterectomy, although a conservative treatment can be chosen in selected cases (strong wish to preserve fertility or contraindication for surgery). [12,22]

The diagnosis of benignity or pre-malignancy of EH is usually made at histological examination.[21] The most used classification system for differentiating premalignant EH is the one proposed by the World Health Organization (WHO) and repeatedly revised. [21,23, 24]WHO system identifies cytological atypia as the crucial criterion of pre-malignancy, indicating atypical EH as premalignant and non-atypical EH as benign. [20, 21] "Endometrial intraepithelial neoplasia" (EIN) is an alternative system which was proposed to overcome several problems risen for WHO criteria, such as low reproducibility and lack of a pathogenetic and molecular basis. [12,21,24]

Before 1994, EH had been classified as "mild", "moderate" and "severe", or alternatively as "cystic glandular", "adenomatous" and "atypical adenomatous". [25]

The 1994 WHO classification system had categorized EH according to two parameters: glandular complexity and cytological atypia. Therefore, four categories of EH were proposed: "simple non-atypical", "complex non-atypical", "simple atypical" and "complex atypical". [21,23,24]Cytological atypia was already considered as the main factor associated with risk of progression to cancer. [6] However, these categories did not reflect the dichotomous nature of EH, which can be a polyclonal proliferation caused by the action of estrogen or a neoplastic process. [13] EIN system was developed to resolve this issue, distinguishing "benign EH" and "EIN" based on the pathogenetic mechanism underlying EH. [13,21,24]

The WHO revised its classification in 2003, proposing three EH categories: "simple", "complex" and "atypical" [23,26] : such system was quite super imposable to those used before 1994 and mentioned above. Finally, in 2014, the WHO proposed a dichotomous classification of EH into "non-atypical" and "atypical", reporting "EIN" as a synonym of the latter one. [20,21] Therefore, WHO adopted the same conceptual basis as EIN system for EH categorization.

CONCLUSION:

To estimate the risk of progression to carcinoma and guide clinical management, the histopathological diagnosis of endometrial hyperplastic lesion is very important.

The overall reproducibility of World Health Organization (WHO) hyperplasia diagnosis is poor, because of nonspecific reporting patterns and intra/inter-observer variation. Due to the heterogeneous nature of endometrial hyperplasia lesions, there has been considerable difficulty in classifying them into clinically relevant and pathologically reproducible groups that correlate risk of malignancy with treatment options and clinical outcome.

Uncertainty in predicting the natural history of individual lesions, inconsistency of diagnosis, and unclear therapeutic implications for each diagnostic group complicates standardized clinical management of women with premalignant endometrial disease. Furthermore, the four classes of WHO hyperplasia do not define biologically distinctive subgroups.

Based on WHO classification many unnecessary hysterectomies were done so a group of pathologists proposed a new classification of endometrial hyperplasia called endometrial intraepithelial neoplasia (EIN) classification based on new criteria. Thus the introduction of EIN represents a fundamental change in our understanding of the development of endometrial hyperplasia. EIN is considered a direct precursor lesion for the development of endometriod endometrial carcinoma, which is backed by molecular evidence that proposes a monoclonal lineage with significant malignant potential. The EIN system has been endorsed by the World Health Organization (WHO) in 2014.

"Endometrial intraepithelial neoplasia" (EIN) is an alternative system which was proposed to overcome several problems risen by WHO diagnostic criteria, such as low reproducibility and lack of a pathogenetic and molecular basis. EIN carries a much greater risk of progression to endometrial cancer.

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