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Clinicopathological Profile of Endometrial Hyperplasia And Endometrial Carcinoma

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ABSTRACT

Endometrial carcinoma is the most common malignancy of female genital tract. Recently, EIN scheme has been adopted as an alternative to WHO classification. This study was planned to study the clinicopathological profile of cases with endometrial hyperplasia and endometrial carcinoma and to study EIN in cases with endometrial hyperplasia. 168 premenopausal and postmenopausal women > 40 years of age with abnormal uterine bleeding were included in the study. Women with coagulopathy, iatrogenic bleeding per vaginum, malignancy other than endometrial carcinoma and those not willing to participate were excluded from the study. Present study showed endometrial carcinoma to be strongly associated with age, menopausal status, BMI, diabetes, hypertension and postmenopausal bleeding. Out of 50 cases diagnosed with endometrial hyperplasia, 4 cases were positive for EIN. EIN system can be used to represent these cases as it predicts disease progression more accurately than WHO-94 classification.

KEYWORDS :

Introduction

Endometrial carcinoma is the most common malignancy of female genital tract in developed countries, with an incidence of 12.9 per 100,000 women and mortality rate of 2.4 per 100,000. It is the fourth most common cancer in women after carcinoma of breast, colorectal and lung .[1] In developing countries , it is the second most common gynecological malignancy(cervical cancer is more common), with an incidence of 5.9 per 100,000 and a mortality rate of 1.7 per 100,000.[2]

Endometrioid endometrial adenocarcinoma accounts for three fourths of endometrial cancers and is thought to develop following a continuum of pre malignant lesions ranging from endometrial hyperplasia without atypical to hyperplasia with atypia and finally to well differentiated carcinoma. Endometrial hyperplasia represents a spectrum of biologic and morphologic alterations of the endometrial glands and stroma ranging from an exaggerated physiological state to carcinoma in situ.[3]

WHO divides endometrial hyperplasia by architecture (simple or complex) and cytological atypia (with or without). It predicts progression to cancer as in simple hyperplasia without atypia is 1%, simple hyperplasia with atypia is 8%, complex hyperplasia without atypia is 3%, and complex hyperplasia with atypia is 29% .[4] Reproducibility of this method amongst pathologists has been poor. Endometrial intraepithelial neoplasia(EIN) has been adopted as an alternative scheme to WHO classification.EIN lesions have been discovered by a combination of molecular , histologic , and clinical outcome studies beginning in 1990s which provide a multifaceted characterization of the disease. The EIN diagnostic scheme is intended to replace the previous "endometrial hyperplasia" classification as defined by WHO in 1994, which has been separated into benign (benign endometrial hyperplasia) and premalignant (EIN) classes in accordance with their behavior and clinical management.[3]

Several risk factors of endometrial hyperplasia and carcinoma are known such as age more than 50 years, postmenopausal status, nulliparity, PCOS, estrogen secreting ovarian tumors, postmenopausal estrogen therapy , tamoxifen therapy, diabetes, hypertension , increasing obesity, changing life style pattern, and dietary factors. All these factors cause unopposed estrogen stimulation on endometrium leading to endometrial hyperplasia and carcinoma.[5]

The prevalence of endometrial carcinoma is increasing globally even in developing countries and their risk factors need to be assessed. This study was planned to find out the clinicopathological profile of cases of endometrial hyperplasia and endometrial carcinoma and to study EIN in cases with endometrial hyperplasia.

MATERIALS AND METHODS

This was a prospective cohort study conducted in Department of Obstetrics and Gynecology of King George's Medical University from July 2013 to August 2014.

Premenopausal and postmenopausal women >40 years of age with abnormal uterine bleeding were included in the study. Women with abnormal uterine bleeding due to coagulopathy, iatrogenic bleeding per vaginum, patients diagnosed with malignancy other than endometrial carcinoma and patients not willing to participate were excluded from the study.

Informed consent was taken from all the patients. A detailed history including age, parity, menopausal status, risk factors such as diabetes, hypertension, infertility, hormone replacement therapy, unopposed estrogen exposure, tamoxifen therapy, smoking, socio economic status, dietary habits etc. were taken. General examination including pallor, weight, height and BMI was done. Systemic examination including per abdomen, per speculum, per vaginal examination was done. Ultrasonographic examination of pelvis for uterus and adnexa was

done. Endometrial biopsies were taken either by endometrial aspiration, dilatation and curettage, hysteroscopy guided biopsy or from hysterectomy specimens and send for histopathological examination.

Sections stained with H and E dye were used to study the histological features of endometrial lesions. Those lesions diagnosed on histopathological examination as endometrial hyperplasia or endometrial carcinoma were analyzed for EIN using EIN diagnostic criteria – 1) gland area > stroma, usually in a localized region 2) cytological alterations between crowded focus and background 3) size > 1mm 4) exclude mimics 5) exclude cancers

Statistical analysis was done using SPSS software.

RESULTS

168 women more than 40 years of age with abnormal uterine bleeding were included in the study. There were 50 cases of endometrial hyperplasia which were reviewed to establish the diagnosis of EIN.

Out of 168 cases enrolled in the study , 107 (63.7%) women had no endometrial pathology, 50 (29.8%) women had endometrial hyperplasia and 11 (6.5%) women had endometrial carcinoma.

On correlating mean age with endometrial pathology it was found that mean age of cases with endometrial carcinoma was significantly higher as compared to cases with normal endometrium and endometrial hyperplasia and the difference was statistically significant (p value< 0.0001).On studying correlation of parity with endometrial pathology, it was found that nulliparity had no significant association with endometrial hyperplasia or carcinoma. Menopausal status was correlated with endometrial pathology. Majority of premenopausal women had normal endometrium (89.7%) followed by endometrial hyperplasia (78%) while majority of post menopausal women had endometrial carcinoma (81.8%). The difference was statistically significant in the post menopausal group with endometrial carcinoma, thus suggesting an increased risk. On correlating mean age of menopause with endometrial pathology no significant difference was found. BMI, diabetes and hypertension were found to be strongly correlated with endometrial pathology. None of the subjects under study had other mentioned risk factors namely PCOS, smoking, hormonal exposure, unopposed estrogen exposure, tamoxifen therapy. Presenting complaints of patients was studied and it was found that menorrhagia was associated with normal endometrium and endometrial hyperplasia while post menopausal bleeding was seen in cases of endometrial carcinoma. Size of uterus was measured by ultrasound and it was found that increase in size of uterus was associated with endometrial hyperplasia & endometrial carcinoma. This difference was found to be statistically significant (Table 1). Mean endometrial thickness measured by USG was more in cases of endometrial hyperplasia followed by endometrial carcinoma as compared to subjects with normal endometrium and the difference was statistically significant. (Table 2) .Cases were also analyzed with respect to histopathological diagnosis. (Table 3)

50 cases diagnosed with endometrial hyperplasia on histopathology were subjected to EIN analysis. 4 of these cases were tested as EIN positive. Of these, 1 (27.3%) had simple endometrial hyperplasia without atypia, 1(20%) had complex endometrial hyperplasia without atypia and 2 (50%) had complex endometrial hyperplasia with atypia. Thus, EIN positivity was significantly higher in complex endometrial hyperplasia as compared to simple endometrial hyperplasia. The difference was statistically significant (p <0.001).

Table 1 – correlation of endometrial hyperplasia and carcinoma with demographic and clinical variable

	Normal	Hyperplasia	Carcinoma	P value
Mean age (in years)	44.86±5.34	46.4±6.17	55.91±8.14	<0.001

	Normal		Hyperplasia		Carcinoma		P value
Parity	No.	%	No.	%	No.	%	
P0(n=6)	3	2.8	2	4	1	1.9	
P1-2(n=62)	41	38.3	18	36	3	27.3	0.302
P3-4 (n=76)	43	40.2	27	54	6	54.5	
>P4(n=24)	20	18.7	3	6	1	1.9	
Menopausal status	no	%	no	%	no	%	
premenopausal	96	89.7	39	78	2	18.2	<0.001
Postmenopausal	11	10.3	11	22	9	81.8	
Mean age of menopause(-years)	47.55±4.57		48.91±4.21		50±3.91		0.444
Duration of menopause(-years)	7.18±5.98		4.91±3.62		8±6.24		0.409
BMI	no	%	no	%	no	%	
18.0-24.9	74	69.2	0	0	0	0	<0.001
25.0-29.9	12	11.2	8	16	1	1.9	
>=30	21	19.6	42	84	10	90.9	
Diabetes	1	1	5	10	3	27.3	<0.001
Hypertension	4	3.7	9	18	5	45.5	<0.001
Presenting complaints							
Menorrhagia	89	83.1	36	72	2	18.2	
Menorrhagia and polymenorrhea	3	2.8	1	2	0	0	
polymenorrhea	2	1.9	1	2	00	0	<0.001
Menometrorrhagia	2	1.9	1	2	0	0	
Postmenopausal bleeding	11	10.3	11	22	0	0	
Mean size of uterus	109.44±87.27		177.77±172.10		122.99±75.37		0.004

Table 2- correlation of mean endometrial thickness (by TVS) with endometrial pathology

Parameter	Total (n=168)	Normal (n=107)	Hyperplasia (n=50)	Carcinoma (n=11)	P value
	Mean endometrial thickness (in mm)	Mean endometrial thickness (in mm)	Mean endometrial thickness (in mm)	Mean endometrial thickness (in mm)	
Overall	10.3±4.9	8.6±4.9	13.5±3.2	11.3±3.6	P <0.001

	N=137	N=96	N=39	N=2	
In premenopausal	10.1±4.7	8.5±4.5	13.8±2.8	13.0±4.2	P< 0.01
	N=31	N=11	N=11	N=9	
In post menopausal	11±5.5	9.6±7.7	12.5±4.3	11±3.6	P= 0.487

Table 3- Distribution of cases according to histopathological diagnosis

S.no	Diagnosis	No.of cases	Percentage
1.	Normal	107	63.7
	Proliferative	73	43.5
	Secretory	26	15.5
	Mixed	5	3.0
	atrophy	3	1.8
2.	Hyperplasia	50	29.8
	Simple without atypia	37	22.0
	Simple with atypia	4	2.4
	Complex without atypia	5	3.0
	Complex with atypia	4	2.4
3.	Carcinoma	11	6.5
	Endometrioid	7	4.2
	Non endometrioid endometrial carcinoma	4	2.4
	Total	168	100

DISCUSSION

Endometrial carcinoma is the most common malignancy of female genital tract in developed countries. Its prevalence is increasing worldwide even in developing countries. The risk factors of endometrial carcinoma are known but need to be reassessed.

We studied clinicopathological profile of cases of endometrial hyperplasia and endometrial carcinoma and assessed cases of endometrial hyperplasia for EIN as per diagnostic criteria mentioned earlier.

In present study it was observed that mean age of cases with endometrial carcinoma was significantly higher as compared to cases with normal endometrium and endometrial hyperplasia. Frederick Amant et al[6] studied typical age incidence curve for endometrial cancer and observed that most cases are diagnosed around menopause with highest incidence around seventh decade of life. M.C. Breijer et al [7] observed that probability of endometrial carcinoma in women with post menopausal bleeding raised from 1 % in younger women less than 50 years of age to more than 23.8% in women more than 80 years of age. Wang ZQ et al[8] divided his patients into two groups- hyperplasia group (atypical endometrial hyperplasia) and cancer group and observed no statistically significant difference between both the groups with respect to age.

Endometrial carcinoma is more common in nulliparous women, risk being 2-3 times more than in parous women. Evans Metcalf et al[9] has reported that nulliparity is associated with endometrial cancer. However in present study as well as in study by Wang ZQ et al[8] no significant association was seen between nulliparity and endometrial pathology.

On comparing the incidence of endometrial pathology in premenopausal and postmenopausal women, it was observed that endometrial carcinoma was more common in postmenopausal women in present study as well as in studies by Frederick Amant et al[6] and Wang ZQ et al.[8]

On studying symptoms, postmenopausal bleeding was associated more with carcinoma while menorrhagia was associated more with normal endometrium and endometrial hyperplasia. Wang ZQ et al[8] reported that amongst patients with post menopausal bleeding, 87% had carcinoma while 53.3% had hyperplasia while in premenopausal patients, 80% cases of carcinoma and 68% cases of hyperplasia were diagnosed.

In present study obesity, hypertension and diabetes were found to be important risk factors in endometrial carcinoma. According to Lindemann et al [10]obesity epidemic contributes to steadily increasing incidence of endometrial cancer for which obese women may have six fold higher risk as compared to lean women. Present study as well as other studies have found increased risk of endometrial carcinoma with obesity especially endometrioid type .According to Fabio Parrazzani et al[11] , factors like obesity, HRT, irregular menstrual cycle, PCOS lead to increased exposure to exogenous or endogenous estrogen, increasing the risk of endometrial carcinoma.

Fischer B et al[12] and Assikis VJ[13] reported two to three times increased risk of endometrial cancer in women with breast cancer being treated with tamoxifen, however we did not have any such women in our cohort.

Endometrial thickness is increased in women with endometrial carcinoma compared to those without the disease. It is an important tool in making diagnosis of endometrial cancer. ACOG recommends endometrial biopsy in patients with postmenopausal bleeding having endometrial thickness more than 4 mm**.** According to Fleischer et al[14] sensitivity was 17% for endometrial thickness of 6mm and 33% using 5 mm as threshold. The positive predictive value was 2% and negative predictive value was 99% at endometrial thickness< 6mm. Tsuda et al[15] found that at a cut off of 3 mm in non bleeding women, sensitivity was 90%, specificity 84%, and positive predictive value 12%. In present study mean endometrial thickness was increased more in cases with endometrial hyperplasia than endometrial carcinoma.

Recently EIN (endometrial intraepithelial neoplasia) has been proposed as a new term to replace the WHO classification. Endometrial intraepithelial neoplasia has been proposed as a descriptive term for monoclonal endometrial pre cancers whose distinctive histopathology is characterized by those morphometric features that have been documented to increase the risk of cancer. Out of 50 cases diagnosed with endometrial hyperplasia, 4 cases tested positive for EIN. In present study EIN positivity was significantly higher in cases with complex endometrial hyperplasia with atypia as compared to simple endometrial hyperplasia without atypia (p <0.001). According to Mutter GL et al[16], EIN is diagnosed by presence of cytological demarcation, glandular crowding(volume percentage stroma <55%), minimum size of 1mm and careful exclusion of mimics(benign conditions with overlapping criteria,: basalis, secretory, polyps, repair etc.) and carcinoma.EIN lesions have been discovered by a combination of molecular, histologic and clinical outcome studies leading to EIN diagnostic scheme tending to replace previous endometrial hyperplasia classification study described by WHO.

Alp Usubutun et al[17] suggested that EIN applies specific diagnostic criteria to designate a monoclonal endometrial preinvasive glandular proliferation from previous studies to confer a 45 fold increased risk of endometrial cancer. R Khanna et al[18] classified endometrial hyperplasia into EIN and non EIN lesions and majority of atypical hyperplasias were reclassified as EIN.

In present study EIN positivity was significantly higher in cases with complex endometrial hyperplasia with atypia as compared to simple endometrial hyperplasia without atypia (p <0.001). R Khanna et al[18] in his study concluded that EIN criterias can be easily applied to routine hemotoxylin and eosin stained sections and is more reproducible than WHO system of classification. He also observed that few of the lesions diagnosed as simple hyperplasia with atypia correspond to EIN and have worse prognosis, thus, EIN could be used successfully to segregate patients into high risk and low risk groups for carcinoma. Semre LG et al[19] reported that EIN occurs in premenopausal women and is associated with unopposed estrogen either endogenous or exogenous.

CONCLUSION

To summarize present study showed endometrial carcinoma to be strongly associated with age , menopausal status, BMI, diabetes and hypertension . Most of the cases of endometrial carcinoma presented with postmenopausal bleeding with enlarged uterus with increased endometrial thickness. EIN was diagnosed more in cases with complex endometrial hyperplasia with atypia. We recommend adopting the system of EIN to represent these cases as previous studies also reported that EIN was the strongest prognostic indicator of future endometrial carcinoma and EIN classification predicted disease progression more accurately than WHO-94 classification.

The study however has its limitations as it was a time bound cohort study. Long term follow up on a larger sample size is required before arriving at a valid, acceptable and reproducible solution.

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