Prevalence of Coexisting Endometrial Carcinoma in Patients with Preoperative Diagnosis of Endometrial Hyperplasia with Atypia

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ABSTRACT

BACKGROUND

Concurrent carcinoma endometrium occurs in around 40 % of hysterectomy specimen done for premalignant endometrial intraepithelial neoplasia. We intend to study the prevalence of coexisting endometrial cancer in patients who were diagnosed with endometrial hyperplasia with atypia and had undergone hysterectomy.

METHODS

This cross-sectional study conducted at Government Medical College, Thrissur, included all women with a pre-operative diagnosis of endometrial hyperplasia with atypia (WHO) undergoing hysterectomy during the study period.

RESULTS

A total of 40 women were found to have atypical endometrial hyperplasia in the study period. The mean age of presentation was 51 ± 2. 7 yrs. and was more common in multiparous postmenopausal women. Postmenopausal bleeding was the most common presenting symptom and more than 50 % of women were overweight. The proportion of concurrent endometrial carcinoma in women with atypical endometrial hyperplasia was found to be 37. 5 %. 93 % of cases with concurrent endometrial carcinoma were of grade I endometrioid type. High risk features were defined as > 50 % myometrial invasion, seen in 47 % patients. Stage 2 endometrial carcinoma was seen in 27 % patients. 53 % patients had less than 50 % myometrial invasion. Stage 1a and 1b endometrial carcinoma was seen in 53 % and 20 % of patients respectively.

CONCLUSIONS

Large dicer of overlap exists between atypical endometrial hyperplasia (AEH) and early-stage endometrial carcinoma. Therefore, we should recognise the limitation of endometrial sampling in distinguishing between these two groups.

KEYWORDS

Atypical Endometrial Hyperplasia, Endometrial Carcinoma, Endometrial Sampling

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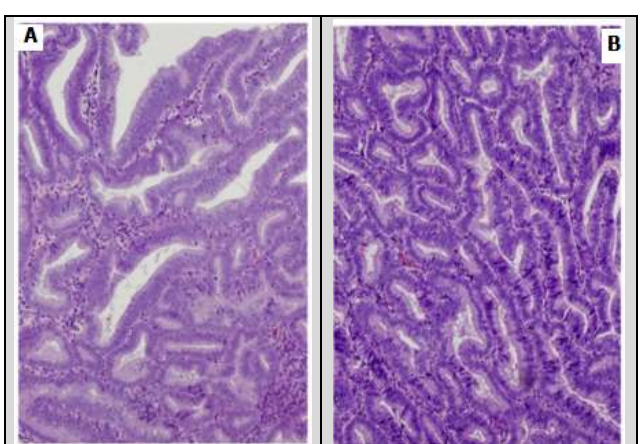
BACKGROUND

Endometrial Hyperplasia is defined as irregular proliferation of endometrial glands and an increase at glands per stroma.[1] In endometrial hyperplasia, there will be excessive cellular proliferation which leads to increased endometrial tissue and the ratio of endometrial glands to stroma will be at a ratio of greater than 1:1 Endometrial hyperplasia is caused by excess oestrogens without progesterone. According to WHO (2014), endometrial hyperplasia is classified into (i) hyperplasia without atypia and (ii) atypical hyperplasia based on cytological atypia.[2,3] According to endometrial intraepithelial neoplasia diagnostic scheme, developed by the International Endometrial Collaborative Group, endometrial hyperplasia is divided into a) benign (benign endometrial hyperplasia) b) premalignant (endometrial intraepithelial neoplasia) c) malignant (endometrial adenocarcinoma, endometrioid well differentiated type).[4,5]

Endometrial proliferation is stimulated by oestrogen. Hyperoestrogenism due to any cause, is one of the primary aetiological factors in both endometrial hyperplasias and endometrial carcinoma.[6,7] The most common gynaecological malignancy in the western world is endometrial cancer. [8] Endometrial hyperplasia is a well-known forerunner of carcinoma (CA) Endometrium. When we compare the incidence of endometrial hyperplasia and endometrial carcinoma, the incidence of endometrial hyperplasia is thrice that of latter and if left untreated can progress to endometrial carcinoma.[9] Confluent glandular aggregates are very extensively seen in stromal invasion. Stromal invasion is also characterized by crowded, hyperplastic glands.[10] Other histologic features suggestive of malignancy are moderate nuclear atypia, mitotic activity, necrosis and stratification. As nuclear atypia increases, the loss of cell polarity also increases. The nucleus which is cylindrical in shape will be enlarged and transformed in to round nucleus. In complex endometrial hyperplasia, there will be histological changes for the uterine glands whereas stroma will be normal. The glands will be crowded, irregular in shape and there will be numerous side buds.



Atypical Endometrial Hyperplasia | ***Endometrioid Adenocarcinoma Grade 1***

Endometrial hyperplasia has been reported to be among the most common over diagnosed lesions in surgical pathology. This has been attributed to the under recognition of benign mimics which includes artefacts, 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. Endometrial hyperplasia may occur at any age from puberty to menopause with highest incidence being in the premenopausal period. [11]

One accepted treatment option for patients with atypical endometrial hyperplasia (AEH) is hysterectomy with bilateral salpingo-oophorectomy. However, certain clinical conditions like infertility in younger women or those with serious comorbidities may force to rethink gynaecologic oncologist to attempt conservative hormonal therapy. But before opting conservative therapy for AEH, we have to exclude concurrent CA Endometrium. Newly diagnosed endometrial carcinoma within a short period of AEH reflects concurrent carcinoma endometrium. Concurrent malignancy may be missed due to under sampling or by over diagnosis by pathologist. We have to ensure patient safety by excluding concurrent carcinoma endometrium. In clinical practice, however, many gynaecologic oncologists have attempted conservative hormone management either to preserve fertility in younger women or to avoid hysterectomy in women who had serious comorbidities or who did not want to undergo surgery if possible. Our long-term objective was to initiate series of trials assessing hormone, nonsurgical therapeutic regimens for the precursor lesion, AEH.

Oestrogens are potent inducers of endometrial proliferation, which means that endometrial hyperplasia commonly precedes or coexists with endometrial cancer.[12] The link between the different histological types of endometrial hyperplasia and cancer is a complex issue. It is believed that endometrial carcinomas in which oestrogen stimulation is an aetiological factor are usually low grade and slow growing, with limited potential for metastasis.[12]

The risk factors for endometrial hyperplasia and carcinoma include postmenopausal status, unopposed oestrogen therapy for long period, nulliparity, obesity, diabetes and hypertension. Evidence states that postmenopausal women supplemented with oestrogens are at increased risk of endometrial hyperplasia and carcinoma if a progestin is not used to oppose the proliferative actions of oestrogen on the endometrium. The degree of risk increases with dose and duration of therapy, with an approximately 10-fold increased risk associated with each decade of use.[13]

For the management of patients with premalignant endometrial lesions, the prerequisites are specific detection of endometrial precancer and exclusion of coexisting carcinoma. Concurrent carcinoma endometrium occur in around 40 % of hysterectomy specimen done for premalignant endometrial intraepithelial neoplasia.[14] In this study, in patients who were diagnosed with endometrial hyperplasia with atypia and had hysterectomy, we intend to study the prevalence of coexisting endometrial cancer.

METHODS

This is a retrospective cross-sectional study conducted over a period of 3 years (January 1, 2014 and December 31, 2016) at Government Medical College, Thrissur.

Study Population

Reports of all women with a preoperative diagnosis of endometrial hyperplasia with atypia (WHO 2014)[2, 3] and who underwent hysterectomy during the study period in gynaecology department of Government Medical college, Thrissur, were included in the study.

Files with incomplete data were excluded from the study.

Sample Size

Sample size is calculated using the formula-
p = proportion of persons affected
q = 100 - p
d = allowable error (15 % of p)

The proportion of concurrent carcinoma in complex endometrial hyperplasia was found to be 48 - 52 %[16] in various studies. So, considering p = 52, the sample size required with an allowable error of 15 % and power of 85 % was calculated using the below formula.

$$n = 4pq / d^2$$
$$4 \times 52 \times 48 / 225 = 44$$

Study Procedure

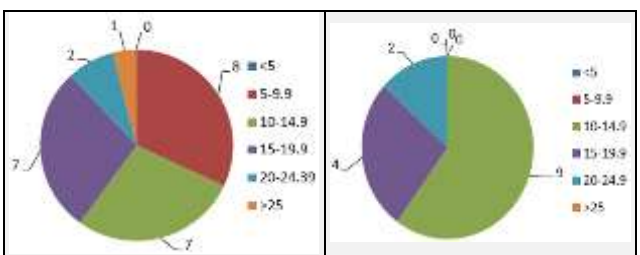
The postoperative histopathological findings of all women undergoing hysterectomy for a preoperative confirmed diagnosis of atypical hyperplasia was analysed retrospectively. The socio-demographic data, clinical presentation, preoperative histopathology, postoperative histopathological report from the specimen was filled up in the proforma. The data was entered in Excel sheet and result analysed using SPSS software version 16.

The percentage of women who had coexistent endometrial carcinoma in the postoperative report was calculated. The socio-demographic and clinical characteristics of these patients were analysed. Descriptive data were expressed using frequencies and percentages. Comparison of atypical endometrial hyperplasia and concurrent carcinoma based on variables such as parity, endometrial thickness, body mass index (BMI) and comorbidities were done using chi square test and unpaired t test was used to compare the age.

RESULTS

Between Jan 1, 2014 and Dec 31 2016, a total of 40 women were found to have atypical endometrial hyperplasia. The study panel consensus diagnosis for the biopsies was less than AEH in 11 patients (27.5 %), AEH in 14 patients (35 %), endometrial carcinoma in 15 patients (37.5 %). The hysterectomy review showed concurrent endometrial carcinoma in 37.5 % of patients. 50 % of women were in the age group of 50 - 59 yrs and mean age of presentation was 51 ± 2. 7 years. 90 % of women were multiparous and 10 % were nulliparous.

Among 40 women, 57 % were in the postmenopausal age group, 53 % were overweight and 12 % were obese. 52 % of women had postmenopausal bleeding, 32 % had heavy menstrual bleeding. 33 % of women had diabetes and 17 % had hypertension. Among 40 women with atypical endometrial hyperplasia 37.5 % had concurrent endometrial carcinoma. Among 15 women with endometrial carcinoma, 9 had endometrial thickness of 10 - 14.9 mm, 4 had endometrial thickness (ET) of 15 - 19.9 mm and 2 had ET of 20-24.9 mm. 93 % of cases with concurrent endometrial carcinoma were of grade I endometrioid type. High risk features, which were defined as > 50 % myometrial invasion were seen in 47 % patients. Stage 2 endometrial carcinoma was seen in 27 % patients. 53 % patients had less than < 50 % myometrial invasion. Stage 1a and 1b endometrial carcinoma was seen in 53 % and 20 % of patients respectively. The progression of endometrial hyperplasia to endometrial carcinoma in women was found in many studies. A 22 - 40 % progression was found in less than a year. Most of these studies followed WHO 1994 classification.



Endometrial Hyperplasia (n=25) | ***Endometrial Carcinoma (n=15)***

Figure 1. Comparison of Endometrial Thickness in Endometrial Hyperplasia and Endometrial Carcinoma

Parameters	AEHn=25	Concurrent Carcinoma=15	Chi Square Test P Value (<0. 01)
Mean age (years)	49 ± 1. 3	52. 7 ± 1. 8	0. 34*
Mean BMI a) < 25 b) > 25	25 10 15	26 4 11	<0. 001
Post-Menopausal	10	13	0. 01
Parity a) Nulliparous b) Parous	1 24	3 12	0. 01
Mean Endometrial thickness a) < 10 b) > 10	15. 6 8 17	14. 5 0 15	< 0. 001
Comorbidities a) Diabetes b) Hypertension	 10 3	 3 4	< 0. 001 0. 03

Table 1. Incidence of AEH Based on Age, Parity, Endometrial Thickness and Other Comorbidities

*** 't' test**

	Frequency	Percentage
Symptomatology		
Post-Menopausal Bleeding	21	52 %
Heavy Menstrual Bleeding	13	32 %
Infrequent Cycles	3	8 %
Others	3	8 %
Post op HPR		
Less than AEH	11	27. 5 %
AEH	14	35 %
Endometrial Carcinoma	15	37. 5 %
Grade		
Grade 1	14	93 %
Grade 2	1	7 %
Grade 3	0	0
Myometrial invasion		
< 1 / 2	8	53 %
> 1 / 2	7	47 %
Stage		
Stage 1a	8	53 %
Stage 1b	3	20 %
Stage 2	4	27 %

Table 2. Summary of all Study Variables Affecting Concurrent Endometrial Carcinoma

DISCUSSION

This study was designed to estimate the proportion of concurrent carcinoma in patients who have a biopsy diagnosis of atypical endometrial hyperplasia, it is believed to be the immediate precursor lesion to endometroid endometrial carcinoma. We found that the proportion of carcinoma in hysterectomy specimen was 37. 5 %. A total of 40 patients were evaluated during the study period.

"In a study by the Gynaecologic Oncology Group, 42 % of women diagnosed with complex atypical endometrial hyperplasia on office endometrial biopsy were found to have endometrial adenocarcinoma at surgery".[6] The high rate of underlying undiagnosed carcinoma among women diagnosed with complex atypical endometrial hyperplasia preoperatively may be because, the histologic criteria for differentiating complex atypical endometrial hyperplasia from low grade adeno carcinoma on endometrial sampling are not well defined and are subjective. Up to 50 % of women who received biopsy diagnoses of hyperplasia with atypia were found to have occult endometrial carcinoma when hysterectomy was performed soon thereafter. 52 % of hysterectomy specimen had a coexisting carcinoma in another study conducted in 2003.[7]

In a study by Shutter and Wright in 2005, endometrial adenocarcinoma was identified in 48 % of the hysterectomy specimen. They did not find any significant impact on the prevalence of adenocarcinoma with respect to age and sampling methods.[13] Postoperative histopathology report (HPR) and grade of the malignancy was also assessed in this study and 93 % of the endometrial carcinoma was of grade 1 disease. Among 15 cases of endometrial carcinoma, 53 % were involving < 1 / 2 of myometrium and 47 % involved the outer 50 % of myometrium. Considering the stage of the disease, 53 % were of Stage 1A. This all has led to the concept of screening for concurrent carcinoma in women with complex endometrial hyperplasia with atypia. It is desirable to detect any disease in its early stage especially if treatment would provide improvement in both quality and longevity of life to the affected person.

Etiologic correlation between endometrial hyperplasia and endometrial carcinoma was explained by Cullen, more than 100 years ago [12.] Subsequent reviews by Taylor in 1932 and by Novak and Yui in 1936 supported this observation. [14]The proportion of concurrent endometrial carcinoma in women with atypical endometrial hyperplasia was found to be 37. 5 % in our study. This is very similar to many other studies which show a range of about 17 - 43 % of concurrent endometrial carcinoma in patients with atypical endometrial hyperplasia. Of the 15 patients of endometrial carcinoma, the incidence of invasive carcinoma (stage 1b and stage 2) was 47 % in our study. Histological criteria for differentiating AEH from early-stage adenocarcinoma with endometrial sampling are controversial and subjective.

This may explain the high rate of unrecognized cancer among women diagnosed with atypical endometrial hyperplasia.

Study	Year	No. of Cases of AEH	Concurrent Carcinoma
Gusberg et al	1963	18	20 %
Tavassoli et al	1978	48	17 %
Kurmann et al	1986	89	17 %
Trimble et al	2006	289	43 %
Elizabeth et al	2009	724	41 %
Katshtoshi et al	2015	20	20 %
Our Study	**2017**	**40**	**37. 5 %**

Mean age for developing concurrent carcinoma was 52. 7 ± 1.8 yrs. in our study. Age wise distribution of concurrent carcinoma was assessed and 50 % of women were in the age group of 50 - 59 years and mean age of presentation was 51 ± 2. 7 years. The association of age at menopause with endometrial cancer remains controversial. In our study, we found that later menopausal age was associated with increased risk of endometrial cancer. Incidence was more in postmenopausal women (86 %). This is comparable to a meta-analysis study in 2015.

Among 15 women with endometrial carcinoma 9 had ET10 - 14. 9, 4 had ET15 - 19. 9 and 2 had ET 20-24. 9. This is comparable to a study by R. Smith Bindman et al. in 2004 which showed risk of carcinoma of endometrium is approximately 7. 3 % if endometrial thickness is > 5mm[15]

Limitations

Hysteroscopy was not performed for patients suspected of malignancy.

CONCLUSIONS

There is a large degree of overlap between the two groups-AEH and early stage endometrial carcinoma. It may be logical to consider staging for both groups, especially in women with associated risk factors. It is important that we recognise the limitations of endometrial sampling in reliably distinguishing between these two groups preoperatively, especially when planning for conservative treatment or surgeries in younger women who may have undiagnosed carcinoma.

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