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Original Research Article

Pathological Spectrum of Endometrium among Perimenopausal and Postmenopausal Women in a Tertiary Care Center

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Abstract:

Background: Endometrium is hormonally sensitive that constantly undergoes cyclical changes throughout reproductive life. Abnormal uterine bleeding (AUB) is a most common age related pathology that affects the quality of life in women. The present study was done to analyse and determine the histopathological patterns, bleeding patterns of endometrium among perimenopausal and postmenopausal women along with co morbidities. To identify the early precursor lesions and malignancies along with PTEN analysis for better management.

Material and Methods: This is a three year prospective study conducted at Government medical college, Anantapuramu, from January 2021 to December 2023.Endometrial samples with clinical diagnosis of abnormal uterine bleeding among perimenopausal and postmenopausal women age group only were included in this study. Histomorphological patterns were studied using Haemotoxylin and Eosin stained sections. Immunostaining of PTEN was done wherever necessary. Statistical data analysis was done using SSPS software.

Results: A total of 242 cases were studied. The prevalence of AUB is most common among perimenopausal age group women (77.6%). Menorrhagia (48.7%) was the common bleeding pattern. The functional cause (57.8%) of AUB was more common than Organic cause (42.1%).The most common histological pattern was the normal cyclical pattern showing proliferative phase (27.3%) followed by hyperplasias. Eight cases of endometrial carcinoma was observed most commonly among postmenopausal age group. Five cases were Stage IA, Three cases were Stage IB. PTEN immunostaing pattern was evaluated. Obesity and hypertension were most common comorbid conditions seen in this study.

Conclusion: The study of histomorphological patterns of Endometrium helps during the workup to exclude organic pathology especially early detection of precursor lesion of malignancy among perimenopausal and postmenopausal age groups. PTEN expression decreases as lesion progress from benign to malignancy. Loss of PTEN function is an early event in endometrial carcinogenesis.

Keywords: Endometrium, Abnormal uterine bleeding, Menorrhagia, Hyperplasia, Carcinoma, PTEN.

Introduction

Endometrium is the dynamic tissue that constantly undergoes cyclical changes in response to the recurrent hormonal changes of the ovulatory cycles. [1] Endometrial diseases are the most common gynaecological problem affecting women worldwide. [1] They constitute around 70% of all gynaecological consultancies in the perimenopausal and postmenopausal age group. [2]

They usually present with abnormal uterine bleeding (AUB). The prevalence rate is 17.9% in India. [1]AUB is a broad term used to describe irregularities in the menstrual cycle involving frequency, regularity, duration, and volume of flow. [1] It has varied presentations like heavy menstrual bleeding, irregular cycles, postcoital bleeding, and postmenopausal bleeding. [1,2] It occurs due to serval factors deranging homeostasis like hormonal imbalances, infections, structural lesions and malignancy [3,4]. The International federation of gynaecology and obstetrics (FIGO) devised a classification named PALM – COEIN for etiology of AUB. PALM stands for structural causes like polyps, adenomyosis, leiomyoma and malignancy. COEIN for nonstructural causes like coagulopathies, ovulatory dysfunction, and endometrial causes, iatrogenic causes and not otherwise classified ones. [3]

Endometrial hyperplasia and malignancy are important neoplastic lesions causing AUB with increased risk in peri-menopausal and post-menopausal women. [5] Endometrial hyperplasia may progress or coexist with endometrioid carcinoma. Early evaluation is essential to confirm the exact nature of the lesion and to rule out malignancy. The WHO 2014 classifies endometrial hyperplasias into 2 categories: hyperplasia without atypia and hyperplasia with atypia. [3] Hyperplasia with atypia shares molecular genetic changes that are typical for endometrial carcinoma. [4] Approximately 60 percent of such cases have coexisting endometrial carcinoma or are at increased risk of developing malignancy. [6,7]

Phosphate and Tensin Homologue (PTEN) is a tumour suppressor gene. Expression of PTEN is low in endometrial cancer than in normal endometrium. In endometrial carcinoma loss of PTEN protein expression or at least some dimunition of expression is seen. Precursor lesions and malignancies shows contiguous groups of PTEN negative islands, while endometrium altered by unopposed estrogen shows isolated PTEN negative glands. Loss of PTEN function by mutational or other mechanisms is an early event in endometrial tumorogenesis and it may occur in response to known endocrine risk factors. Thus it is a useful immunohistochemical marker for precursor lesions. Individual PTEN negative glands in estrogen exposed endometria are the earliest change seen in stage of endometrial carcinogenesis. Proliferation into dense clusters that form discrete premalignant lesion follows.[8] PTEN mutations have been seen in 55% of cases with endometrial hyperplasia. [9] Therefore Loss of PTEN function has been proposed as an early event in pathogenesis of endometrial carcinoma.

Material and Methods

The present prospective study was done in the Department of Pathology, Government medical college, Anantapur,Andhrapradesh. The period of study was three years, from January 2021 to December 2023 with institutional ethical committee approval.

All the endometrial biopsies/curretages and hysterectomy specimens sent for Histopathological examination with complaints of AUB were included in the study. The relevant clinical documents were collected. Women with AUB of gestational causes, patients below 40 years of age, inadequate and Autolysed samples were excluded from this study.

Histological features of all the cases were studied using Haemotoxylin and Eosin stained sections. The various histomorphological patterns was studied and classified. PTEN Immunostaining was performed on diagnosed cases of malignancy and ambigious cases of hyperplasia with atypia to malignancy using monoclonal antibodies. PTEN Immunostaining pattern was studied and classified according to percentage of cell stained and intensity of staining on immune stained slides. The immuno expression was evaluated as : 0 – absent, staining : mild : +1, moderate : +2, intense : +3.[10] Statistical analysis was done using SPSS software version.

Results

The study comprises 242 endometrial biopsies which were clinically diagnosed as AUB and that were analysed by histopathological examination. Based on the clinical data, Patient's age was categorized into peri-menopausal (40-49 years) and post-menopausal (> 50 years) age groups.

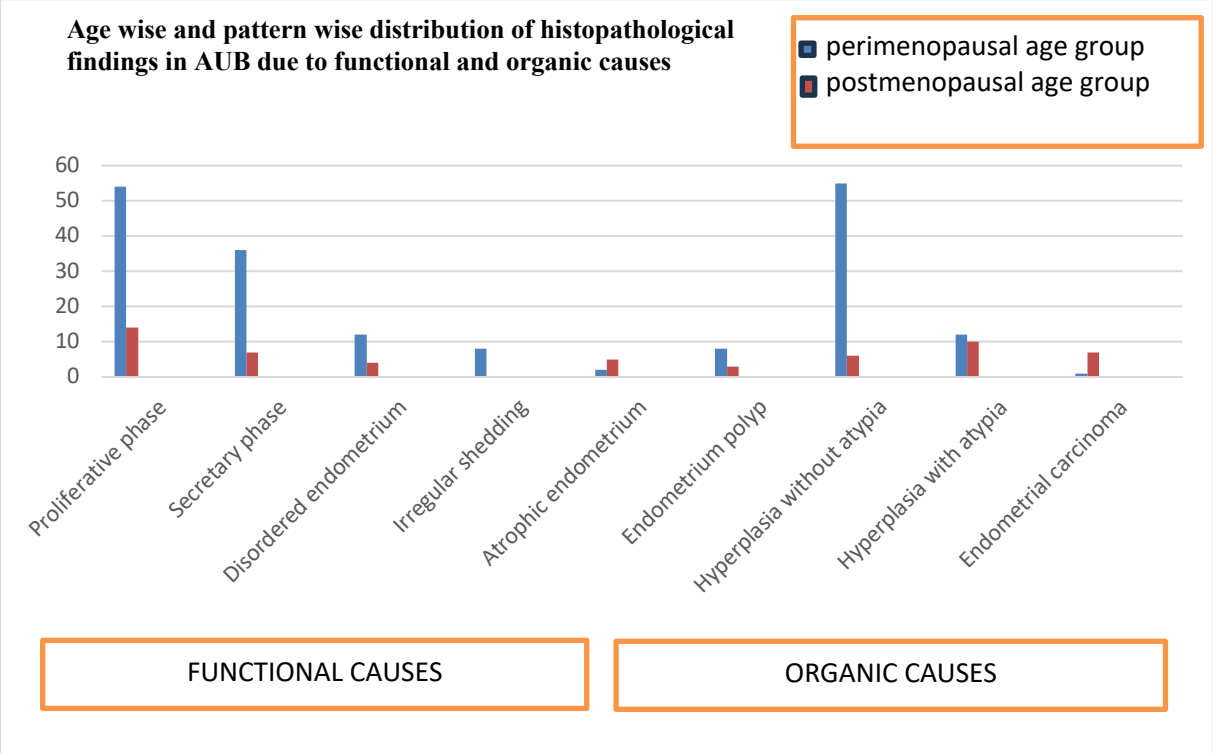
Out of 242 cases, maximum numbers of patients were in the peri-menopausal age group (77.6%)(Table 1).Majority of the cases of AUB were multiparous women(56.2%)(Table1). In this study 52.8% of the patients were of overweight, 20.6% patients were normal weight, and 22.3% were obese (Table 1). Majority of the women with clinical presentation of AUB were associated with Hypertension (34%) followed by Diabetes(31%) and Thyroid dysfunction (17.4%) (Table 1). The commonest bleeding pattern observed was menorrhagia (118 cases)(48.7%) followed by metrorrhagia (80 cases)(33%) and post-menopausal bleeding (44 cases)(18.18%).

The predominant histopathological finding was proliferative endometrium (27.3%) followed by Hyperplasia without atypia (25.2%)(Graph 1). Out of 242 cases of AUB, the functional cause (57.8%) of AUB was more common than organic cause (42.1%)(Graph 1). In the perimenopausal and postmenopausal age groups functional cause of AUB was more common than organic cause. (Graph 1).

In peri-menopausal age group, endometrial hyperplasia without atypia (29.3%) and proliferative endometrium(28.7%) were the most common patterns followed by secretory endometrium(19.1%),disordered proliferative endometrium(6.4%),hyperplasia with atypia (6.4%),irregular shedding(4.3%),endometrial polyp(4.3%),atrophic endometrium(1.1%) and endometrial carcinoma(0.5%)(Graph 1) in the decreasing order. In the post-menopausal women most frequent histological pattern observed was proliferative endometrium(25.9%) and hyperplasia with atypia(18.5.%)[Graph 1,Fig 1] followed by endometrial carcinoma (13%)(fig.2,3,4), secretory phase (13%), hyperplasia without atypia (11.1%), atrophic endometrium (9.3%), disordered proliferative endometrium (7.4%) and endometrial polyp (5.6%) in the descending order.

Table 1: Demographic and clinical data distribution of cases

Parameters	Number of cases	Percentage (%)
Age(years)		
Perimenopausal group (40-49)	188	77.6
Postmenopausal group(>50)	54	22.3
Parity		
Nulliparous	13	5.2
Primiparous	93	38.4
Multiparous	136	56.2
BMI		
19-24.9kg/m^2(normal weight)	50	20.6
25 – 29.9kg/m^2(overweight)	128	52.8
>30kg/m^2(obese)	54	22.3
No data	10	4.1
Medical comorbidity		
Hypertension	82	34
Diabetes	75	31
Thyroid dysfunction	42	17.4
Unknown	43	17.8



Graph 1: Age wise and pattern wise distribution of histopathological findings in AUB due to functional and organic causes

Out of 8 cases of endometrial carcinoma, five cases presented with histological grade II, two cases with grade I and one case was seen in grade III. 3 cases presented with less than half myometrial invasion and 3 cases presented with more than half myometrial invasion. Two cases did not show myometrial invasion. 4 cases showed lymphovascular invasion. According to FIGO staging, five cases were stage IA, three cases were stage IB.

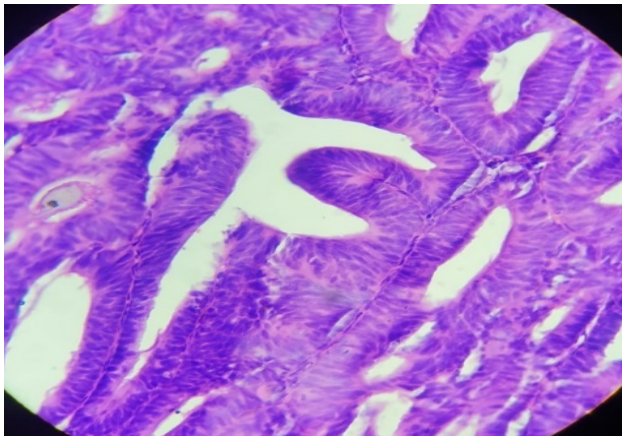


Figure 1: HPE : 40X: Hyperplasia with Atypia

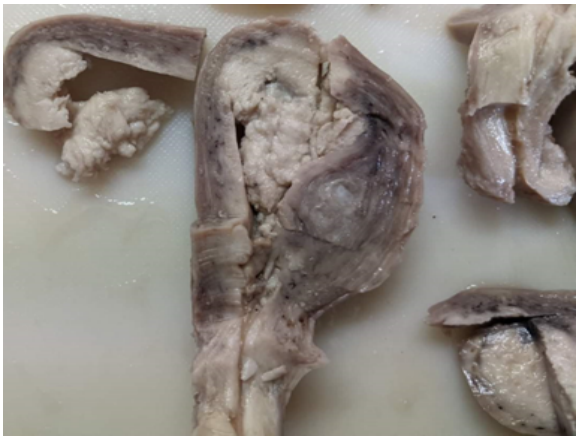
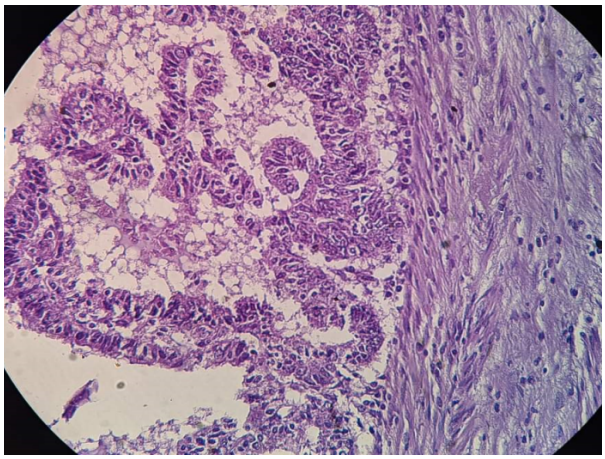


Figure 2: Gross: Endometrial carcinoma, cavity filled with irregular grey, white mass



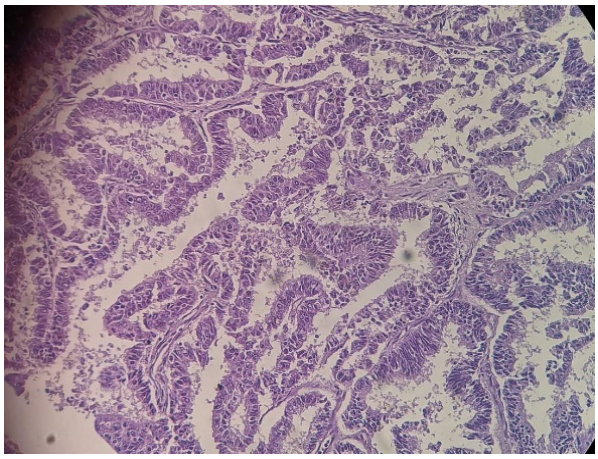


Figure 3&4: HPE:40X: Endometroid carcinoma NOS type with squamous differentiation

Among eight cases of endometrial carcinoma, six cases of stage IA/IB showed absent PTEN staining and two cases with stage IA showed mild PTEN positivity. Out of 22 cases of hyperplasia with atypia, six cases showed ambiguity in histological pattern. PTEN immunostaining was done, four cases showed mild positivity and two cases showed absent staining.(Table: 2)

Table 2: PTEN immunoexpression based on intensity of staining

Histopathological diagnosis	Number of cases	PTEN staining			
		Absent (%)	1+mild (%)	2+ Moderate (%)	3+ Intense (%)
Hyperplasia with atypia (ambiguous cases)	06	02	04	-	-
Endometrial carcinoma	08	06	02	-	-

Discussion

A total of 242 cases of endometrial samples, with a clinical diagnosis of AUB were analysed to identify the endometrial causes and also observe the incidence of various pathologies in perimenopausal and postmenopausal age groups and their relation to parity and other comorbid factors. PTEN immunostaining was performed and evaluated wherever necessary.

In this study, the incidence of AUB was high among the perimenopausal age group (77.6%) than postmenopausal age group (22.3%).Similar findings were observed in Vijayaraghavan et al, [11] Sajitha et al, [12] Jagadale kunda et al, [13] Khan et al, [14] Doraiswami et al, [15] Rajshri P. Damle et al [16] and Bhat et al [17] studies. As women approach menopause, there is a decline in oestradiol levels and number of ovarian follicles resulting in anovulatory cycles leading to various patterns of abnormal bleeding**.** [18]

Majority of the cases of AUB were of multiparous (56.2%) women which is a similar finding in other studies.[11,14,19,20] In the present study, high body mass index (BMI) was observed in women with endometrial hyperplasia and malignancy. Out of 83 cases of hyperplasia, 55 cases were overweight, 28 cases were obese. All malignancy cases(8) were obese women. Similar findings were observed by other studies [11,12,21]. Hypertension is the most common co morbid condition that is associated with AUB in the present study (34%)

which is a similar finding in Rajini Vaidya et al [1] study.

In obese women, there is an increased risk of endometrial hyperplasia and endometrial carcinoma by the increased availability of peripheral estrogens as a result of aromatization of androgens to estrogens in adipose tissue and lower concentrations of sex hormone-binding globulins. [22] Also the occurrence of other concurrent risk factors like hypertension, diabetes mellitus and increased dietary fat intake may contribute to the pathology in this group.

The menstrual disorders increase with advancing age. Menorrhagia (48.7%) was the most common bleeding pattern seen in perimenopausal age group. Similar findings were also noted in other studies. [1,11-14,23-25]Functional causes (57.8%) of AUB were more common than organic causes (42.1%) in this study, which is comparable with findings of Sharma et al [19], Vijayaraghavan et al [11], and Dwivedi et al [21] studies.

Normal cyclical endometrium patterns are commonly seen in the present study which is similar to other studies [11-14,19,21]. Among which, Proliferative phase (27.3%) was the most common followed by secretory phase (17.8%) among all age groups of women in the present study. Similar findings were observed by Vijayaraghavan et al [11], Jagadale et al [13],Sharma et al [19] and Nisha et al [26] except for the study done by Sajitha et al[12] in which secretory phase endometrium was the commonest. Bleeding in the proliferative phase may be due to anovulatory cycle and in the secretory phase is due to ovulatory dysfunction. [3]

Disordered proliferative endometrium was seen in 6.6% of cases. Majority of the cases were in perimenopausal age group women. Similar findings were observed by Sajitha et al [12], Rajshri P. Damle et al [16] and Saadia A et al [27]. Earliest stage detection of this pattern is useful to prevent spectrum of disease progression from proliferative pattern to hyperplasia and endometrial carcinomas.

In this study, 3.3% of cases are with irregular shedding of endometrium seen among perimenopausal age group, similar findings were observed by Sajitha et al [12], Rajshri P. Damle et al [16] and Baral R et al. [28]

Atrophic endometrium is the most common cause of bleeding in postmenopausal stage. [29] Though the exact cause of bleeding in atrophic endometrium is not known, it is postulated to be due to local hemostatic mechanisms. The expanding cystic glands render the overlying thin-walled blood vessels vulnerable to injury. [28] In this study atrophic endometrium was seen in 2.9 % of cases, most commonly among postmenopausal age group with postmenopausal bleeding pattern. Similar findings were noted in Doraiswami et al [15], Dwivedi et al [21], Cornitescu FI et al [29], Ara S et al [30] studies.

In the present study, among organic causes of AUB, endometrial hyperplasia was the most common pattern. Hyperplasia without atypia was observed in 25.2% of total cases and 9.1% cases is endometrial hyperplasia with atypia (Fig 1). Majority of these cases were seen among perimenopausal age group. Similar finding were observed by Vijayaraghavan et al [11],Sajitha et al [12],Jagadale et al [13],Khan et al[14],Sharma et al [19]. Endometrial hyperplasia is commonly seen in peri-menopausal age due to failure of ovulation. Persistent unriped follicles expose the endometrium to an abnormally excessive and prolonged estrogenic action. [4] As endometrium hyperplasia is thought to be a precursor for endometrial carcinoma, the identification of this pattern is important.

In the present study endometrium polyp was seen in 4.5% of the cases, most commonly among perimenopausal age group women, which is in concordance to Sajitha et al [12], Doraiswami et al [15].

In the present study, the incidence of endometrial carcinoma was 3.3%. Eight cases were endometrioid carcinoma NOS type (Fig 2), four cases showed endometrioid carcinoma with squamous differentiation.

The most common presentation in these patients was postmenopausal bleeding and incidence of endometrial carcinoma was 13.1% in the postmenopausal group. Similar findings were observed by Vijayaraghavan et al [11], Sajitha et al [12],Jagadale kunda et al [13], Khan et al [14],Baral R et al. [28]The intensity of PTEN immuno stain will be decreased from benign to malignant lesions.

In this study, Mild PTEN immunostaining was seen in 6 cases, of which 4 cases were showing atypical hyperplasia and 2 cases are with endometrial carcinoma. Eight cases showed absent staining, of which 6 cases were endometrial with carcinoma and 2 cases are with atypical hyperplasia. Similar findings were observed by khan et al [14], Sharma et al [19], Scully et al [31] and Westin et al [32] in their studies.

Conclusion

Endometrium is vulnerable for most of the pathological lesions. The histopathological study of endometrium with abnormal uterine bleeding above the age of 40 years plays an important role in diagnosing various histological patterns and aetiopathological factors.

Timely evaluation of precursor and malignant lesions helps in early diagnosis and management with excellent prognosis. Loss of PTEN function by mutational or other mechanisms is an early event in endometrial tumour genesis that helps in precursor and malignant endometrial lesions.

Hence PTEN antibody is used for early stage cancer detection and can be used to target adjuvant therapy in endometrial malignancies.

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