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## Original Research Article

# Histopathological evaluation of endometrial patterns in workup of abnormal uterine bleeding

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## ABSTRACT

**Background:** Abnormal uterine bleeding (AUB) is defined as bleeding pattern that differs in frequency, duration and amount from the normal cyclical flow. Endometrium in AUB vary depending on etiology and age. The present study attempts to categorize the histopathology of endometrium in abnormal uterine bleeding in women of various age groups.

**Methods:** A hospital based prospective study was carried out in 220 cases of abnormal uterine bleeding. Paraffin processed endometrial biopsies analyzed correlating the clinico-radiological data. Endometrial samples of infertility and pregnancy related bleeding were excluded.

**Results:** 220 cases of AUB from 25 years to 78 years of age were evaluated under three groups, reproductive (23%), perimenopausal (52%) and postmenopausal (25%). AUB was most common in the perimenopausal group. The predominant pattern seen was physiological cyclical endometrium (67.2%). Disordered proliferative endometrium (18.63%) was the predominant abnormal pattern. Malignant lesions were (99.5%) in postmenopausal age and disordered proliferative endometrium seen predominantly (65.85%) in perimenopausal age group. As per PALM-COEIN classification, uterine structural abnormalities (PALM) were found in 70 (31.9%), non-structural causes (COEIN) in 150 (68.1%). Endometrial thickness >16 mm on radiology were seen in endometrial carcinoma.

**Conclusions:** Endometrial morphology vary with ovulatory abnormalities, anovulation and uterine abnormalities. Acronym PALM-COEIN is useful in categorizing AUB. The incidence of disordered proliferation, hyperplasia and malignancy seen in extremes of age, reiterates that early clinic-radiological workup and endometrial study are the mainstay in early detection of lesions.

**Keywords:** Abnormal uterine bleeding, Endometrium, Curettage, PALM COEIN

## INTRODUCTION

Abnormal uterine bleeding (AUB) is considered one of the most common problems accountings for about one-third of all outpatient gynecological visits.<sup>1</sup> AUB is defined as bleeding pattern that differs in frequency, duration and amount from a pattern observed during a normal menstrual cycle or after menopause. The normal menstrual cycle lasts 28±7 days, the flow lasts 4±2 days, and the average blood loss is 40±20 ml, upper limit is 80 ml.<sup>2</sup>

AUB can be due to a variety of causes. It may be related to anovulation, leiomyoma, polyps, adenomyosis or neoplasia. Systemic diseases such as endocrine disorders, bleeding disorders or drugs also can be the causative factor. Dysfunctional uterine bleeding (DUB) has been used as a diagnosis of exclusion, where the underlying pathology has not been defined.<sup>3</sup> Use of a classification system with a standardized nomenclature for treating women of reproductive age with AUB was approved by the International Federation of Gynecology and Obstetrics

(FIGO) executive board as the PALM COEIN system. Following this, several ill-defined terminologies such as menorrhagia and DUB became obsolete. In addition to inter menstrual spotting or bleeding, symptoms of AUB are now primarily defined by regularity, frequency, duration and volume, and underlying causes are classified by the PALM-COEIN system.<sup>4</sup> The acronym PALM COEIN classifies uterine bleeding abnormalities in non-gravid women of reproductive age group by etiology. The acronym comprises two separate entities: structural abnormalities: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia (PALM) and nonstructural causes of AUB: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified (COEIN). Studies reveal that coagulopathies (AUB-C) are reported to affect 13% of the women presenting with AUB.<sup>1</sup> In ovulatory (AUB-O) anovulatory cycles may contribute to AUB by unopposed estrogen effects on the endometrium causing marked proliferation and thickening resulting in bleeding. This was observed at the extremes of reproductive age. In women with leiomyoma, the co-existing ovulatory dysfunction may exacerbate menstrual loss. Endometrial AUB (AUB-E) occurring in the context of a structurally normal uterus with regular menstrual cycles without evidence of coagulopathy is likely to have an underlying endometrial cause. Iatrogenic (AUB-I) causes of AUB include exogenous therapy/use of an intrauterine device (IUD) than may lead to unscheduled endometrial bleeding. AUB not otherwise classified (AUB-N) have pathology that are either rare or poorly defined that do not easily fit within other categories.

The importance of endometrial biopsy or curettage done to obtain material for histopathological evaluation for a diagnosis and further management cannot be over emphasized especially in perimenopausal females who are at a risk of developing malignancy. The most frequent indications for this procedure are: the workup of abnormal uterine bleeding; cancer screening, particularly following medications such as tamoxifen that are associated with endometrial abnormalities; evaluation of infertility; and endometrial dating. The endometrium may be accessed directly by endometrial biopsy, ultrasound, hysteroscopy, or dilation and curettage.<sup>5</sup>

A wide range of morphologic patterns in both normal and abnormal endometrium offer a diagnostic challenge to practicing pathologists. Clinical information about the patient's age, menstrual history, pregnancy, hormone therapy, contraceptive device, endocrinologic disorders, sonographic reports on uterine size and endometrial thickness are important in each case.<sup>6</sup>

### Aim

Aim of the present study was to determine the histopathological patterns of the endometrium in women presenting with abnormal uterine bleeding in a tertiary hospital, and to study the spectrum of endometrial lesions in different age groups.

## METHODS

### Sample size

For 5% significance level ( $\alpha$ ), minimum required size is given by.

$$N = Z\alpha^2 pq/d^2 = (1.96)^2 pq/d^2$$

Precision rate is calculated as  $d=5$ ,  $q=100-P$ , where  $P=17.09\%$  and  $N=218$ .

### Methodology

The present study on AUB was conducted for a period of 1 year from January 2017 to December 2017 in the department of pathology, Government Medical College, Ernakulam in South India. Samples of abnormal uterine bleeding from women above 18 years of age presenting in gynecology department of the hospital were included in the workup. Endometrial tissue obtained by routine diagnostic purposes including Endometrial curetting gs, endometrial pipelle biopsy and specimens of hysterectomy done for AUB were included in the study.

Exclusion criteria was to exclude samples of infertility, bleeding related to pregnancy, isolated cervical lesions, suboptimal bloody and inadequate tissue material. Clinical details and Endometrial thickness measured by ultrasonography were taken for correlation. The routine investigations for abnormal uterine bleeding included complete blood count, platelet count, prothrombin time (PT), Activated partial thromboplastin time (aPTT) to rule out coagulation disorders. Thyroid function tests, screening for diabetes mellitus were done in all cases to rule out systemic illnesses.

Tissue fixed in 10% formalin, Paraffin processed, haematoxylin and eosin-stained sections were examined under light microscope. Systematic examination of endometrial glandular features, gland to stroma ratio, stromal features, appearance of vessels and pattern uniformity were assessed on microscopy. In samples with abnormal uterine bleeding, histopathology reports were grouped into eight microscopic endometrial patterns as: proliferative glands and supportive non neoplastic stroma; disordered proliferate endometrium; secretory pattern; atrophy; hormonal and pregestational effect; hyperplastic glandular pattern without atypia; atypical hyperplasia; and glandular malignancy/carcinoma.<sup>7</sup> Patients were categorized into the following age groups: reproductive age group of 18-40 years, perimenopausal age group of 41-50 years and post- menopausal 51 to 60 years of age and above.<sup>8</sup> Hormonal effects have characteristic morphological appearance with atrophic or weak secretory-type glands set in a pseudo decidualised stroma. In endometrial polyps, diagnostic features were glands set in fibrous stroma containing thick-walled stromal blood vessels.

Data was entered into Microsoft excel data sheet and was analyzed using statistical package for the social sciences (SPSS) 22 version software. P value (probability that the result is true) of  $<0.05$  was considered as statistically significant after assuming all the rules of statistical tests.

## RESULTS

The present study was an evaluation of 220 (n=220) endometrial samples of abnormal uterine bleeding. A total of 120 endometrial pipelle biopsies, 51 endometrial curettages and 49 hysterectomy specimens were included in the present study. Distribution of AUB cases according to age groups given in Table 1.

**Table 1: Distribution of AUB cases according to age group (n=220).**

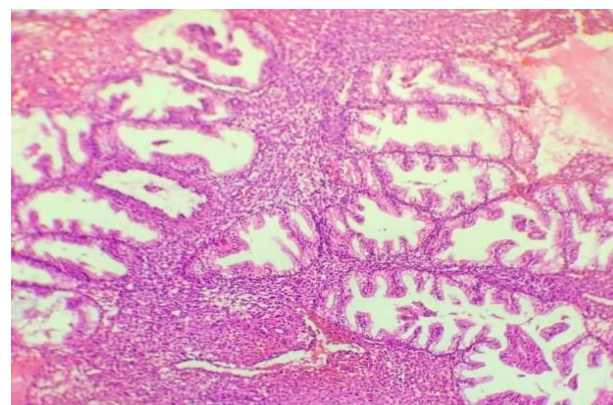
Age group (years)	Total	%
18-30 (reproductive)	07	3.18
31-40 (reproductive)	45	20.45
41-50 (perimenopausal)	115	52.27
51-60 (post-menopausal)	41	18.63
61-70	06	2.72
71-80	06	2.72
Total	220	100

The age of patients in the study ranged from 25 to 78 years with a mean age of 51.5 years. Among the 220 cases of AUB, 201 (91.3 %) belonged to 31-60 years' age group, 6 cases (2.72%) were below the age of 30 years and 13 cases (5.9%) cases were above the age of 60 years. Cases of AUB were seen maximum in the perimenopausal age group of 41-50 years, total of 115 cases (52.27 %). This was followed by 52 cases (23.63%) in the reproductive age group of 18-40 years. In the menopausal and post-menopausal period of 51-60 years, 41 cases (18.63%) presented with AUB. Out of 13 cases above the age of 60 years, 5 cases were (5.9%) endometrial adeno carcinomas. 87% of the patients in the study were multiparous. Age group wise distribution of endometrial patterns shown in Table 2. Normal cyclical patterns of secretory endometrium and proliferative endometrium were seen in 148 cases (67.27%) of AUB, secretory endometrium in 83 cases (36.36%) and proliferative endometrium in 65 cases (29.54%). There were 41 (19.09%) cases of disordered proliferative endometrium, of which two third cases (65.85%) were in the perimenopausal age group of 41-50 years.

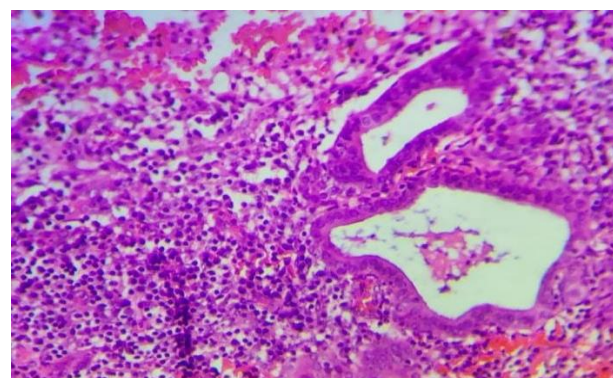
Endometrial hyperplasia without atypia was seen in 3 (1.34%) and atypical hyperplasia was seen in 4 cases (1.81%). Of the total 8 cases (3.6%) of endometrial malignancies, 7 cases were endometrioid adenocarcinoma-type 1 and one case was of type 2-serous carcinoma. Mean age of endometrial carcinoma was 64.5 years. There was significant association found between age group and endometrial pattern ( $p<0.0001$ ,  $\chi^2=181$ ).

An attempt to classify AUB according to etiology using PALM COEIN classification was done, as shown in Table 3. AUB associated with uterine structural abnormalities (PALM) were seen in 70 (31.9%) cases, the remaining 150 cases (68.1%) were grouped under nonstructural AUB (COEIN). The structural lesions (PALM) identified on sonography and hysterectomy were leiomyoma (40 cases), endometrial polyps (3 cases), adenomyosis (12 cases), hyperplasia (7 cases) and carcinoma (8 cases). Maximum number of nonstructural (COEIN) causes were AUB (O) in 87 cases (39.5%). This was seen in younger age and perimenopausal bleeding associated with irregular cycles. The other causes of AUB observed in this category included four cases (1.81%) of (AUB-I) hormonal/iatrogenic effect and one case (0.45%) of chronic endometritis (AUB-E), a case associated with disordered proliferative endometrium. There was significant association found between age group and etiology of AUB ( $p<0.0001$ ,  $\chi^2=52.7$ ).

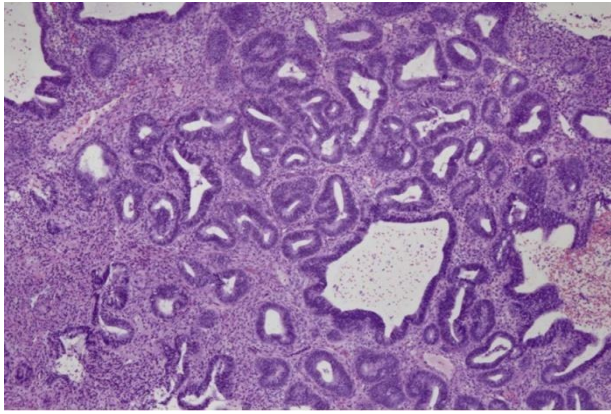
Radiological data and thickness of endometrium recorded using ultrasonography study correlated with endometrial pathology. More than 16 mm endometrial thickness was seen in 6 postmenopausal cases of endometrial carcinoma. For endometrial thickness  $\geq 16$  mm the sensitivity and specificity for detecting endometrial carcinoma was 66.67 and 99.07% respectively.



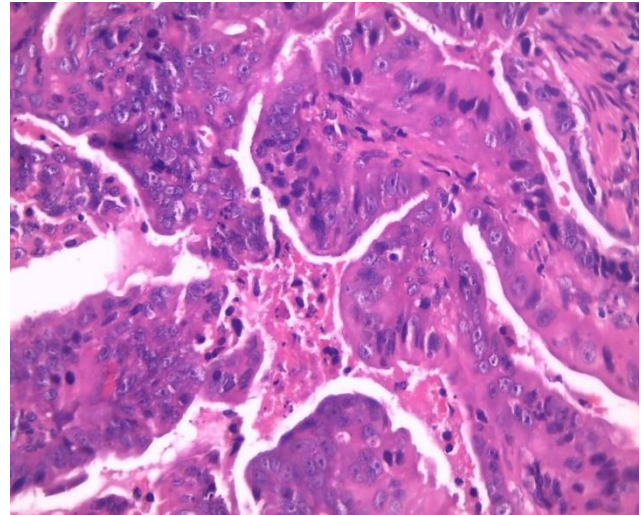
**Figure 1: Secretory endometrium (H&E 100x).**



**Figure 2: Chronic endometritis, stromal inflammation and plasma cells (H&E 400x).**



**Figure 3: Disordered proliferative endometrium (H&E 100x).** This pattern features glands that vary in size and shape. Glands are dilated, exhibit shallow budding. The hallmark is dys-synchronous development of glands set within easily discernible stroma.



**Figure 4: Adeno carcinoma endometrium (H&E 400x).**

**Table 2: Distribution of endometrial patterns age group wise (n=220).**

Endometrial pattern	Age group in years (%)					Total (%)
	18-30	31-40	41-50	51-60	>60	
<b>Cyclical endometrium</b>						
Proliferative	1	14	34	16	0	65 (29.54)
Secretory	5	22	47	9	0	83 (37.72)
<b>Atrophic</b>	0	0	0	5	7	12 (5.45)
<b>Disordered</b>						
Proliferative	0	6	27	8	0	41 (18.63)
Hormonal	-	1	3	0		4 (1.81)
<b>Hyperplasia without atypia</b>	0	0	2	1	0	3 (1.34)
<b>Atypical hyperplasia</b>	1	1	2	0	0	4 (1.81)
<b>Carcinoma</b>	0	1	0	2	5	8 (4.09)
<b>Total</b>	7 (2.72)	45 (20.5)	115 (52.27)	41 (18.63)	12 (5.9)	220 (100)

**Table 3: AUB categorization according to PALM COEIN (n=220).**

Endometrial patterns	Nonstructura l-68.1% (COEIN) (%)	Uterine structural lesions 31.9%(PALM) (%)				Total (%)
	AUB- (COEIN)	Polyp AUB-P	Adeno- myosis AUB-A	Leio- myoma AUB-L	Carcino- ma AUB-M	
<b>Proliferative</b>	35 (53.84)	2 (3.3)	7 (11.67)	21 (35)	0	65 (100)
<b>Secretory</b>	71 (85.54)	0	1 (1.20)	11 (13.25)	0	83 (100)
<b>Atrophic</b>	8 (66.66)	0	0	4 (40)	0	12 (100)
<b>Disordered proliferative</b>	38+(1*) (92.68)	1 (2.43)	0	1 (2.43)	0	41 (100)
<b>Hormonal AUB-I</b>	1 (25)	0	1 (25)	2 (50)	0	4 (100)
<b>Hyperplasia without atypia</b>	0	0	2	1	0	3 (100)
<b>Atypical hyperplasia</b>	3 (75)	0	1 (25)	0	0	4 (100)
<b>Carcinoma</b>	0	0	0	0	8 (100)	8 (100)
<b>Total***</b>	150	3	12	40	8+(7**) 220	220

One case of chronic endometritis\* (AUB-E) was seen in disordered proliferative endometrium. 7 cases of endometrial hyperplasia\*\* included in AUB-M. The discrepancy in total number is due to more than one lesion in a group\*\*\*

**Table 4: Distribution of endometrial thickness among various histopathological patterns.**

Endometrial thickness (mm)	No. of cases	Proliferative endometrium	Disordered proliferative	Secretory endometrium	Endometrial hyperplasia	Atrophic endometrium	Endometrial carcinoma
1-4	10	2	0	0	0	8	0
4.1-8	97	50	24	19	0	4	0
8.1-12	80	13	14	52	1	0	0
12.1-16	22	0	3	12	5	0	2
≥16	7	0	0	0	1	0	6
<b>Total</b>	<b>220</b>	<b>65</b>	<b>41</b>	<b>83</b>	<b>07</b>	<b>12</b>	<b>8</b>

## DISCUSSION

AUB accounts for about 20% outpatient visits in gynecology practice.<sup>8</sup> In the present study of AUB, endometrial morphology was evaluated, correlating with patient's age, date of last menstrual period, history of hormonal treatment and radiological findings. The morphological features of a cyclical or atrophic endometrium, hyperplasia or carcinoma were recorded and categorized.

220 cases from 25 years to 78 years of age were evaluated under three age groups, reproductive age group from 18-40 years, perimenopausal group from 41-50 years and post-menopausal age group above 51 years of age. Perimenopausal period begins with the first onset of menstrual irregularity and ends after 1 year of amenorrhea has occurred, thereby defining the final menstrual period (FMP).<sup>9</sup> In the present study, maximum number of cases (52.27%) were seen in the perimenopausal group. Studies done by Selvi et al, Sajitha et al, and Hoxhaj et al showed similar findings and abnormal uterine bleeding was most prevalent in the perimenopausal age group.<sup>10-12</sup> In the present study, there were 52 cases (23.63%) of AUB in the reproductive age group and in post-menopausal age group there were 53 cases (24.07%). Similar observations were seen in study of Vaidya et al and Doraiswamy et al.<sup>13,14</sup>

Normal physiological cyclical endometrium was the commonest pattern seen in 148 (67.27%) cases. Secretory endometrium was the most common histological pattern seen in 83 cases (37.72%) followed by proliferative endometrium in 65 (29.54%). The predominant pattern in the reproductive age group in the present study was secretory endometrium seen in 51.92%. Similar observation of 47.27% was made by Selvi et al.<sup>10</sup> Secretory endometrium accounting for 29% followed by proliferative endometrium in 25%, was the observation by Hoxhaj et al.<sup>10</sup>

Disordered proliferative endometrium in 41 (18.63%) cases, were observed in the present study. In the perimenopausal age group, disordered proliferative

endometrium was seen in 27 cases (23.5%). Similar finding by Doraiswami et al described 47.6% in perimenopausal age.<sup>14</sup> Compared to data of other studies, Vaidya et al had 12.8% cases and Sajitha et al had 12.5% cases of disordered proliferative endometrium.<sup>13</sup>

In the post-menopausal age group of 51 years to 60 years, there were 41 (18.63%) cases of AUB. Disordered proliferative endometrium was seen in 8 cases (19.5%), hyperplasia in 1 case (2.4%) atrophy in 5 cases (12.2%) and carcinoma in 2 cases (4.9%). Total 4 cases of atypical endometrial hyperplasia were identified, one each in the reproductive, perimenopausal and 2 cases in the post-menopausal age groups. Endometrial hyperplasia without atypia was associated with structural abnormalities in two out of three cases.

There were 12 cases (5.45%) of AUB above 61 years of age, the two patterns seen were, endometrial atrophy in 7 cases (58.3%) and adenocarcinoma in 5 cases (41.6%). Among the neoplastic lesions, seven out of eight cases (87.5%) of adeno carcinoma were found in above 51 years of age. Observations made by Hoxhaj et al (60%) and Vaidya et al (10.94%) were that endometrial hyperplasia was more prevalent in the perimenopausal age group.<sup>12,13</sup> Conclusion by Dhangal is that hyperplasia and carcinoma of the endometrium occurred with increasing frequency with increasing age.<sup>15</sup> All cases of atrophic endometrium were found in the post-menopausal age group.

AUB associated with uterine structural abnormalities were seen in 70 (31.9%) cases, the remaining 150 cases (68.1%) were grouped under AUB (COEIN). The uterine structural abnormalities of AUB identified in the study population were uterine leiomyoma in 40 cases (18.8%), adenomyosis in 12 (5.5%), endometrial hyperplasia in 7 (3.18%) cases, carcinoma in 8 (4%) and endometrial polyps in 3 cases (1.3%). Lotha et al described leiomyoma uterus as the commonest cause of AUB in 52.7% followed by ovulatory dysfunction in 41.2%.<sup>20</sup> In the present study, pipelle endometrial biopsy sampling and radiology was used for correlation in majority of cases and hysterectomy in few cases. Maximum number of nonstructural causes of AUB (O) was seen in 87 cases (39.5%). Anovulatory bleeding

in this group seen in younger age and perimenopausal age presented as bleeding associated with irregular and infrequent cycles. This was comparable with findings of Yusun et al abnormal uterine bleeding due to ovulatory dysfunction was the most frequent finding accounting for 57.7%.<sup>21</sup> Similar observation in the study done by Singh et al showing ovulatory dysfunction in 52.83% followed by leiomyoma in 29.25%.<sup>22</sup> Gouri et al described 27% ovulatory dysfunction, 24.67% leiomyoma, 12.66% adenomyosis, 5% malignancy and hyperplasia and 2% polyps in their study.<sup>23</sup>

Ultrasonography findings of endometrial thickness correlated with findings in histopathology in all cases of post-menopausal AUB diagnosed as endometrial hyperplasia and endometrial carcinoma in the present study. Findings by Pillai et al those patients with hyperplastic endometrium and/or endometrial thickness greater than 8 mm, a histopathological study of the endometrium is indicated to rule out atypical changes or endometrial malignancy.<sup>24</sup>

**Table 5: Comparative analysis of various reference studies with the present study.**

Authors (year)	No. of cases	Proliferative (%)	Secretory (%)	Disordered proliferative (%)	Endometrial polyp %	Atrophic (%)	Hyperplasia (%)	Carcinoma (%)
Sajitha et al <sup>11</sup> (2014)	156	12.2	16.7	12.2	5.12	5.12	25	4.5
Bhatta <sup>16</sup> (2012)	122	26.23	16.39	6.56	2.46	7.38	18.03	5.74
Vaidhya <sup>13</sup> (2013)	403	18	20	12.8	1.24	7.6	12.8	3.6
Junudevi <sup>17</sup> (2014)	500	36.8	6.5	5.11	2.2	36.2	18.8	2.6
Hoxha <sup>12</sup> (2014)	221	25	29	2.4	-	5	7	--
Rijurani <sup>18</sup> (2015)	150	37.2	18.6	11.6	-	26.7	2.2	2.2
Gorla <sup>19</sup> (2016)	270	45.56	32.51	9.63	6.6	0.74	10.37	1.1
Present study	220	29.54	37.72	18.63	1.3	5.45	3.15	4.09

There was significant association found between age group and etiology of AUB ( $p < 0.0001$ ,  $\chi^2 = 52.7$ ) comparable with the results of the studies by Pillai et al (87%) and Gorla et al (90.37%).<sup>17,24</sup>

### Limitations

Being a hospital-based study with small sample size, it has its limitations in extrapolating statistics to general population.

### CONCLUSION

The importance of histopathological study of the endometrial biopsy coupled with clinical correlation is invaluable in understanding the disease process in order to determine the underlying ovulatory disturbances or structural causes abbreviated PALM COEIN. The patterns of endometrium in various age groups indicates that it varies from normal cyclical patterns, changes due to hormonal effects to anovulatory cycles and neoplasms. Structural uterine lesions are less common than ovulatory dysfunction. The present study highlights the importance of simple procedures as pipelle endometrial sampling and endometrial biopsy in AUB, correlation with endometrial thickness by ultrasonography and histomorphology which play a pivotal role in the management of AUB.

Histopathological study of the endometrium is indicated to rule out atypical hyperplasia or endometrial malignancy in post-menopausal age. Categorizing the causes of AUB using PALM-COEIN system facilitates better diagnostic and treatment concepts.

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