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Original Research Article

## Clinicopathological analysis of AUB in perimenopausal and postmenopausal women in cancer care centre: special reference to carcinoma endometrium

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### ABSTRACT

**Background:** Abnormal uterine bleeding (AUB) may be defined as any variation from normal menstrual cycle including alteration in its regularity, frequency, duration of flow and amount of blood loss. Postmenopausal bleeding is a danger sign for malignancy. The study aimed to study the histopathology spectrum of hysterectomy specimens and bleeding patterns in perimenopausal women and postmenopausal women.

**Methods:** It was a retrospective observational study done at Government Medical College and Cancer Hospital, Aurangabad (MS) from January 2017 to January 2021. Total sample size was 100 women. Perimenopausal and postmenopausal women undergoing hysterectomy were analysed for the age, parity, etiology, histology and the malignant changes.

**Results:** 22 cases of AUB were observed in the age group of less than 40 years. 56% cases presented with heavy menstrual bleeding 58% cases had prolonged menstrual bleeding. 36% cases had endometrial cause (hormonal disturbances), 12 % had endometrial polyp and 35 cases out of 100 had endometrial carcinoma. Both type 1 and type 2 cases of carcinoma endometrium are seen in this study.

**Conclusions:** Excessive uterine bleeding is a common gynaecological problem in all age groups with significant patient morbidity. The spectrum of endometrial lesions seen in AUB and cancer cases shows that the histopathological examination of endometrium is gold standard diagnostic tool in evaluation of AUB and postmenopausal bleeding and there is an age specific association of endometrial lesions.

**Keywords:** AUB, Cancer endometrium, Histopathology of endometrium

### INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as any variation from the normal menstrual cycle, including changes in regularity and frequency of menses, in duration of flow, or in amount of blood loss.<sup>1</sup> More than 70% of all gynecological consultations in the peri and postmenopausal age group is due to abnormal bleeding complaint.<sup>2</sup> AUB is further categorised which is based on volume of menstruation, regularity, frequency and duration related to reproductive status. In 2011, the FIGO

classification system (PALM-COEIN) was published in order to standardize terminology, diagnosis and investigations in women presenting with AUB.<sup>3</sup> Excessive bleeding or intermenstrual spotting and postmenopausal bleeding are common conditions affecting women at all ages.

It is important to reach correct clinical diagnosis and identify the causative factor and treat it adequately. We conducted this study with the aim to study the histopathology spectrum of hysterectomy specimens and

bleeding patterns in perimenopausal women and postmenopausal women.

## METHODS

It was a retrospective observational study done at Government Medical College and Cancer Hospital, Aurangabad (MS) from January 2017 to January 2021. Total sample size was 100 women.

### Inclusion criteria

Perimenopausal women age group of 40 years and above till 1 year beyond menopause who were admitted with complaints of AUB and underwent hysterectomy and women presenting with postmenopausal bleeding and underwent hysterectomy were included in the study.

### Exclusion criteria

Women who were less than 40 years of age undergoing medical treatment of AUB were excluded from the study.

After obtaining informed consent from selected patients, the relevant data such as age, parity, menstrual symptoms (past and present menstrual history), and medical/surgical history was noted from the case records. General, systemic and gynaecological examination and other associated findings in clinical examination were recorded. Following history and examination, investigations including CBC, coagulation profile, thyroid function test, LFT, RFT were noted. After all required workup clinical diagnosis and allocation to PALM COEIN was done. Besides a thorough history taking and examination in all these women, ultrasonographic evaluation was done to assess uterus (size, polyp, fibroid, adenomyosis, and endometrial thickness) and ovarian status and recorded. The clinical presentations and ultrasonographic findings were noted. MRI was done in cases of cancer endometrium. Medical management was started to those appropriate. Hysterectomy was done in indicated cases. Histopathologic report of hysterectomy specimens including endometrial, myometrial, and cervical findings were noted. Data were expressed as number, percentage and results were analyzed using Graph Pad Software, Inc; Version 3.1

## RESULTS

Table 1 shows the relation between age and parity, maximum number of cases (40) were in the age group of 41 - 50 years with parity of 3 and higher. As evident in the study incidence of AUB among perimenopausal age group was maximum in multiparous women. Grandmultiparous women were 30% in the study. Postmenopausal women were 38% in the study.

Table 2 shows 56 women had heavy menstrual bleeding and 58 women presented with prolonged menstrual bleeding. 34 women presented with postmenopausal

bleeding. Dysmenorrhoea was also seen frequently as associated symptom.

**Table 1: Distribution of cases according to age and parity (n=100).**

Parity	Age <40 years	41-50 years	51-60 years	>60 years	N=100	%
1	3	2	0	2	7	7
2	10	13	7	2	32	32
3	6	11	7	7	31	31
4	3	6	1	8	18	18
>5	0	8	1	3	12	12

**Table 2: Distribution of cases according to clinical presentation (n=100).**

Menstrual disturbances	N=100	%
Heavy menstrual bleeding	56	56
Irregular menstrual bleeding	17	17
Frequent menstrual bleeding	35	35
Prolonged menstrual bleeding	58	58
Dysmenorrhoea	26	26
Postmenopausal bleeding	34	34

Note: Combination of two or three menstrual disturbances were seen in one patient.

**Table 3: Distribution of cases according to PALM-COEIN Classification (n=100) on hysterectomy specimen.**

PALM-COEIN	N=100	%
AUB-E	36	36
AUB-M	35	35
AUB-L	20	20
AUB-A	22	22
AUB-P	12	12
AUB-O	10	10
AUB-N	2	2

Note: Combination of two or three pathologies were seen in one patient.

Table 3 shows that the most common lesion seen was endometrial pathology (proliferative endometrium in 25 patients, secretary endometrium in 11 patients) followed by cancer of endometrium in 34 cases. Fibroid was seen in 20 cases and adenomyosis was seen in 22 cases. 2 cases presented with myometrial hypertrophy and AV Malformation.

Table 4 shows 65 patients were non-malignant and had proliferative (25%), secretary (11%) and atrophic endometrium. Foreign body granulomatous reaction was seen in 2 patients. 35 patients had cancer endometrium. Out of which 29 had adenocarcinoma (endometrioid) type and the rest had very rare types of cancer endometrium.

Table 5 shows that 45.7% patients presented with stage 1 A. 17.5% patients were seen in stage 1B and 3A. No

patients were operated in stage 4. Only 2.8% presented in stage 3 C.

**Table 4: Different histological subtypes of endometrial reports in non-malignant and malignant cases in hysterectomy specimens.**

Histological subtypes	N=100	%
<b>Proliferative</b>	25	25
<b>Secretory</b>	11	11
<b>Simple hyperplasia without atypia</b>	8	8
<b>Atrophic endometrium</b>	4	4
<b>Foreign body granulomatous reaction</b>	2	2
<b>Disordered proliferative</b>	1	1
<b>Malignant subtypes</b>		
<b>Adenocarcinoma</b>	29	29
<b>Clear cell carcinoma</b>	2	2
<b>Adenosquamous carcinoma</b>	1	1
<b>Stromal tumor of endometrium</b>	1	1
<b>Mixed Mullerian tumour</b>	1	1
<b>Carcinosarcoma of endometrium</b>	1	5

Note: More than one histological subtypes co-existed in one patient.

**Table 5: Distribution of cancer endometrium cases.**

Stage	FIGO Grade 1	Grade 2	Grade 3	N=35	%
<b>IA</b>	6	1		16	45.7
<b>IB</b>		3	1	6	17.1
<b>II</b>		4		3	8.5
<b>IIIA</b>		5	2	6	17.1
<b>IIIB</b>			4	3	8.5
<b>IIIC</b>			1	1	2.8

## DISCUSSION

Abnormal uterine bleeding (AUB) is one of the most common and significant presenting complaint in the gynaecology clinic. It causes considerable morbidity and affects the patient significantly.<sup>4</sup> A spectrum of histologic changes are noted in the endometrium in AUB and postmenopausal bleeding which vary according to the age of the patient and includes functional pattern or organic lesions. Histopathologic study of endometrial tissue is a major diagnostic tool in patients presenting with AUB and to rule out malignancy.

In our study 65 specimens showed benign pathologies while 35 were malignant on evaluation and post hysterectomy. This is because ours is a regional cancer institute. Patients are referred from all over the state whenever malignancy is suspected. Perimenopause is defined by World Health Organisation (WHO) as the 2 to

8 years preceding menopause and the 1 year after the final menses and postmenopausal bleeding is bleeding from the genital tract after 1 year of menopause.<sup>5</sup> This age group of patients are prone for hormonal disturbances, structural lesions and malignant changes in the endometrium. This is because of the derangement in the structure of the uterus (such as leiomyoma, polyps, adenomyosis, malignancy, or hyperplasia), or disruption of the hypothalamic-pituitary-ovarian axis (through ovulatory/endocrine disorders) and some premalignant and malignant changes in this age group.<sup>6</sup> Clusters of cases in this age group could be due to decreased ovarian function resulting in low estrogen level which can no longer maintain the endometrial growth Table 1.

In our study 40 patients presented in the perimenopausal age group and 38 patients presented with postmenopausal bleeding. Present study significantly shows that the incidence of menstrual disorders increases with advancing age. We observed that age was as an important factor governing the histological progression. Age was directly associated with increasing aggressiveness of lesions since more progressive lesions were found in peri and postmenopausal age group as compared to reproductive age group. Multiparous and grandmultiparous (30%) women were commonly seen in our study. This finding is compatible with the studies carried out by Bolde et al.<sup>7</sup>

In Table 2, Our study showed that among the study population (post hysterectomy patients) 56% women presented with heavy menstrual bleeding, 58% with prolonged menstrual flow, 35% with frequent bleeding, 26% with pain in abdomen and 34% with postmenopausal bleeding. The hypothalamic-pituitary-ovarian axis fails to develop the necessary hormonal feedback to result in ovulation and a subsequently stable endometrium in perimenopausal age group of patients. The clinical manifestations are irregular menstrual cycle, irregular menstruation, and even amenorrhoea.<sup>8</sup> Previous study suggested that endometrial causes of bleeding are associated with increased surface area and brittleness of the blood vessels, resulting in endovascular blood flow increase to overcome platelet aggregation. This may be due to polyps, fibroids, adenomyosis or hyperplasia which is seen frequently in this age group of patients.<sup>9</sup> These findings are similar to the study done by Bolde et al.<sup>7</sup>

Table 3 shows the distribution of patients according to the PALM-COEN classification proposed by FIGO in 2011 which divided AUB into structural and nonstructural cause in our study AUB-E and AUB-O was seen most commonly as a eiteological cause (46%) cases which signifies the underlying hormonal imbalance in our patients.<sup>10</sup> Consistent with previous studies, a changing menstrual cycle is the most important hemorrhage pattern for those with AUB-O and AUB-E. The reason for this is the ovulatory dysfunction caused by the malfunction of the hypothalamic-pituitary-ovarian axis.<sup>11</sup> In the absence of ovulation, a corpus luteum does not develop and the ovary fails to secrete progesterone. This results in continual

endometrial proliferation without progesterone withdrawal-induced shedding and bleeding, which manifests as a changed menstrual pattern.

AUB-M is seen in 35% cases in our study. Every postmenopausal woman with bleeding undergoes an endometrial sampling to rule out malignancy. The frequency of endometrial carcinoma was high in our study (35%). Type 1 endometrial carcinoma was seen in majority (29 cases) while Type 2 in 6 participants which is considered to be more aggressive (17.1%, 6/35). It was seen most commonly in post-menopausal age group (95%) followed by perimenopausal (3 cases). Type 1 is estrogen-related endometrioid carcinoma. Type 2 is nonestrogen-related, non-endometrioid carcinoma. Studies suggest that the most common type of endometrial carcinoma is endometrioid adenocarcinoma, which is composed of malignant glandular epithelial elements with an admixture of squamous metaplasia. It develops from endometrial hyperplasia in the setting of excess estrogen exposure.<sup>12</sup>

AUB-L was seen in 20 cases and AUB-P was in 12 cases. Uterine fibroids is a common disease in women, with a high incidence.<sup>12</sup> The symptoms of AUB are more related to the location and size of the myoma, and the incidence of AUB-L is closely related to the increase in endometrial surface area because of fibroids.<sup>13</sup> Myoma and endometrial causes of bleeding are associated with increased surface area and brittleness of the blood vessels, resulting in endovascular blood flow.

Approximately 10% to 40% of women with AUB have endometrial polyps, and the severity of the symptoms was not related to the diameter, location, and number of polyps. This study found that AUB caused by endometrial polyps accounted for 12% of cases, slightly lower than that reported by Clark et al, that is, AUB caused by AUB-P was 20%~30%.<sup>8</sup>

AUB-A was seen in 22% cases in this study. It was the most common disorder associated in AUB with endometrial disorders, fibroids and even malignancy cases. The main bleeding pattern is a prolonged duration of flow, accounting for 58% of cases in our study, followed by HMB. It may be associated with increased uterine surface area because of increased uterine volume.<sup>14</sup> AUB-N was seen in 2 cases. They were myometrial hypertrophy and AV malformation.

Table 4 shows different subtypes of endometrial histopathological features in cases with excessive bleeding. In AUB cases, endometrial hyperplasia, proliferative, secretory and disordered proliferative patterns were seen. 4 cases show atrophic endometrium and 2 cases showed foreign body granulomatous reaction in the endometrium. Copper T insertion for prolong periods can lead to the foreign body granulomatous reaction in the endometrium. However Bhatta et al reported a lower value of 29.16%.<sup>15</sup> Proliferative endometrium was also a predominant finding in less than

40 years (35.2%) in our study which is comparable to the study done by Doraiswami et al who reported 33.3%.<sup>16</sup>

Out of 100 cases, 29 cases presented with type 1 endometrioid lesion and 6 cases presented with type 2 nonendometrioid lesions in malignant cases. Type I tumors, which account for 80% of endometrial carcinomas, are associated with a hyperplastic endometrium, and are associated with unopposed estrogen stimulation. They are of endometrioid histology, are estrogen responsive, and have a favorable prognosis. Type II endometrial carcinomas, by contrast, often arise from an atrophic endometrium. They include papillary serous carcinomas and clear cell carcinomas, are estrogen independent, and have a less favorable prognosis. Endometrial sarcomas are much less common. Subtypes of sarcomas include carcinosarcomas, endometrial stromal tumors, leiomyosarcomas, and adenocarcinomas.<sup>17</sup> In our study rare type 2 subtypes of cancer endometrium were seen. This is due to the regional cancer institute status, we get a huge referral for cancer endometrium. Hence the proportion of cancer cases is huge in our study.

Table 5 shows the distribution of cancer endometrium cases in our study at presentation. We found 16 cases (45.7%) in stage 1A with 6 cases in grade 1 cells. This has extremely good prognosis. Most women, over 70%, have FIGO stage I cancer, which has the best prognosis.<sup>18</sup> Stage III cancers has a worse prognosis, but these are relatively rare, occurring in only 13% of cases. In our study we had 10 cases of cancer endometrium in stage 3. Most of them were associated with grade 3 types of cells. There were no stage 4 cases in the study as they become inoperable and have a less survival period. 3 patients presented in stage 2. All the cases underwent Wertheim's hysterectomy with lymph node dissection. IHC was done in all type 2 cases. They received chemoradiation and are on regular followup. Type 1 cases belonging to stage 1A are kept on follow-up. Chemotherapy, radiotherapy, hormonal therapy and targeted therapies are the various options of treatment in these cases.<sup>19</sup>

## CONCLUSION

Excessive uterine bleeding is a common gynaecological problem in all age groups with significant patient morbidity. USG, endometrial biopsy and histopathological report are the diagnostic tool. A structured approach to establishing the cause using the FIGO PALM-COEIN classification system will facilitate accurate diagnosis and inform treatment options. With the marked increase in endometrial cancer, the authors would encourage all gynaecologists to continue to excise their clinical judgement for those women aged >40 years with HMB and do endometrial biopsy to rule out malignancy.

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