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ORIGINAL ARTICLE

FIGO's PALM-COEIN Classification of Abnormal Uterine Bleeding: A Clinico-histopathological Correlation in Indian Setting

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Abstract

Introduction Abnormal uterine bleeding (AUB) is the commonest menstrual problem during perimenopause. The International Federation of Gynaecology and Obstetrics working group on menstrual disorders has developed a

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classification system (PALM-COEIN) for causes of the AUB in non-gravid women. The present study was conducted with the aim to study the two components of this system in clinical practice in general and to establish a clinico-pathological correlation of AUB with context of PALM component in particular.

Materials and Methods Two hundred and thirty-six perimenopausal women (aged 40 years and above till 1 year beyond menopause) admitted with complaints of abnormal uterine bleeding were studied. After thorough history and examination, a clinical diagnosis was made as per PALM—COEIN classification. Relative contribution of various causes of PALM (structural) and COEIN (functional) components was analysed. After all indicated investigations, endometrial sampling and hysterectomy specimen were assessed by histology. A clinicopathological correlation was analysed statistically.

Result PALM and COEIN components contributed almost equally for AUB when assessed clinically. On the other



hand, the histological examination revealed significantly more cases of PALM (structural or anatomical) component of AUB, i.e. 50.23 versus 63.98 % ($p \le 0.05$) The difference was mainly attributed to the detection of more cases of AUB-M (malignancy and hyperplasia) in highly significant proportions ($p \le .01$) and coexistent cases of AUB-A;L. AUB-L was the commonest (41.1 %) aetiology overall.

Conclusion The PALM-COEIN classification system should take into account both the clinical and histopathological diagnoses in women having AUB around perimenopause as the two diagnostic modalities are complementary to each other and clinical impression should be placed into proper perspective of this classification in order to optimise outcome.

Keywords Abnormal · Uterine bleeding · Perimenopause · PALM–COEIN · FIGO · Histopathology

Introduction

Abnormal uterine bleeding (AUB) is one of the common presenting complaints encountered by a gynaecologist. It is a significant cause of hysterectomy and thus is a major health problem [1]. AUB is also associated with significant social and physical morbidities in all societies and may be a reflection of serious underlying pathology [2].

AUB may be acute or chronic and is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration and occurs in the absence of pregnancy [3, 4].

AUB is the commonest menstrual problem during perimenopause which is defined as the period of 2–8 years preceding menopause and 1 year after the final menses [5]. Follicular development at this time has been demonstrated to be erratic, with consequent variability in oestrogen levels and an increased percentage of anovulatory cycles making them more likely to experience abnormal uterine bleeding.

In addition to the erratic ovulation, there may be many structural or functional aetiologies for the AUB. The International Federation of Gynaecology and Obstetrics working group on menstrual disorders has recently developed a classification system (PALM–COEIN) for causes of the AUB in non-gravid women [6]. There are nine main categories, which are arranged according to the acronym PALM–COEIN: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified.

PALM side of the classification refers to structural causes that may be evaluated by imaging techniques and/or histopathology and the COEIN side by investigating the

underlying medical disturbances. Perimenopausal women show a significant number of underlying organic pathology. The onus here in AUB management is to exclude complex endometrial hyperplasia and endometrial cancer. Evaluation of endometrium and/or organ histopathology have the dual advantage of finding an accurate reason causing the AUB and to rule out endometrial or other cancers or a potential for the cancer in future like endometrial hyperplasia with atypia.

A thorough histopathological work up and clinical correlation is mandatory as there is always a possibility of reallocation of category. Assessing a correlation can ascertain the degree of accuracy of clinical assignment to the category of AUB and may provide an insight as to when one must go for a pathological correlation particularly that of the PALM aspect of PALM–COEIN, whereas for COEIN (functional) aspect, the same is done using other investigations namely haematological and endocrinological work up.

FIGO recommends endometrial tissue testing as a first-line management in women of perimenopausal age group who have AUB [7, 8]. Histology clinches the diagnosis and guides the management plan. When planning hormone therapy, it is mandatory to rule out a precancerous neoplasia like suspicious hyperplasia or sub-clinical endometrial cancer. A histological assessment therefore remains the cornerstone in the current practice as it puts the clinical diagnosis in the accurate perspective and allows standardization of treatment.

The present study was conducted with the aim to study and analyse the structural (PALM) and the functional (COEIN) component of the PALM-COEIN system of AUB in perimenopausal age group women of our region. This was followed by the histopathological studies and correlation of cases wherever applicable particularly for the structural (PALM) component and for categories of AUB-E or AUB-O of the COEIN (functional) aspect.

Materials and Methods

The present study was conducted at the tertiary centre, government medical college of Madhya Pradesh from 1 July 2014 to 30 June 2015. A total of 236 perimenopausal women (aged 40 years and above till 1 year beyond menopause) who were admitted with complaints of abnormal uterine bleeding comprised the study population. Women who were <40 years of age and those beyond 1 year of menopause were excluded from the study.

The demographic details were noted, and a structured history of previous and current menstrual history, history of contraception use and medical/surgical history was followed by general, physical, systemic and gynaecological examination. On gynaecological examination, cervix (position of cervix, any erythematous lesion, hypertrophy, mobility, presence of polyp or ectopy), uterus (size, position, consistency, and mobility) and adnexae (any palpable enlarged lump, tenderness and mobility) were assessed. Clinical diagnosis and allocation to PALM–COEIN was done. A pelvic ultrasound to assess the uterus (uterine size, endometrial thickness, presence of endometrial polyp, adenomyosis or fibroids) and ovarian status (presence of any cyst, mass and its characteristics) was done. Endometrial biopsy and hysterectomy specimens (wherever applicable) were obtained and sent for histopathology. As per the histopathological findings, possible underlying causes were categorised. Clinical diagnosis was then correlated with histopathology-based final diagnosis.

For evaluation of the COEIN aspect, ovulatory dysfunction was defined as unpredictable timing and variable amount of bleeding, while endometrial disorders referred to cases when AUB occurred in line with predictable/cyclic pattern. Iatrogenic category was categorised by the identification of hormone steroid intake during the preceding 3 months and/or onset of symptoms following contraceptive device or method. Following a thorough history and complete clinical examination, investigations including complete blood count, coagulation profile when applicable (for all previously known cases of defects of coagulation from younger age and AUB dating back from menarche), thyroid function test and blood sugar level estimations were done, and the results were correlated with the clinical allocation. Endometrial histology was correlated in cases of AUB-O and AUB-E with the clinical assignments.

Data were analysed by SPSS version 16, and descriptive statistics were presented as frequencies, percentages and bar charts. Z-test was applied to know the significance of the correlation.

Result

Out of 1704 gynaecological admissions during the study period, there were 236 perimenopausal women who presented with the complaints of abnormal uterine bleeding and were included in the study.

The majority (97.46 %) of these women were less than 50 years of age, and most of the study population lived in urban area (59.7 %). An overwhelming majority (50.80 %) women were grandmultipara and 78.01 % belonged to poorer sections of society, i.e. class III or less of modified Prasad classification. Most women experienced symptoms of abnormal uterine bleeding for a period of 6 months to 1 year before seeking treatment (43.6 and 35.1 %, respectively). The most common presenting symptom in

our study was heavy menstrual bleed (32.6 %) followed by intermenstrual heavy menstrual bleed in 28.3 % cases.

Table 1 shows distribution of cases as per clinical diagnosis. The PALM and COEIN components accounted for 50.23 and 49.57 %, respectively. Leiomyoma (AUB-L) was assigned to be the major aetiology in 97/236 (41.1 %) in overall and 97/119 (81.51 %) in the structural group, whereas ovulatory disorders (AUB-O) were the proposed major contributor in the functional group accounting for 88/236 (37.28) of overall and 88/117 (75.27 %) of the later group cases.

In total 22 (9.3 %) women were obese, 15 (6.3 %) were hypertensive, nine (3.8 %) had thyroid abnormalities, and only four (1.6 %) had diabetes mellitus (Table 2).

Table 3 shows the histopathology changes in above women. The majority had secretory changes in 98 (41.52 %) and proliferative in 88 (37.28 %). This was followed by simple adenomatous hyperplasia as the third common finding in 21 (8.9 %) women who were without atypia in 19/21 (90.47 %) instances (Table 4).

On histopathology-based diagnosis (Table 5), The PALM component turned out to be accounting for 151/236 (63.98 %) cases of AUB which was 32 (13.74 %) cases

Table 1 Distribution of cases as per clinical diagnosis

Diagnosis	Total cases $(n = 236)$	% (100)
PALM		
n = 119 (50.423 %)		
AUB-P (polyp)	07	2.96
AUB-A (adenomyosis)	09	3.81
AUB-L (leiomyoma)	97	41.1
AUB-M (malignancy and hyperplasia)	06	2.54
COEIN		
n = 117 (49.57)		
AUB-C (coagulopathy)	00	0.0
AUB-O (ovulatory disorders)	88	37.28
AUB-I (iatrogenic)	00	0.0
AUB-E (endometrial)	29	12.28
AUB-N (not yet classified)	00	0.0

Table 2 Distribution of associated risk factors

Risk factor	No. of cases	%
Obesity	22	9.30
Thyroid disorders	9	3.80
History of PCOS	0	0.00
Hypertension	15	6.30
Diabetes mellitus	4	1.60
Family history of endometrial carcinoma	0	0.00



Table 3 Distribution of cases based on endometrial pattern on histopathology

	No. of cases	%
Secretory phase	98	41.52
Proliferative phase	88	37.28
Hyperplasia	21	8.9
Adenocarcinoma	03	1.2
Tubercular	00	0.0
Inflammatory	01	0.4
Proliferative phase with dilatation of glands	22	9.3
Atrophic	05	2.1

Table 4 Distribution of cases of endometrial hyperplasia

No. of cases = 21	%
19	90.48
01	4.76
00	0.0
01	4.76
	cases = 21 19 01 00

Table 5 Distribution of cases as per histopathology-based diagnosis

Diagnosis	Total cases $N = 236$	% (100)
PALM 151 (63.98 %)		
AUB-P (polyp)	09	3.81
AUB-A (adenomyosis)	20	8.47
AUB-A;L (adenomyosis and leiomyoma)	10	4.23
AUB-L (leiomyoma)	88	37.28
AUB-M (malignancy and hyperplasia)	24	10.16
COEIN 85 (36.01 %)		
AUB-O (ovulatory disorders)	72	30.5
AUB-E (endometrial)	13	5.5

more than those assigned by clinical criteria, whereas AUB-O and AUB-E classes of COEIN component only could be evaluated histologically and constituted 85/236 (36.01%) of overall AUB cases. The difference was significant statistically ($p \le 0.05$) on clinical and the diagnostic correlation (Table 6). Values did not differ significantly in cases of AUB-L and AUB-O. On the other hand, histopathology could diagnose more cases in comparison with clinical-based diagnosis in the categories of AUB-A (8.47 vs. 3.81%), AUB-M (10.16 vs. 2.54%) and cases having both adenomyosis and leiomyoma (4.23% vs.

nil). The difference was significant statistically in all three. The only instance where clinical diagnosis was ascribed to significantly more number of cases than those confirmed by histology was in AUB-E (12.28 vs. 5.5 %).

Discussion

The PALM-COEIN classification has an advantage of consideration of the entire range of possible aetiologies but should be followed by further investigation to arrive at a more accurate and consistent diagnosis in perimenopausal group of women so as to rule out organic diseases particularly precancerous lesions and cancers. The demographic profile and the pattern of menstrual complaints were in accordance with other researchers [9–13]. Chronic anovulation is a predominant phenomenon in perimenopause which is associated with an irregular and unpredictable pattern of bleeding that varies in amount, duration and character. In our study the PALM and COEIN components contributed almost equally for AUB when assessed clinically with AUB-L being the major contributor in PALM group. Leiomyomas are known be predominant in the age group presently studied. In addition, 9.3 % women were obese. Obesity by increasing the overall lifetime exposure to oestrogen by peripheral aromatisation of adrenal androgens increases the incidence of polyps, leiomyomas and endometrial carcinoma (relative risk 3–10 %). The risk of leiomyomas is seen to be increasing by 21 % for each 10-kg increase in body weight [14, 15]. Obesity has proved to be a main predisposing factor for AUB [16].

Although hysteroscopy and directed biopsy is the gold standard in diagnostic work up of AUB, endometrial sampling is still the most common available practice in public hospitals. Histopathological pattern of endometrium in women with AUB is quite variable depending upon age, parity, and ethnicity. Endometrial hyperplasia was present in 8.9 % of our cases, out of which most were simple adenomatous hyperplasia without atypia (91.3 % cases of endometrial hyperplasia) The incidence of endometrial hyperplasia is grossly variable, yet incidence of endometrial carcinoma is small in all cited studies [9, 10, 17, 18].

Leiomyoma as the leading cause of AUB in perimenopause is also noted by various researchers [11, 12, 17]. Age is the most important risk factor, with lifetime risk in women over the age of 45 years to be more than 60 %. Higher association of AUB is seen with submucosal type, compared with intramural and subserous type [15].

In perimenopausal years, ovulatory disorders are common due to derangements in the hypothalamo-pituitary-ovarian axis resulting in derangements of follicular



Table 6 Correlation of clinical and histopathology-based diagnosis

Category	Clinical PALM n = 119 (50.423 %)	Histopathology PALM 151 (63.98 %)	p value <.005 (HS)
AUB-P (polyp)	2.96 %	3.81 %	>0.05 (NS)
AUB-A (adenomyosis)	3.81 %	8.47 %	<.05 (S)
AUB-A;L (adenomyosis and leiomyoma)	0.0 %	4.23 %	<.01 (HS)
AUB-L (leiomyoma)	41.1 %	37.28 %	>0.05 (NS)
AUB-M (malignancy and hyperplasia)	2.54 %	10.16 %	<.01 (HS)
	COEIN n = 117 (49.57)	COEIN 85 (36.01 %)	<.005 (HS)
AUB-O (ovulatory disorders)	37.28 %	30.5 %	>0.05 (NS)
AUB-E (endometrial)	12.28 %	5.5 %	<.05 (S)

maturation, ovulation or corpus luteum formation, and anovulatory cycles are most frequent, and chronic anovulation is associated with an irregular and unpredictable pattern of bleeding. This explains why ovulatory disorders were found to be the second most common cause of AUB in this study and most other studies.

The other important cause of AUB was AUB-M, i.e. malignancy and hyperplasia. The unopposed oestrogenic action on the endometrium in the anovular cycles found in perimenopausal women predisposes them to develop hyperplasia and eventually endometrial carcinoma. In the present study, endometrial hyperplasia accounted for 8.9 % cases and adenocarcinoma for 1.2 % cases. The average age for women with endometrial carcinoma is 61 years, but 5–30 % cases occur in premenopausal woman [19].

Clinico-pathological correlation of different components of PALM side and AUB-O along with AUB-E categories of the COEIN revealed significantly more cases to have structural causes (PALM) of AUB on histopathological basis in comparison with clinical assignment of the PALM component.

On analysis of various categories, in AUB-P (polyp) the difference in clinical and histopathological diagnosis was not significant (p > .05). Most of the cases were cervical polyps in present study which could be diagnosed clinically by per speculum examination. This observation differs from others [12] who found the difference to be highly significant in case of polyps. The variation may be attributed to greater number of endometrial polyps in the later study. In present study too, the histopathology identified higher number of polyps although not to significant proportions.

In AUB-A (adenomyosis) the difference in clinical and histopathological diagnosis was significant, (p < .05). This is due to the fact that symptoms and signs of adenomyosis

and leiomyoma can be so similar that it can be impossible to differentiate them clinically [15, 20]. This very reason explains the difference in clinical and histopathological diagnosis of a combination of AUB-A;L (adenomyosis and leiomyoma) which was highly significant (p < .01). This finding emphasises the importance of histological examination as a complementary diagnostic tool in PALM component of AUB. Our observation is in accordance with others [8, 12].

In AUB-L (Leiomyoma) the difference in clinical and histopathological diagnosis was not significant (p > .05). The explanation may be that most symptomatic fibroids can be easily diagnosed by history and clinical pelvic examination.

In AUB-M (malignancy and hyperplasia) the difference in clinical and histopathological diagnosis was highly significant (p < .01). This is due to the fact that the clinical picture including menstrual history is not specific and that bimanual examination reveals an ordinary small uterus that shows no obvious departure from the normal senile one in most cases. Similar observation was made by others also [21]. Although clinically indistinguishable from non-malignant causes, the genital malignancies have a protracted course and grim prognosis. Early detection and prompt management may lead to a better outcome in all these women. The significant difference in clinical and histopathological diagnosis in cases of genital malignancies and hyperplasia reiterates the complementary role of the two modalities where a case of AUB is provisionally classified to one category, but after histopathology it may be reclassified, and in the process, a correct diagnosis is made so that the woman is benefitted. As the experience of the clinician improve in context of PALM-COEIN classification system both in clinical and in histopathological diagnoses, there will be improved outcomes in women healthcare system.

In AUB-O (ovulatory disorders) the difference in clinical and histopathological diagnosis was not significant (p > .05). This is due to the fact that perimenopausal women have more anovulatory cycles. In the majority of women with true anovulatory bleeding, the menstrual history alone can establish the diagnosis with sufficient confidence that treatment can begin without additional lab evaluation or imaging. In frequent, irregular, unpredictable menstrual bleeding that varies in amount, duration and character and is not preceded by any recognisable or consistent pattern of premenstrual molimina or accompanied by any visible or palpable genital tract abnormality is not difficult to interpret. Conversely, regular monthly periods that are heavy or prolonged are more likely related to an anatomical cause or a bleeding disorder than to anovulation.

In AUB-E (endometrial disorders) the difference in clinical and histopathological diagnosis was significant (p < .05), with the clinically assigned cases being higher in number than those detected by histopathology. This may be because most women in this category tend to have no definable cause of AUB. AUB-E is presently reserved as a diagnosis of exclusion among other causes of AUB and may represent a primary endometrial disorder. Most AUB-E cases appear to be due to disturbances of metabolic molecular pathways such as those involving tissue fibrinolytic activity, prostaglandins and other inflammatory or vasoactive mediators. The specific routine tissue assays which are not available at present may lead to negative histopathology in some cases. If available, these sophisticated tests may have a potential in order to establish a clearer diagnosis in the future. So far no such validated tests are available for clinical use, to attribute AUB-E as the primary cause of a woman's symptoms, so one has to rule out all other causes of AUB in clinical examination followed by a histological confirmation. In the present study there were significantly greater number of cases assigned to AUB-E on clinical ground can be justified by this arbitrary approach. If the histological confirmation is not there, the final classification as per pathological diagnosis may be to any other category it belonged to.

Conclusion

PALM and COEIN components contributed almost equally for AUB when assessed clinically. On the other hand, the histological examination revealed significantly more cases of PALM (structural or anatomical) component of AUB, i.e. 50.23 versus 63.98 % ($p \le 0.05$) The difference was mainly attributed to the detection of more cases of AUB-M (malignancy and hyperplasia) in highly significant proportions ($p \le 0.01$) and coexistent cases of AUB-A;L.

Although there was no significant difference in cases of AUB-P, AUB-L and AUB-O, all can cause heavy and irregular menstrual bleed which may be clinically indistinguishable from those caused by premalignant or malignant causes which are more common around the menopause. For management part also clinical impression should be placed into proper perspective of this classification so that accurate diagnosis based on proper work up can help in optimising the treatment protocol. This dictum may require periodic modification and revision based upon further research.

Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

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