



## HISTOPATHOLOGICAL PATTERN OF ABNORMAL UTERINE BLEEDING IN A SAMPLE OF IRAQI PATIENTS

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### ABSTRACT

Abnormal uterine bleeding (AUB) is a common gynecological problem. The FIGO applied the PALM-COEIN classification system for Causes of AUB. The present study aims to study this pathological problem the AUB, in a sample of Iraqi women, and categorize the causes of AUB in different age groups according to the PALM-COEIN classification. This is a retrospective study, involved 700 cases of AUB. Specimens included hysterectomy, myomectomies, hysteroscopy biopsy and endometrial biopsies, Biopsy sections were reviewed, and the underlying causes of AUB were categorized according to FIGO guideline. majority of AUB are of PALM causes (70.14 %), while COEIN causes formed (29.86%). AUB-L (Leiomyoma) was the most common cause, followed by AUB-O (Ovarian disorders). The FIGO systems (PALM and COEIN), can be adopted as a practice in evaluation of AUB. Histopathological assessment revealed more cases of PALM component of AUB than COEIN causes.

**KEYWORDS:** PALM, COIN, Uterine bleeding, Leiomyoma, Polyp, Hyperplasia.

### INTRODUCTION

Abnormal uterine bleeding (AUB) is any bleeding that deviates from normal menstruations, as an abnormality in the quantity, frequency and duration of menstruation during reproductive life. Any vaginal bleeding in postmenopausal women is AUB.<sup>[1,2]</sup> AUB is a common gynecological problem and a common presenting symptom in women of reproductive age. It has a list of different causes in various age groups.<sup>[3,4,5]</sup> Its prevalence varies from 5% to 65%, it affects 10%–30% of female over 35 years and accounts for one-third of outpatient visits to the gynecology clinic, and more than 70% of gynecologic consultations in the premenopausal and the postmenopausal female, however still more than 50% of patients with AUB don't seek medical care.<sup>[3,6,7]</sup> The International Federation of Gynecology and Obstetrics (FIGO), published the concept of non-gestational acute AUB to be differentiated from the chronic AUB. Acute AUB is a severe uterine bleeding attack that require immediate intervention to prevent further bleeding and any hemodynamic instability. Acute AUB may present with an existing chronic AUB or without. Chronic AUB, is bleeding that present for most of the past 6-month.<sup>[4,5,6]</sup> AUB has been considered as a major health problem, it has a negative impact on the health of women, affects the

quality of life, socially and physically, it is one of common causes of anemia, it can be a reflection of underlying serious illness, and it can be significant indication for hysterectomy.<sup>[7-9]</sup> AUB is the most common menstrual problem in perimenopause period, (the period of 2–8 years preceding menopause and up to one year after the last menses). Follicular development at this time is seen to be more erratic, with consequent variability in levels of estrogen hormone and an increased frequency of anovulatory cycles making them more likely to have AUB.<sup>[10]</sup> Many terms are used to define the presenting signs and symptoms of AUB, like menorrhagia, metrorrhagia, menometrorrhagia, hypermenorrhea, polymenorrhea, and dysfunctional uterine bleeding (DUB) (a term widely used to refer to an etiology of absent ovulation).<sup>[11]</sup> This heterogeneity in the terminology, causes confusion in the prevalence of AUB and in the management and treatment outcomes.<sup>[11]</sup> To facilitate the clinical investigations and management for AUB affected women, the (FIGO), in 2007, developed a system on the Terminology and Definitions of the symptoms of AUB, (FIGO AUB System 1), (abnormalities in frequency, duration, regularity and flow volume of menstrual bleeding). Furthermore, in 2011, the FIGO added a Classification system for Causes of AUB, (FIGO AUB System 2), the PALM-COEIN

classification, that classify the causes of AUB. "PALM" refers to structural pathology, (that can be assessed histologically or with imaging techniques), those are polyps (AUB-P), adenomyosis (AUB-A), leiomyoma (AUB-L), and malignancy/hyperplasia (AUB-M). While, COEIN side refers to non-structural pathologies, (can't diagnosed histologically nor can be imaged), but diagnosed from the clinical assessment aided with laboratory investigations, and includes coagulopathy (AUB-C), ovulatory dysfunction (AUB-O), endometrial disorders (AUB-E), iatrogenic (AUB-I), and not otherwise classified (AUB-N).<sup>[11]</sup> Since then, these two systems are widely used, and considered as a guidance in diagnosis and management of AUB. However in 2018 the FIGO recommended a revision for both systems. For the Terminologies and Definitions of symptoms AUB (FIGO AUB System 1), they added the "intermenstrual bleeding" and reassigned the Latin terms, (menorrhagia, metrorrhagia, and dysfunctional uterine bleeding) with more practical, easy understandable terms and definitions. And for (FIGO AUB System 2), the basic classification system is unchanged, but a sub classification of the causes is suggested (such as classification of leiomyoma types and the extent of adenomyosis). This updating aimed to improve the utility of these systems for clinical management and research work.<sup>[9,11]</sup> Clinical correlation, histopathological work up, and other investigations (haematological and endocrinological), are necessary, for accurate assessment and management of AUB. Although endometrial biopsy is not required for all patients with AUB, still it remains the cornerstone in assessment of AUB, and has the advantages of the diagnosis and guiding the management plan.<sup>[12]</sup> Most studies recommended endometrial biopsies for all women over 45 years. FIGO suggested endometrial biopsy as the first-line management in perimenopausal and postmenopausal women with AUB (for the diagnosis of hyperplasia or malignant changes).<sup>[7,8]</sup> And because obesity increases the risk of endometrial malignant change, even in young women, endometrial biopsy is indicated, with other imaging

evaluations of the uterus.<sup>[13]</sup> Data on AUB in Iraqi patients are limited. Shedding light on this pathology is important for local health planners, to implement appropriate plans for management of AUB and to decrease maternal morbidity and mortality.

**Aim of the study:** to study the AUB, a pathological problem in a sample of Iraqi women, and categorize the causes of AUB in different age groups according to the PALM-COEIN classification.

## MATERIALS AND METHODS

This is a retrospective study of 700 cases of AUB. conducted in the Teaching Laboratory of Pathology/Medical City Teaching Hospital. The study based on the archived data of AUB over the last two years(2021, 2022). Clinical data (patient age and type of surgical procedure and specimens) were reported. Histopathological sections were assessed and causes of AUB were categorized according to FIGO guideline.

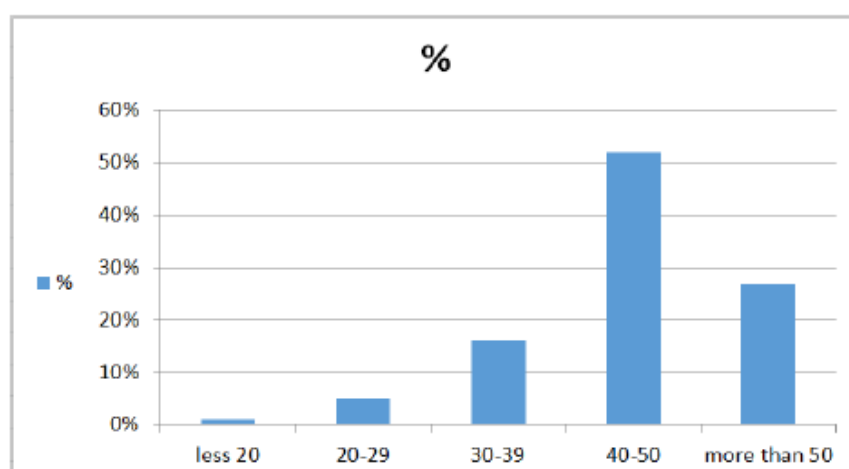
**Inclusion criteria;** Women with AUB were included in the study.

**Exclusion criteria;** Cases with inadequate materials for histopathological assessment, cases of bleeding complicating pregnancy and postpartum or cases of bleeding secondary to lower genital system pathology (vaginitis, cervicitis, cervical polyp, cervical malignancy), and uterine prolapse were excluded.

**Statistical analysis;** Microsoft excel 2010 The results were analyzed using descriptive statistics, frequency, range, mean, mode, median and standard error.

## RESULTS

A total of 700 cases of AUB were reviewed. The patient age ranged from 15 - 90 year, with a mean of 46.04 year ( $\pm 0.40$  SE), a median of 46 year and a mode of 45 year. the most frequent age group )52%(was 40-50 year (Figure 1).



**Figure 1: Age distribution of patients with AUB.**

Type of Biopsy in majority of cases were Hysterectomy (n=389, 55.57%) and endometrial biopsy (n=242, 34.57%). The residual were myomectomy (n=58, 8%), and hysteroscopy biopsy in 11 cases only (1.57%).

Hysterectomy was the most frequent surgical procedure in patients above 40 year age. While endometrial biopsy and myomectomy were the best surgical procedures for patients younger than 40 year (Figure 2).

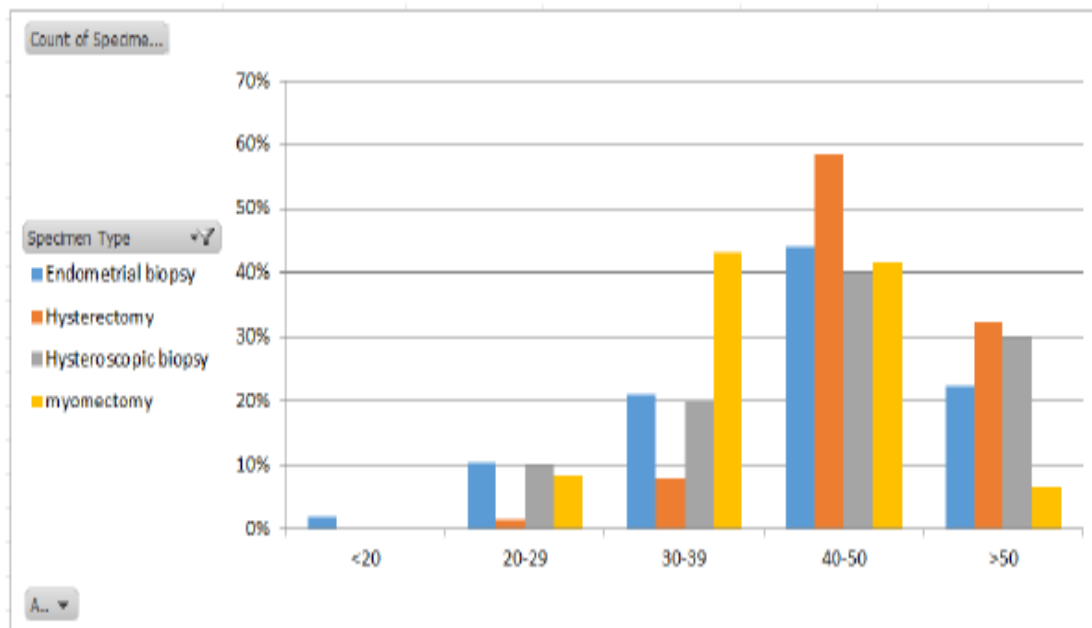


Figure 2: Surgical procedure in relation to age group.

The distribution of the studied cases according to the histopathological diagnosis are shown in table 1. The total cases were 700, distributed into a majority of PALM causes (70.14 %) and COEIN causes (29.86%). Only AUB-O and few cases of AUB-N classes of

COEIN system, can be evaluated from endometrial biopsy, and formed 209 cases (29,86 %) of overall AUB cases. AUB-L was the most common cause, followed by AUB-O. Histopathological sections are shown in figure 3.

Table 1: Distribution of AUB as per histopathological diagnosis of the causes.

Causes of AUB by Histopathological diagnosis	No. of cases	%
PALM	491	70.14%
AUB-P Polyp	127	18.14
AUB-A Adenomyosis*	117*	--
AUB-L Leiomyoma	222	31.71
AUB-M Malignancy & Hyperplasia	142	20.28
Typical hyperplasia	82	11.71
Atypical hyperplasia	12	1.71
Endometrial carcinoma	44	6.28
Leiomyosarcoma	4	0.57
COEIN*	209	29.86%
AUB-O Ovulatory disorder	201	28.71
AUB-N Not otherwise classified	8	1.14

NOTE: \* Adenomyosis were diagnosed in 117 out of 389 cases of hysterectomy and all were in association with other structural pathology. \* COEIN\* (C=coagulopathy), (O=ovulatory dysfunction), (E= endometrial disorders), (I=iatrogenic), and (N= Not otherwise classified).

The distribution of endometrial biopsies of AUB-O, revealed that proliferative endometrium formed the

majority of the cases (53.43%) (table 2).

**Table 2: Distribution of cases of hormonal imbalance, based on histopathological diagnosis.**

Endometrium histology	No. of cases	%
Proliferative endometrium	109	53.43
Secretory endometrium	73	36.31
Atrophic endometrium	9	4.47
Irregular shedding endometrium	5	2.48
Decidualized endometrium	5	2.48
Total	201	100

The average age for women with endometrial carcinoma is 61 years, but 5–30 % cases occur in premenopausal woman. The distribution of causes of

AUB by the PALM-COEIN classification, according to age is shown in table 3.

**Table 3: Distribution of AUB as per histopathological diagnosis of causes for each age group.**

Causes of AUB by Histopathological diagnosis	Age (Year)									
	>20year N=5 (1%)		20-29 N=37 (5%)		30-39 N=109 (16%)		40-50 N=361(52%)		<50 N=188 (27%)	
	n	%	n	%	n	%	n	%	n	%
PALM (n = 491) (70.14%)										
Polyp (n= 127)	1	20%	8	21.62%	17	15.59%	59	16.34%	42	22.34%
Adenomyosis (n = 117)*	0	0%	0	0%	8	2.05%	73	18.76%	36	9.25%
Leiomyoma (n= 222)	0	0%	8	21.62%	40	36.69%	129	35.73%	45	23.93%
Malignancy & Hyperplasia (n = 142)										
Typical hyperplasia (n= 82)	0	0%	0	0%	6	5.50%	55	15.23%	21	11.17%
Atypical hyperplasia (n= 12)	0	0%	0	0%	1	0.91%	5	1.38%	6	3.19%
Endometrial carcinoma (n=44)	0	0%	1	2.70%	1	0.91%	9	2.49%	33	17.55%
Leiomyosarcoma (n= 4)	0	0%	0	0%	0	0%	1	0.27%	3	1.59%
COEIN (n = 209) (29.86%)										
Ovulatory disorder (n= 201)	2	40%	19	51.35%	43	39.44%	100	27.70%	37	19.68%
Chronic endometritis (n= 8)	2	40%	1	2.70%	1	0.91%	3	0.83%	1	0.53%

NOTE: \* Adenomyosis were diagnosed in 117 out of 389 cases of hysterectomy and all were in association with other structural pathology.

Out of the total 389 hysterectomy for AUB, adenomyosis was diagnosed in 117 cases (30.07%), distributed along all age group but most in patients above 40 year old

(table 2&4). And 56 (14.39%) hysterectomy specimens revealed more than one pathology (table 5).

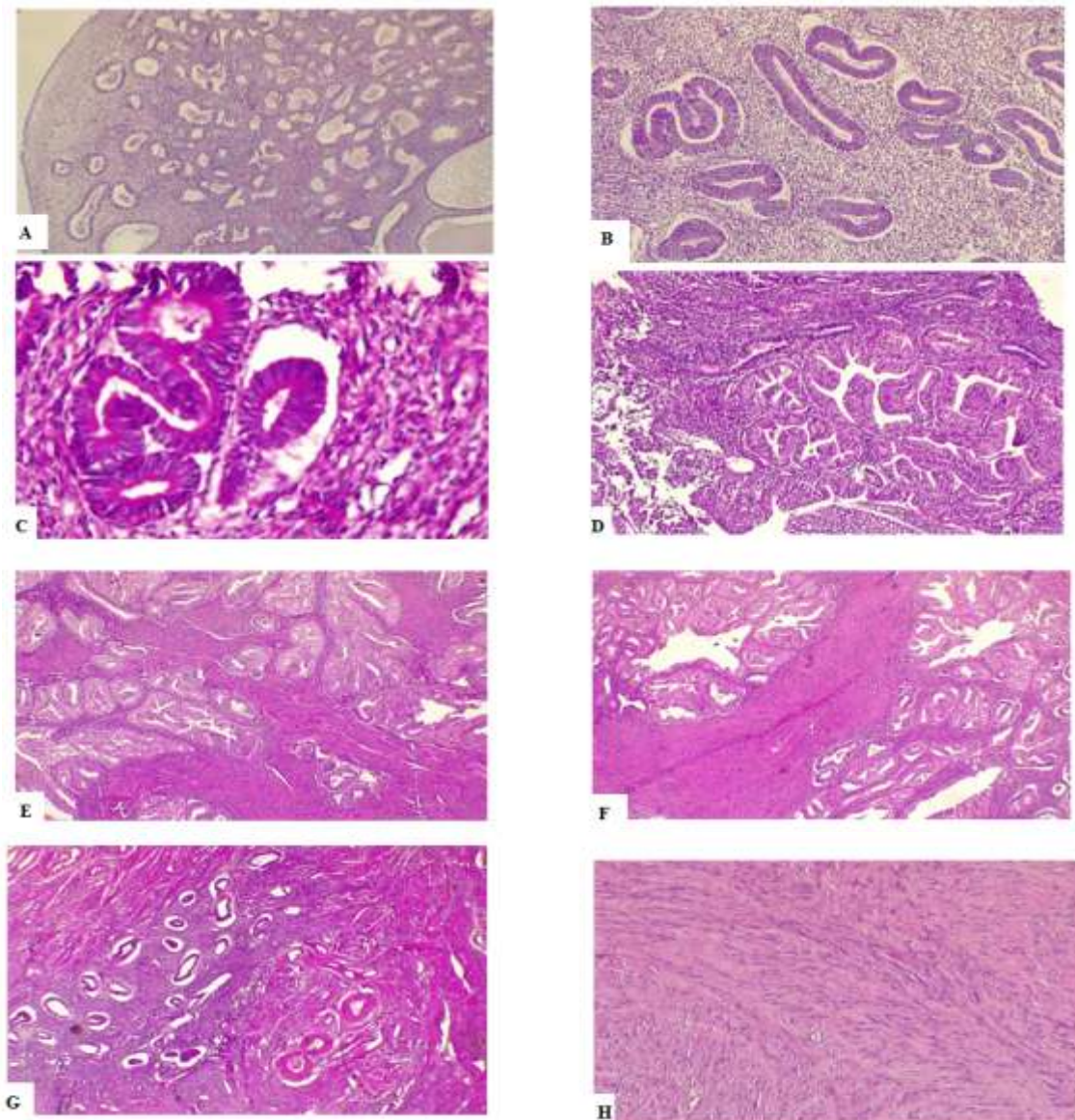
**Table 4: Adenomyosis and associated pathology in 117 studied cases.**

Adenomyosis and associated pathology	No. of cases	%
Adenomyosis with leiomyoma	40	34.18
Adenomyosis with hormonal imbalance	31	26.49
Adenomyosis with typical hyperplasia	25	21.36
Adenomyosis with atypical hyperplasia	5	4.27
Adenomyosis with endometrial carcinoma	5	4.27
Adenomyosis with polyp	11	9.40
Total	117	100

**Table 5: The 56 Hysterectomy specimens\* with two pathologic lesions.**

Histological Patterns	No. of cases	%
Endometrial hyperplasia with polyp	3	0.77
Endometrial hyperplasia with leiomyoma	36	9.25
Endometrial polyp with leiomyoma	17	4.37

\*Total number of hysterectomy specimens were 389



**Figure 3 (A-H); Histopathological sections of different pathological cases.**

A. Endometrial polyp (Cystically dilated glands and a fibrous stroma with thick wall vessels). B. Disordered proliferative endometrium (compact small glands in edematous stroma). C. Endometrial hyperplasia without atypia (mild irregular gland architecture with crowding). D. Endometrial hyperplasia with atypia (crowded irregular glands and cytological atypia). E&F. Well differentiated endometrioid adenocarcinoma with villoglandular pattern. G. Adenomyosis (Intramural foci of endometrial glands and stroma). H. Leiomyoma (elongated spindle cells with fibrillary cytoplasm). (H&E Magnification X100 except Fig.1 X40)

## DISCUSSION

The FIGO's classification system (PALM-COEIN), for women with AUB, has the advantage of categorization of the wide range of etiology of AUB, determination of proper planning, recording, and management, with an improved outcome. Our results revealed an increase in frequency of AUB with age, and the commonest was in their 40s. Endometrial biopsy is the most common and available practice in diagnostic work up of AUB in most studies, although other techniques like hysteroscopy and directed biopsy are considered as standard diagnostic tool for AUB.<sup>[14,15]</sup> In the current study endometrial biopsy formed (34.57%) of the studied cases, while

Hysterectomy formed (55.57%) of the cases, myomectomy (8%), and hysteroscopy biopsy (1.57%). Hysterectomy was the most frequent surgical procedure in patients above 40 year age. While endometrial biopsy, hysteroscopy biopsy and myomectomy were the choice for patients younger than 40 year (Figure 2). The selection of surgical procedure mainly related to the probable cause of AUB per age group. Regarding the causative diseases of AUB, the structural cause (PALM), was responsible for 70.14% of AUB enrolled in this study, versus 29.86% of cases due to COEIN system. Similar results were reported by other researchers. This is could be related to the possibility of diagnosis of PALM cases with routine histological examination,

versus the difficulty in confirming the diagnosis of some COEIN cases, and considering as a diagnosis of exclusion.<sup>[1,5,6,11]</sup> The frequency of AUB-L and AUB -O were high in this study, followed by AUB- M, AUB-P and AUB-E. Various results were reported in other studies, some showed same rank of our results other are not. The variation in the reported prevalence of causes of AUB in different cited studies related to the definition of AUB, the diagnostic method applied, and the population and committee studied.<sup>[8,9,16,17]</sup> Histopathological examination revealed differences in the distribution of the causes of AUB with age group. The structural cause (PALM) expressed a peak, as a cause of AUB, in women at 30s years and older. AUB-L (leiomyoma) is the commonest benign tumor in women at reproductive age. The association between leiomyoma and AUB is not well understood. However the submucosal type may cause distortion and penetration of the uterine cavity. In our study AUB-L was the commonest cause of AUB, and most in women in their 30s, and up to 50 year. This is probably related to the prominent hormonal effect during this age period. Our results are in accordance with other studies.<sup>[18-20]</sup> In this study AUB –M (endometrial hyperplasia and malignancy), ranked the third common cause of AUB. Endometrial hyperplasia formed 13.42 % of the cases, most were typical hyperplasia without atypia. Endometrial carcinoma found in (6.28%) of the cases. About 93% of AUB – M cases were women above 40 year old, and 75% of malignant cases were above 50 year. AUB-M is an important cause of AUB. Although its frequency as a cause for AUB, is variable in the cited studies.<sup>[14,22-24]</sup> Endometrial cancer is the 6th most common cancer in women worldwide.<sup>[25]</sup> In Iraq it ranks the 16th among cancer in women.<sup>[26]</sup> It is rarely occurred before menopause.<sup>[22]</sup> AUB-P (polyp) encountered in 127 women (18.14%), and 79.52% of cases were above 40 year in age. Adenomyosis, (the presence of endometrial glands and stroma in the myometrium), diagnosed histologically in 117 out of 389 cases of hysterectomy (30.07%). Majority (93.16%) were in women above 40 year. And all were in association with other structural pathology, mostly with leiomyoma (34.18%) and ovulatory disorders (26.49%) of the cases (table 4). There is relatively a poor agreement on the diagnostic criteria of adenomyosis, with imaging or histopathological facilities. It has been reported that histopathological confirmation of adenomyosis in hysterectomy specimens varies from 5 to 70%.<sup>[27,28]</sup> Coexistence of two structural causes (PALM) were seen in 56 cases in this study (table 5). Most frequent association were leiomyoma with endometrial hyperplasia, and polyp.. These observations are in accordance with other studies.<sup>[18,27,28]</sup> AUB-O (ovulatory dysfunction), is usually secondary to hormonal disorders (hypothalamus, pituitary, ovarian axis), hyperprolactinemia, hypothyroidism, obesity, malnutrition, physical and emotional stress, systemic diseases or could be idiopathic. It tended to occur more in women at menarche and at perimenopause. In this study, AUB-O, was the second most common cause of

AUB. Expressed in women less than 20, and in their 20s, 30s, 40s, and 50s, indicating its association with wide range of pathological disorders. In other studies AUB-O, ranked between the first and the second most common causes of AUB.<sup>[1,2,4,11]</sup> Histopathological profile of the endometrium in patients with AUB is variable and depending upon many variable factors.<sup>[1,4,5,6]</sup> AUB- E (endometrial disorders), represent a primary endometrial disorder that interfere with normal local hemostasis and metabolic pathways of the endometrium. Their diagnosis required advanced ancillary techniques, rarely available. So all other causes of AUB should be rolled out in clinical and histological assessment.<sup>[11]</sup> The updated FIGO classification (PALM- COEIN) system (2018), revised the drugs interfering with the hypothalamus- pituitary-ovarian axis causing AUB, to be categorized as “AUB-I”, And not “yet” classified to not “otherwise” classified.

## CONCLUSION

The FIGO systems (PALM and COEIN), can be adopted as a practice in evaluation of AUB. Histopathological assessment revealed more cases of PALM component of AUB than COEIN causes. The difference was mainly related to the diagnosis of high proportions of AUB-L (leiomyoma) and coexistent cases of AUB-L with adenomyosis, endometrial hyperplasia and polyp. Diagnosis of PALM cases were depended on endometrial biopsy, hysterectomy, myomectomy and hysteroscopy biopsy, versus diagnosis of COEIN cases, most of its components considered as a diagnosis of exclusion.

**Approval for the study;** Obtained from the Research Committee of Scientific Council of Pathology/Arab Board for Medical Specialization in Pathology.

**consideration;** Data were collected from archives of Department of Pathology /Medical City Teaching Hospital, the teaching hospital rule was considered as there files are allowed for research purposes (after legal approval), while keeping all information confidential, and no charge for patients.

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