

Histopathological Interpretation of Abnormal Uterine Bleeding After the Age of 40 Year

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ABSTRACT:

BACKGROUND:

To delineate the frequency and pattern of uterine lesions which result in abnormal uterine bleeding (AUB) after the age of 40 years.

OBJECTIVE:

To delineate the frequency and pattern of uterine lesions which result in abnormal uterine bleeding (AUB) after the age of 40 years and to compare the result with other similar studies

METHOD:

Histopathological examination of the tissues obtained by curettage and/or hysterectomy play an important role in the diagnosis of the lesions which cause AUB..

RESULTS:

Organic intrauterine lesions was found in 69 (19%) of the cases. These included chronic endometritis (7.7%), endometrial polyp (6%), malignancy (3.9%) and submucous leiomyoma (1.4%). On the other hand, the commonest histopathological finding in patient with AUB due to dysfunctional cause was endometrial hyperplasia which was found in (30.3%) of the cases, (27%) were simple endometrial type (cystic glandular hyperplasia).

Postmenopausal bleeding is found in 76 cases (21%). Atrophic endometrium was the commonest finding of postmenopausal bleeding, which represented (34.2%). Endometrial adenocarcinoma was found in 3.3%.

Eighty-two cases underwent hysterectomy after initial curetting due to persistent uterine bleeding, the endometrial lesions of (79) patients were confirmed at hysterectomy making the diagnostic accuracy of D and C (96.3%). Other uterine lesions were found at hysterectomy such as adenomyosis and leiomyoma.

CONCLUSION:

Dysfunctional uterine bleeding was the predominant cause of AUB in women above (40) years of age.

KEY WORD : AUB , curettage, endometrium

INTRODUCTION:

Abnormal uterine bleeding (AUB) is defined as any bleeding that does not correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle^(1,2,3,4,5). It is a common gynaecologic problem and the principal reason for gynaecological consultation^(6,7,8,9), accounting for up to (20%) of office visits to gynaecologists^(10,9). It is a symptom and not a disease that occurs in different patterns^(11,12). The causes of Abnormal Uterine Bleeding can be categorized into two broad categories:

I-Organic causes: such as genital tract infections, tumors (benign or malignant), adenomyosis

,conception ,systemic disorders and iatrogenic^(1,10,11).

II-Dysfunctional uterine bleeding: caused by ovulation or oligoovulation^(2,10,13).

Postmenopausal Bleeding (PMB) is defined as that uterine bleeding which occurs after ⁽¹²⁾ months of the last menstrual period^(14,15,16). It is an important symptom which requires careful and prompt evaluation, because it may be a symptom of endometrial neoplasia ^(15,17,18).

Endometrial sampling should be considered in all women with abnormal uterine bleeding particularly in those above the age of (40) years, and in women who are at increased risk of endometrial cancer ⁽¹⁹⁾. The most common methods of endometrial sampling in current clinical use are⁽¹⁹⁾:

- 1-Diagnostic dilatation and curettage (D&C).
- 2-Endometrial biopsy.
- 3-Hysteroscopy.

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PATIENTS AND METHODS:

This study was carried out over a period of ten months extended from the 1st of October 2003 till the 1st of August 2004. Three-hundred sixty three patients with different patterns of abnormal uterine bleeding admitted for endometrial sampling were included in this study. All obstetric causes of AUB (including abortion and pregnancy related cases) were excluded.

The patients were presented to both AL-Batool Teaching Hospital and AL-Khansaa Teaching Hospital in Mosul city. Their ages ranged from (41) to (75) years with a mean age of (47.9 ± 11) . The clinical data collected from every patient included name, age, address, parity, smoking habit, pattern and duration of bleeding, date of last period, mode of contraception [oral, parenteral, intrauterine contraceptive device (IUCD) or tubal ligation], history of previous D&C and related medical history especially history of Tuberculosis, diabetes and/or hypertension and history of hormonal therapy were included. Complete physical examination was performed and any abnormal findings of pelvic examination from D&C report were recorded.

Endometrial specimens obtained by curetting in (271) patients, while the remaining specimens (92) obtained by hysterectomy.

The tissues obtained by curettage and/or hysterectomy was examined in the laboratories of AL-Zahrawi and AL-Khansaa Teaching Hospitals, where it was first fixed in (10%) neutral formalin. The specimens were processed in routine fashion and stained with H & E.

RESULTS:**A-Clinical findings**

The clinical findings of patients were analyzed, including age, parity, patterns of abnormal uterine bleeding, contraception, associated medical diseases, history of previous D&C and smoking habit.

1.Age distribution

The age of sampled women ranged between (41 - 75) years with a mean age of (47.9) years. Figure (1) shows the age distribution of the sampled women.

2.Parity

The parity of the patients ranged from (0 to 14). Only 21(5.8%) patients were nulliparous, five of them (23.8%) showed endometrial carcinoma. While 342 (94.2%) patients were multiparous with a mean value of (5.3). Figure (2) shows parity distribution of the studied women.

3.Patterns of abnormal uterine bleeding

Patients in this study presented with menorrhagia in (34%). Postmenopausal bleeding constitutes (21%), as shown in table (1).

4.Contraceptions

The history of contraception in the form of oral contraceptive pills was positive in 30 (8.2%) patients, and parenteral form of contraception in 14 (3.8%) patients. However, 29 (7.9%) patients used

intrauterine contraceptive device (IUCD) while operative contraception in the form of tubal ligation was the case in 9 (2.4%) patients.

5.Significant medical history

History of hypertension was positive in 55 (15.1%) cases, diabetes mellitus in 38 (10.4%) of cases, while history of both diabetes and hypertension was revealed in 20 (5.5%) of the cases.

6.History of previous D&C

History of previous D&C was obtained in 82(22.5%) cases within a period of (1-18) months before hysterectomy due to persistent uterine bleeding.

B-Histopathological Findings

According to histopathological finding endometrial histopathology was analyzed separately and categorized into organic and dysfunctional endometrial causes. Organic intrauterine lesions were found in 69 (19%) of the total cases. These lesions were restricted to the endometrium, and they included chronic endometritis, polyp, malignancy and submucosal leiomyoma as shown in table (2).

The commonest histopathological finding in patient with AUB due to dysfunctional cause was endometrial hyperplasia which was found in 110 (30.3%) of cases, 98 (27%) of them were simple endometrial hyperplasia, 8 (2.2%) cases were complex (adenomatous) hyperplasia, and only 4 (1.1%) cases were atypical hyperplasia (with both architectural and cellular atypia). Most of the cases were diagnosed in perimenopausal women. Those with atypical hyperplasia, (3/4) of them underwent hysterectomy which confirm the diagnosis, except one patient in which in addition to atypical hyperplasia which was diagnosed by D&C, there is near by foci of invasive endometrial adenocarcinoma of endometrioid type which confined to the endometrium (stage I). The other patient (1/4) was lost from the study.

Chronic endometritis was found in 28 (7.7%) cases which was non-specific in type, 12(42%) of them had a history of using IUCD. Tuberculosis was not detected in any patient.

Malignancy was present in 14 (3.9%) cases. The commonest type was endometrial adenocarcinoma

of endometrioid type, which was found in 12 (3.3%) cases, and all of them were encountered in postmenopausal women. Endometrial stromal sarcoma of low-grade type was detected in 2 (0.5%) cases by D&C; one of them was diagnosed in a postmenopausal woman. In these (2) cases hysterectomy was done and it confirmed the diagnosis. Table (3) shows the relation between the mean age of menopause and the mean age of different histopathological lesions while figure {3} show the relative frequency of diabetes and hypertension in different pathological groups. In this study endometrial tissue was obtained by hysterectomy in 92 (25.3%) of the cases, (82) of them had a history of a previous diagnostic curettage within a period of (1 – 18) months due to the same complaint (persistent uterine bleeding). In (79) patients, histopathological findings at D&C were similar to the findings of hysterectomy specimens. The remaining (3) cases a differences were observed between the histopathological reports of curettage and hysterectomy specimens. Two of them were diagnosed by D&C as simple endometrial hyperplasia, while at hysterectomy they were proved to be endometrial polyps. The other single case was diagnosed by D&C as proliferative endometrium, while at hysterectomy it was proved to be simple endometrial hyperplasia. Of these (45/92) hysterectomies specimens revealed other pathologies affecting the uterine wall in addition to endometrial lesions detected in these cases. These included adenomyosis in 25 (27.1%) cases, leiomyoma in 19 (20.6%) cases, and both of them in one case (1.1%).

Postmenopausal bleeding

Out of all cases of abnormal uterine bleeding included in the study, (76) women were postmenopausal, presented with PMB, within a period of (1-20 years) after their last menstrual date. Their ages on admission to the hospitals ranged from (45 to 75) years, with a mean age of (52.2 ± 7.08) years. Several histopathological findings were detected among postmenopausal women as shown in table (4). The benign lesions detected in postmenopausal women constituted (82.9%), the commonest benign finding was atrophic endometrium which represented (34.2%) of these lesions.

The malignant lesions detected in (13) postmenopausal women which constituted only (17.1%) of postmenopausal lesions, 12 (15.8%) of them showed endometrial adenocarcinoma on histopathological examination, while only 1 (1.3%) case showed endometrial stromal sarcoma of low grade type.

DISCUSSION:

Abnormal uterine bleeding is a common gynaecological problem for which women seek medical advice. Whilst most patients have benign lesions, thorough investigation is necessary, particularly in the peri and postmenopausal women to exclude the presence of malignant lesions or their precursors^(7,12).

Parity

Most of the patients included in this study 342 (94.2%) cases were multiparous, while only 21 (5.8%) cases were nulliparous. Regarding nulliparous patients, five of them (23.8%) showed endometrial carcinoma on histopathological examination. This indicates that nulliparity is an important risk factor for endometrial carcinoma as had been reported by (Gusberg SB & Milano C, 1981)⁽²⁰⁾ this could be attributed to the association of nulliparity with anovulatory cycles that result in increased estrogen exposure and lack of progesterone effect⁽²⁰⁾.

Clinical Presentation

Patients included in the present series were complaining of different patterns of AUB, and the majority of them presented clinically with menorrhagia (34%). Similar findings were reported by others (Debdas AK and Bahol A, 1984)⁽²¹⁾ and (Mahmood MF, 1988)⁽²²⁾.

The type of histopathological finding obtained by D&C do not always bear relation to the clinical history or amount of blood loss. This may be attributed to the curettage performed early in a developing cycle, or because the changes may be patchy and the area chosen for histological examination may not be representative⁽²³⁾.

Histopathological findings

In the present study, D&C aided in identifying the etiology (i.e the organic causes) of AUB in (19%) of the total cases, which included chronic endometritis, polyp, malignancy and submucous leiomyoma. This result is higher than that reported by (Mackenzie IZ and Bibby JG, 1978)⁽²⁴⁾ who showed that the frequency of intrauterine pathology that caused AUB was low especially in younger women. This result supports the importance of diagnostic D&C in patients older than (40) years of age as it helps in identifying the organic causes of AUB in this age group, and to introduce a rational basis for their management.

Endometrial hyperplasia

Endometrial hyperplasia was the commonest histopathological finding revealed in the endometrial specimens obtained in the current work. The diagnosis of this condition is important because it carries a malignant potential, although

this is variable according to the type of hyperplasia^(25,26,27,28). In the present study, endometrial hyperplasia was detected in 110 (30.3%) cases. This figure was higher than those revealed by other investigators (Razzak AH & Abdulmajeed AM, 1999)⁽¹²⁾ and (Al-Dahwi RN & Al-Taie ID, 1984)⁽²⁹⁾. This difference may be present because this study included only the women above (40) years of age, in whom endometrial hyperplasia was more common.

From the beginning of the last century, many authors have studied the relation between endometrial hyperplasia and carcinoma and they showed a wide variation in percentage of progression of endometrial hyperplasia to carcinoma^(25,30,31,32,33,26,28,34,35,20). In this study we find a single case of atypical hyperplasia with foci of endometrial carcinoma in hysterectomy specimen. This provided a rational for management of atypical hyperplasia on basis of cytologic atypia since this is the most useful criterion in predicting the likelihood of progression to carcinoma. In addition, the presence of concomitant architectural alteration appears to identify a particularly high risk patients^(28,36,35).

Chronic Endometritis

In the present study chronic non-specific endometritis was detected in 28 (7.7%) of cases. This finding is in agreement with that reported by (Greenwood SM & Moran JJ, 1981)⁽³⁷⁾.

Chronic endometritis due to specific infection like tuberculosis was not detected in any patient, this finding is remarkably similar to that reported by (Razzak AH & Abdulmajeed AM, 1999)⁽¹²⁾. Absence of T.B. endometritis in the present series may be explained by several reasons. One of them is that T.B. endometritis may be missed because the granulomas tend to concentrate in the superficial functional layers of the endometrium and caseous necrosis is almost always lacking in the endometrial specimens, because the foci of infection are shed continuously with the endometrium during menstruation. On the other hand, T.B. endometritis is commonly silent and discovered by chance. For all these reasons multiple levels of curetting specimen must be examined if T.B. endometritis is suspected.

Malignant lesions

Malignancy, in the present series, was found in 14 (3.9%) of cases and the most common malignancy was endometrial carcinoma of endometrioid type, which was diagnosed in 12 (3.3%) cases. This figure is lower than that reported in an other study (Muenzer RW, *et al*, 1974)⁽³⁸⁾ and all cases of endometrial carcinoma were detected in postmenopausal period, which was in agreement

with other studies (Salih RM, 2002)⁽³⁹⁾, (Fleischer AC, *et al*, 2001)⁽⁴⁰⁾, (Gorodecki J, *et al*, 1979)⁽⁴¹⁾ and (Muenzer RW, *et al*, 1974)⁽³⁸⁾. Although the rate of diagnosis of endometrial neoplasia in this study did not reflect the real prevalence of these lesions in Iraq, it may reflect their low frequency in Mosul locality.

Several risk factors for the development of endometrial carcinoma had been identified. Most of these risk factors are related to prolonged unopposed estrogen stimulation of the endometrium, among these are nulliparity, hypertension, and diabetes^(34,42,43). Nulliparity is an important risk factor for endometrial cancer as it was confirmed by (Gusberg SB & Milano C, 1981)⁽²⁰⁾ who reported that (21.6%) of patients with endometrial cancer were nulliparous. In the present study, the mean parity in these patients was (3.7), and the relative frequency of nulliparity was (23.8%). This is in accord with (Gusberg SB & Milano C, 1981)⁽²⁰⁾. Other risk factors such as hypertension and diabetes had been significantly associated with endometrial cancer, but a causal relationship had not been confirmed yet⁽³⁴⁾. In the present series hypertension was present in 6 (50%) cases with endometrial carcinoma, while diabetes was present in 4 (33.3%) cases, and both of them in 1 (8.3%) case. This finding is consistent with that observed by (Buzghia FM, 1999)⁽¹⁵⁾ which is higher than these seen in the cases of normal endometrium as shown in figure (3).

In this study, the patients with endometrial carcinoma were older than women with other pathology (mean age of 58.7 ± 11.5) and this was higher than the mean age of menopause (52.2 ± 7.08). The difference between these two mean ages was statistically highly significant ($P = 0.006$), thus in almost in all cases, the presentation was of PMB, this finding was in agreement with (Fleischer AC, *et al*, 2001)⁽⁴⁰⁾ who stressed on that the most usual clinical manifestation of the presence of endometrial carcinoma was the PMB. This result urges the importance of D&C in older women, especially those with this complaint. This observation was also found by others (Gorodecki J, *et al*, 1979)⁽⁴¹⁾ and (Mackenzie IZ & Bibby IG, 1978)⁽²⁴⁾.

In the present study, no significant statistical difference was detected between the mean age of menopause (52.2 ± 7.08) years and the mean age of atrophic endometrium (54.5 ± 4.6) years, ($P = 0.099$). The most frequent complaint of patients with atrophic endometrium was PMB. This means that atrophic endometrium occurred almost always at or around menopause.

Postmenopausal bleeding

The cessation of menstruation is the cardinal symptom of the menopause. PMB is considered as an important and alarming symptom both to the patient and to the gynaecologist, and it requires a complete evaluation as quickly as possible in order to ensure the absence of malignancy and to identify and treat high risk patients such as those with endometrial hyperplasia⁽¹⁵⁾. In this study the mean age of postmenopausal women was (52.2 ± 7.08) years which was in agreement with the mean age reported in UK which was (51.4) years⁽⁴⁴⁾, in Sweden it was (50) years⁽⁴⁵⁾, and in Libya was (54.2) years⁽¹⁵⁾, however, it was lower than that reported in Belgium which was (61.6) years⁽⁴⁶⁾.

In this study, the lesions associated with PMB were categorized into malignant and benign lesions. The malignant lesions were found in 13 (17.1%) of the cases, where one patient (1.3%) had endometrial stromal sarcoma of low grade type and 12 (15.8%) patients had endometrial adenocarcinoma. This finding similar to those reported by other investigator varying between (10.5%) by (Patel SRP, 1967)⁽⁴⁷⁾ in Australia, (10.8%) by (Gebauer G, *et al*, 2001)⁽⁴⁸⁾ in Germany, (13.1%) by (Keirse MJNC, 1973)⁽⁴⁶⁾ in Belgium, and (16%) by (Pacheco JC & Kempers RD, 1968)⁽⁴⁹⁾ in USA. Although the frequency of PMB is due to malignancy is now only half that of (30) years ago, it remains sufficiently high to require thorough investigation⁽⁴⁶⁾. Several reasons had been blamed for this apparent decrease in the frequency of malignant lesions as a cause of postmenopausal bleeding, first is the large decline in the use of estrogen as hormone replacement therapy, and

second is an increased interest or facilities for early diagnosis of premalignant lesions⁽⁴⁶⁾.

The benign lesions were encountered in 63 (82.9%) cases. This figure is similar to previous observations like (71.6%) by (Patel SRP, 1967)⁽⁴⁷⁾, (76.2%) by (Keirse MJNC, 1973)⁽⁴⁶⁾, and (82%) by (Pacheco JC & Kempers RD, 1968)⁽⁴⁹⁾. Atrophic endometrium was the first most common finding among the benign lesions. It was diagnosed in (34.2%) of cases, which was in agreement with previous observations including (20%) by (Pacheco JC & Kempers RD, 1968)⁽⁴⁹⁾, (24%) by (Buzghia FM, 1999)⁽¹⁵⁾ and (25%) by (Mahmood MF, 1988)⁽²²⁾, but it was higher than those reported by (Patel SRP, 1967)⁽⁴⁷⁾ and (Keirse MJNC, 1973)⁽⁴⁶⁾. Accuracy of D&C in the diagnosis of the pathological lesions of the endometrium.

Of the total (92) hysterectomy specimens, (82) cases had a previous diagnostic curettage within a period of (1-18) months due to persistent uterine bleeding. The endometrial lesions of (79/82) patients were confirmed at hysterectomy making the diagnostic accuracy of D&C as (96.3%), which is similar to that reported by (Mahmood MF, 1988)⁽²²⁾. However, there were some differences between the histopathological reports of curettage and hysterectomy specimens in the remaining 3 cases. The possible explanation for this discordance include inadequate sampling and fragmentation of the specimen at curettage which cause difficulty in interpretation as well as inter-observer variations in histopathological assessment.

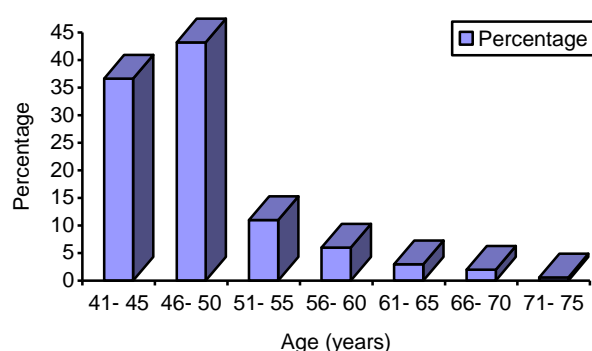


Figure 1: Age distribution of the sampled women

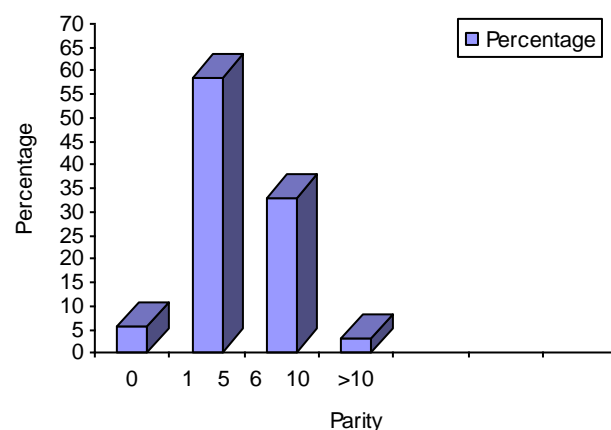


Figure 2: Parity distribution

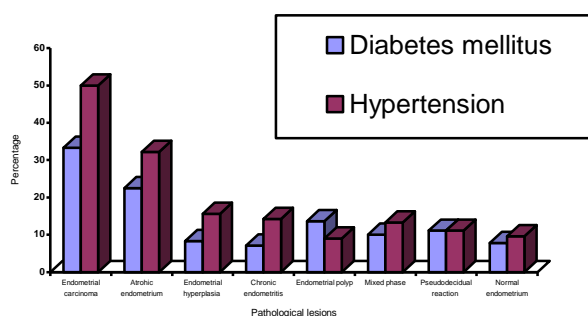


Figure 3: The relative frequency of diabetes and hypertension in different pathological lesions.

Table 1 : The frequency of the different patterns of abnormal uterine bleeding among the studied patients

Patterns of Bleeding	No. of patients	Percentage %
Menorrhagia	124	34
Postmenopausal Bleeding	76	21
Continuous Bleeding	71	20
Menometrorrhagia	48	13.2
Polymenorrhagia	26	7
Metrorrhagia	13	3.5
Polymenorrhoea	5	1.3
Total	363	100

HISTOPATHOLOGICAL INTERPRETATION OF ABNORMAL UTERINE BLEEDING

Table 2: Frequency of different histopathological findings of endometrial specimens by D&C or hysterectomy

Histopathological Findings	No. of Cases	Percentage %
Normal Endometrium	114	31.4
Proliferative Phase	60	16.5
Secretory Phase	50	13.8
Menstrual Phase	4	1.1
Endometrial Hyperplasia	110	30.3
Atrophic Endometrium	31	8.5
Irregular (mixed) Phase Endometrium	30	8.3
Chronic Endometritis	28	7.7
Polyp	22	6
Malignancy	14	3.9
Pseudodecidual Reaction	9	2.5
Submucous Leiomyoma	5	1.4
Total	363	100

Table 3: Comparison between the mean age of menopause(52.2 years) and those of different histopathological findings.

Histopathological Diagnosis	Mean Age	P –Value	Significance
Normal Endometrium	46.1	0.001	VHS*
Endometrial Hyperplasia	49.8	0.002	HS**
Mixed Endometrium	46.1	0.001	VHS
Chronic Endometritis	46.9	0.001	VHS
Pseudodecidual Reaction	44.4	0.002	HS
Atrophic Endometrium	54.5	0.099	N.S***
Polyp	49.5	0.092	N.S
Endometrial Cancer	58.7	0.006	HS

* Very Highly Significant.

** Highly Significant.

*** Not Significant.

Table 4: Frequency of various histopathological findings in women with PMB.

Histopathological Findings	No. of Patients	Percentage %
Atrophic Endometrium	26	34.2
Endometrial Hyperplasia	14	18.4
Malignancy	13	17.1
Endometrial polyp	12	15.8
Proliferative Phase	8	10.6
Chronic Endometritis	2	2.6
Secretory Phase	1	1.3
Total	76	100

CONCLUSION:

1-Dysfunctional uterine bleeding was the predominant cause of AUB in women above (40) years of age.

2-The commonest endometrial pathology was endometrial hyperplasia.

3- Although atrophic endometrium was the commonest finding in postmenopausal women , PMB should always be taken seriously because it usually reflects an organic pathology.

4-D&C may miss other uterine lesions such as adenomyosis and /or leiomyoma, therefore persistent uterine bleeding after curetting may indicate the presence of these two pathological lesions.

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