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# Atypical uterine bleeding-Histopathological audit of endometrium A study of 638 cases

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**Abstract:** *Background:* AUB is one of the most common problems in women of all ages especially those in the peri-menopausal age group. The abnormal bleeding can be caused by a wide variety of disorders and it is one of the commonest complaints leading to endometrial sampling. *Objectives:* Our study aimed at determining the types and frequencies of endometrial pathologies in patients presenting with abnormal uterine bleeding at our hospital which caters largely to women of low socioeconomic status. *Material and Methods:* The present study was conducted at the Hakeem Abdul Hameed Centenary Hospital, New Delhi. This was a retrospective age specific comparative analysis of 638 women presenting with abnormal uterine bleeding, who underwent endometrial sampling at our hospital. The pattern of endometrial histopathological changes were identified and classified. *Results:* Age of the patients ranged from 15 to 70 years, maximum patients (35.89 %) in the age group 41-50 years. The most common clinical presentation was represented by menorrhagia (41%) Various patterns on histopathology were secretory endometrium(28.99%)the commonest, followed by proliferative endometrium (24.92%). Incidence of malignancy was low in the present study. *Conclusion:* Endometrial curetting and biopsy is an important diagnostic procedure in evaluation of AUB.. Endometrial causes of AUB are age related, therefore it is specially recommended in women of the perimenopausal age presenting with AUB, to rule out preneoplasia and malignancy.

**Keywords:** Endometrium, atypical, bleeding, histopathology

## Introduction

Endometrium is a dynamic, hormonally sensitive and responsive tissue which constantly and rhythmically undergoes changes in the active reproductive life. Abnormal uterine bleeding (AUB) may be defined as a bleeding pattern that differs in frequency, duration and amount from a pattern observed during a normal menstrual cycle or after menopause [1]. AUB is one of the most common problems in women of all ages especially those in the peri-menopausal age group. The abnormal bleeding can be caused by a wide variety of disorders and it is one of the commonest complaints leading to endometrial sampling. It may represent a normal physiological state, and observation alone may be warranted. Alternatively, the bleeding can be a sign of a serious underlying condition necessitating aggressive treatment. Dilatation and curettage is a useful and cost effective method of detecting intrauterine pathologies and very few lesions escape detection [2]. Wide range of morphologic patterns resulting from both normal and abnormal changes offer a diagnostic challenge to practicing pathologists. Our study is aimed at determining the types and frequencies of endometrial pathologies in patients presenting with abnormal uterine bleeding at our hospital which caters largely to women of low socioeconomic status.

## Material and Methods

The present study was conducted at the Hakeem Abdul Hameed Centenary Hospital, New Delhi. Our hospital caters to a predominant population belonging to low socioeconomic status residing in the nearby localities. This was a retrospective age specific comparative analysis of 638 women presenting with abnormal uterine bleeding, who underwent endometrial sampling at our hospital. The study spanned a period of 4 years and 4 months from January 2008 to April 2012. Data on the age and presenting clinical features were retrieved from the accompanying laboratory request forms, or

patients records where ever available. All endometrial biopsies and curettages of women with abnormal uterine bleeding were retrieved and reviewed, the pattern of uterine histopathological changes identified and classified. Endometrial tissue collected by sampling procedures such as dilatation and curettage (D&C), endometrial biopsy and fractional curettage which had been sent to the pathology lab for evaluation were included in the study. The total tissue submitted was processed. Paraffin blocks were prepared and tissue section (4-6µ) cut. The sections were stained with hematoxylin and eosin stain (H&E) and sent for microscopic examination by the pathologist. The clinical presentation on including the age of the patient and the endometrial histology were correlated and results compared with those in literature.

## Results

A total of 638 patients underwent diagnostic D&C for AUB during the study period and the curettage was submitted for histopathological examination. The age of the patients studied were categorized into six groups (Table 1), patients with AUB ranged from 15 to 70 years with a mean age of 31.5years and a median age of 33years. Maximum patients (35.89 %) with abnormal uterine bleeding presented in age group 41-50 years closely followed by 33.22% in the age group 31-40yrs. The adolescent group (<20yrs) comprised of 2.82%patients while least number of patients were seen in the 60-70 years age group (0.62%)

**Graph-1: Distribution of cases according to age**

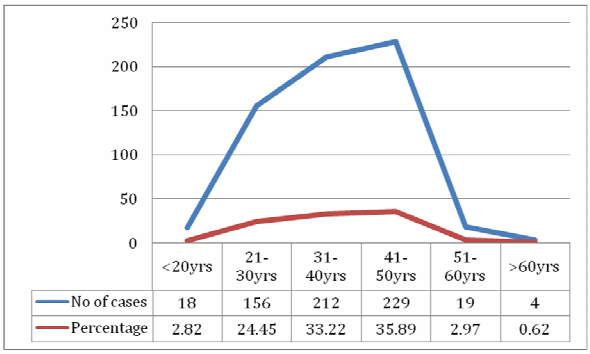
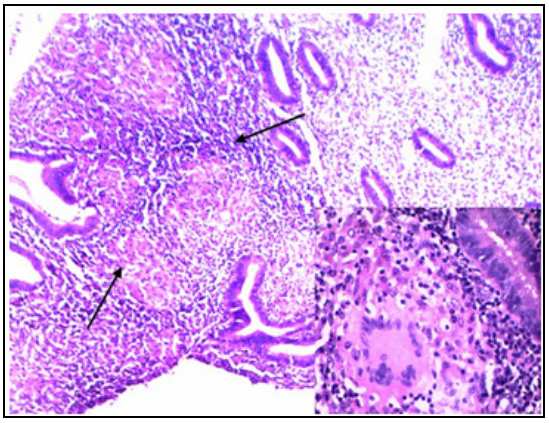





**Figure-1: Microphotograph of endometrial granulomas (arrows) with Langhans giant cells. (Inset) (H&E, 10X)**



Data on the clinical presentation was limited, out of the 638 cases of AUB the details of patterns of bleeding were available in only 462 patients. Out of these, the most common clinical presentation was represented by menorrhagia (41%) followed by metrorrhagia (18%) menometrorrhagia, polymenorrhea, polymenorrhagia amongst others. (Figure 2)

**Graph-2: Distribution of cases according to clinical presentation**

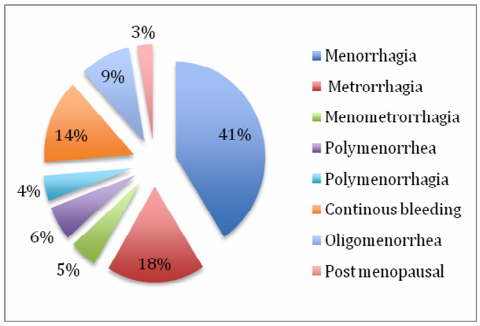
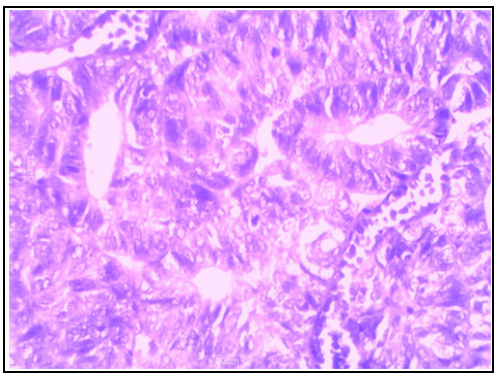



**Figure-2: Microphotograph of endometrial adenocarcinoma showing closely packed glands lined by epithelial cells with cytological atypia. (H&E, 40 X)**



An age specific comparative analysis of the clinical presentation (Table1) revealed that menorrhagia was the commonest complaint in the 41-50 years accounting for 41.2% of the cases presenting with the complaint. Metrorrhagia was also a frequent presentation in the 41-50 year age group seen in 41.4% patients with the complaint. Amongst the other clinical presentation those with oligomenorrhea were seen more in the pre and perimenopausal age group whilst continuous bleeding was more common in the 21-30 year age group.

**Table-1: Clinical presentation of atypical uterine bleeding according to age**

| Pattern of bleeding | <20years | 21-30years | 31-40years | 41-50years | 51-60years | >60years |
|---|---|---|---|---|---|---|
| Menorrhagia | - | 42 | 69 | 78 | - | - |
| Metrorrhagia | - | 20 | 28 | 34 | - | - |
| Menometrorrhagia | - | 8 | 8 | 7 | | |
| Polymenorrhea | - | 5 | 7 | 15 | - | - |
| Polymenorrhagia | - | 4 | 12 | 4 | - | - |
| Continous bleeding | 16 | 41 | 3 | 6 | - | - |
| Post menopausal | - | - | - | 4 | 7 | 2 |
| Oligomenorrhea | - | 5 | 17 | 20 | - | - |

Evaluation of the endometrium revealed various patterns on histopathology (Table 2), functional causes accounted for majority of the diagnosis of which secretory endometrium seen in 185 cases (28.99%) was the commonest. Out of these, the maximum number of cases with secretory endometrium was seen in the age group 41-50years (38.9%) closely followed by the 31-40 year age group (36.7%) (Table3). Proliferative endometrium on histopathology was the second most common diagnosis seen in 159 patients (24.92%), age specific analysis revealed 40.8% cases in the age group 41-50years and 38.9% cases in the 31-40 years age group (Table 3). The other diagnoses, which made up for the rest of the functional causes of AUB were disordered proliferative endometrium 31cases(4.85%), irregular shedding 15(2.3%) and ripening 6 (0.9%) and luteal phase defects 12 cases (1.8%) and anovulatory 6 (0.9%).

**Table-2: Distribution of AUB patients according to histopathological pattern**

| Histopathological Pattern | No. of patients | Percentage |
|---|---|---|
| Proliferative | 159 | 24.92 |
| Secretory | 185 | 28.99 |
| Hyperplasia | 37 | 5.79 |
| Endometritis | 39 | 6.11 |
| Polyp | 11 | 1.72 |
| Exogenous Hormone | 11 | 1.72 |
| Disordered proliferative | 37 | 5.7 |
| Atrophic | 7 | 1.10 |
| Carcinoma | 3 | 0.47 |
| Irregular Shedding | 15 | 2.35 |
| Irregular Ripening | 6 | 0.94 |
| Luteal phase defects | 12 | 1.88 |
| Complications of pregnancy | 98 | 15.36 |
| Inadequate | 18 | 2.82 |

Definite endometrial pathology was seen most commonly as chronic endometritis in 39cases (6.1%) out of which 11patients had undergone diagnostic D&C for secondary infertility. Three of these 11 cases were of tubercular origin (Figure 1). 51.2% of the endometritis cases were seen in the 41-50 year age group. Endometrial hyperplasia was a close second, diagnosed in 37 patients (5.79%) who presented with AUB, 64.8% of these were in the perimenopausal age group (41-50yrs).On categorizing the histopathological types of endometrial hyperplasia, majority of our cases (64.8%) were of simple hyperplasia without

atypia. Simple hyperplasia with atypia were seen in 16.2%, complex hyperplasia with atypia in 5.4% and without atypia in 13.5% were seen. An increase in cases of endometrial hyperplasia with increase in age was noted (Table 3). Other lesions in this category were endometrial polyp 11cases (1.7%) and atrophic endometrium 7(1.1%). While atrophic endometrium was seen in the peri and postmenopausal ages polypoid lesions were seen in ages between 21-50 years. Frequency of malignancy was low seen in 3(0.4%) cases. All cases of endometrial malignancy were of endometroid adenocarcinoma (Figure 2) and presented with postmenopausal bleeding.

**Table-3: Histopathological distribution of cases of AUB according to age group**

| Endometrial histology | <20years | 21-30yrs | 31-40yrs | 41-50yrs | 51-60yrs | >60yrs |
|---|---|---|---|---|---|---|
| Proliferative | 2(1.2%) | 20(12.5%) | 62(38.9%) | 65(40.8%) | 10(6.3%) | - |
| Secretory | - | 44(23.7%) | 68(36.7%) | 72(38.9%) | 1(0.5%) | - |
| Hyperplasia | - | 2(5.4%) | 10(27.0%) | 24(64.8%) | 1(2.7%) | - |
| Endometritis | - | 8(20.5%) | 10(25.6%) | 20(51.2%) | 1(2.5%) | - |
| Polyp | - | 2(18.2%) | 3(27.7%) | 6(54.5%) | - | - |
| Exogenous Hormone | - | 3(27.7%) | 1 (9%) | 6(54.5%) | 1(9%) | - |
| Disordered proliferative | - | 4 (12.9%) | 11 (35.4%) | 15 (48.3%) | 1 (3.2%) | - |
| Atrophic | - | - | - | 3 (42.8%) | 2 (28.5%) | 2 (28.5%) |
| Carcinoma | - | - | - | - | 1 (33.3%) | 2 (66.7%) |
| Irregular Shedding | - | 5 (33.3%) | 5 (33.3%) | 5 (33.3%) | - | - |
| Irregular Ripening | - | 2 (33.4%) | 1 (16.6%) | 3 (50%) | - | - |
| Luteal phase defects | - | 3 (25%) | 6 (50%) | 3 (25%) | - | - |
| Complications of pregnancy | 16 (16.3%) | 50 (51%) | 29 (29.6%) | 3(3.0%) | - | - |
| Anovulatory | - | 3 (50%) | 3 (50%) | - | - | - |
| Inadequate | - | 10 (55.5%) | 3 (16.6%) | 4 (22.2%) | 1 (5.5%) | - |
| Total | 18 | 156 | 212 | 229 | 19 | 4 |

Inadequate sampling was seen 2.8% cases, 55.5% of these were in the 21-30 year age group. Complications of pregnancy is a frequent cause of AUB. Pregnancy related bleeding was seen in 98 cases (15.3%) in the present study, 88 patients of which were of products of conceptions, 9 were of hydatidiform mole and 1case of choriocarcinoma (Figure 3). Out of the vesicular mole cases 7were of partial and 2 of complete mole type.51% of the pregnancy related complication cases were present in the 21-30year age group while 16.3% of the cases were in the adolescent age(<20years).

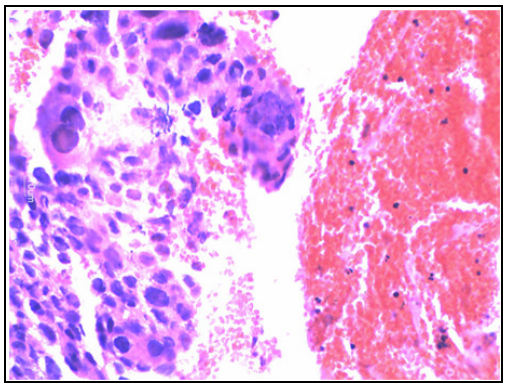


**Figure-3: Microphotograph of choriocarinoma with areas of hemorrhage and atypical trophoblastic cell. (H&E, 40X)**

## Discussion

Abnormal uterine bleeding is a common gynecological problem accounting for up to 20% of the visits to the gynecologists [3]. Dilatation and curettage is a useful and cost effective method of detecting intrauterine pathologies and very few lesions escape

detection [2,4]. It is commonly used in developing countries with limited resources as a standard and often the only mean of assessing abnormal uterine bleeding. Histopathological evaluation of the curettage specimen is necessary in identifying the cause of AUB. The clinical differential diagnosis is different for various age groups and histopathological examination of material obtained on endometrial curettage helps in diagnosis of these diseases presenting with AUB. This carries special significance in the perimenopausal age group because of increased incidence of intrauterine lesions in this age group. Abnormal and excessive endometrial bleeding occurs in reproductive women of all ages but is more common in adolescent and perimenopausal women [5]. Many studies have revealed that occurence of menstrual disorders of excessive type increased with age [6-7]. A gradual increase in patients with respect to age was noted in the present study also. The largest age group of patients with AUB in our study was 41-50 years, accounting for 229 (35.9%) cases in concordance with 33.5% [7] and 32.1% [8] in other studies, however our results were less as compared to 48.1% [6] and much more than 30% [9] reported in literature. An increased number of cases in this age could be due to the fact that as menopause approaches, decreased number of ovarian follicles and their increased resistance to gonadotrophic stimulation, results in a low level of estrogen, which cannot keep the normal endometrium growing [10]. Lesser number of patients was seen in the higher ages may be due to earlier evaluation, detection as well as management of the disease.

The clinical details of all the patients were not available, they could be retrieved in only 462 cases. Analysis of these revealed menorrhagia as the most common presenting complaint accounting for 189 (41%) patients with most of them in the 41-50year age group, gradually increasing from the 21-30year age group. (Table1) Menorrhagia as a common complaint has often been reported in literature, it varied between 51.9% [6] and 53.3% [11-12]. Although these are higher than those observed in the present study trends similar to ours have been seen, 41% reported by Moghal [13]. Predomina-ntly menorrhagia was confined to perimenopausal age in our study, while one study reports 80%of the perimenopausal patients with this complaint [14] in contrast another reports only 11% patients [15]. Metrorrahgia, seen in 18% cases was the second commonest clinical presentation, showing an increase in cases with respect to age of presentation. This was in concordance with 18% reported in literature [15] although other studies have reported a much lower incidence of 6.5% [11] and4.3-5% [14], on the other hand incidence of 35.4% have also been sited [6]. Continous bleeding per vaginum was another common bleeding complaint seen mostly amongst patients presenting with pregnancy related complications.

Histopathological evaluation of endometrial curetting yielded various patterns ranging from physiological to pathological lesions of the endometrium. The commonest histopathological diagnosis was secretory endometrium (28.9%) closely followed by proliferative endometrium (24.9%) together they accounted for 344cases (53.9%). (Table2) This was in concordance with 24.9% cases of secretory endometrium reported as the commonest diagnosis in a study followed by 21.7%cases of proliferative endometrium [8]. Although, a higher number of secretory phase endometrium (35.4%) have been reported [6], the pattern of proliferative phase endometrium in our study compared favourably with trends in literature [6,9,13]. A wide variation in the secretory phase endometrium has been reported ranging from 14% [16] to 63.5% [17].

Pregnancy is the first consideration in women of childbearing age who present with abnormal uterine bleeding. Patients presenting with abnormal uterine bleeding in this age range should be investigated and evaluated for pregnancy [18]. Pregnancy related bleeding was seen in 98(15.36%) cases, 51% of which were in the age group 21-30years. A similar 57.6%cases with bleeding as a complication of pregnancy has been reported in this age [19]. Potential causes of pregnancy-related bleeding include spontaneous pregnancy loss (miscarriage), ectopic pregnancy, placenta previa, abruptio placentae, and trophoblastic disease. In the present study 10 cases were of trophoblastic disease out of which 9 were of hydatidiform mole and 1case of choriocarcinoma. Out of the vesicular mole cases 7 were

of partial and 2 of complete mole type. Hydatidiform mole both partial and complete have been reported by Baral et al [20].

Chronic endometritis was diagnosed in 39 cases (6.1%), the detection rate being higher in the 41-50year age group (51.2%). A favourable comparison can be drawn with other studies in literature [8,6,21]. However, a much higher incidence of 24% has also been reported [9, 22]. The diagnosis of chronic endometritis is made on the basis of presence of plasma cells. Chronic endometritis is often a result of intra uterine contraceptive devices (IUCD), pregnancy and incomplete abortions. Three cases (7.6%) out of the 39 chronic endometritis cases were of tubercular origin. The diagnosis of endometrial tuberculosis depends mainly on the histopathological examination, since the presenting clinical features are in no way indicative of the disease. However, infertility has commonly been associated with endometrial tuberculosis. In a study, conducted on 500 biopsies of proved cases of endometrial tuberculosis, no characteristic endometrial pattern was found to be specific for a tuberculous lesion. A deviation from normal pattern such as proliferative, mixed and hyperplastic endometrium was however noted in a number of cases [23].

Endometrial hyperplasia is a common diagnosis especially in perimenopausal women often causing symptoms of irregular or prolonged bleeding due to anovulatory cycles in majority of cases. Heavy bleeding is secondary to sustained level of oestrogens. The overgrowth not only affects glands and stroma but there is also abnormal vascularisation [12]. The incidence of hyperplasia in the present study was 5.7% accounting for 37 cases presenting with AUB. It was much lower than 18.3% and 30.8% observed by other authors [6, 20]. Simple hyperplasia accounted for 64.8% of the cases similar to 66.6% observed in another study [12]. Majority of the studies have observed an increased incidence similar to our findings in the perimenopausal age group [6-8]. The importance of histopathological evaluation of the endometrium in women of this age group cannot be underestimated as AUB in perimenopausal women could be due to an underlying malignancy.

Besides hyperplasia prolonged estrogen stimulation also results in the formation of endometrial polyps (EMPs). In the present study 11(1.7%) cases of benign polyps were observed. The incidence was much lower than 12.9% and 12% observed by other authors [15, 24]. 54.5% of which were seen in the 41-50year age group this was in concordance with Saraswathi et al [7]. A lower incidence in younger women is attributed to a possible regression mechanism characteristic of endometrium of reproductive age group [7]. Endometrial polyps are commonly encountered in routine surgical pathology practice, but opinions differ on whether they are intrinsically a marker for concurrent or subsequent malignancy. Careful search for malignancy, particularly in women with multiple risk factors is advised in daily practice [25]. Incidence of endometrial carcinoma in the present study is low, seen in 0.47%cases only. All the three cases were in the postmenopausal age group. Higher incidences of 2% [22] and 4.4% [7] have been reported.

Disordered proliferative pattern of the endometrium is somewhat difficult to define, it refers to a proliferative phase endometrium that does not seem appropriate for any one time in the menstrual cycle [7]. It occupies the lower end of spectrum which passes through hyperplasia to endometrial carcinoma on the other end [7]. Early diagnosis of the lesion will be of assistance to the practicing gynecologists in order to prevent further disease progression In the present study it was seen in 31(4.8%) cases which is much lower than 23% and 20.5% reported in literature [24,7]. Luteal phase insufficiency (1.8%), irregular ripening (0.9%) and shedding (2.3%) and anovulatory cycles (0.9%) are the other functional disorders observed in the present study.

Amongst the anovulatory cases three cases each were in the 21-30years and 31-40years age group this was in discordance with 66.6% cases of anovulatory endometrium in the age group 41-50 years reported in literature [22]. A higher number of cases in the perimenopausal age group has been explained by the fact that perimenopause is the transition

from normal ovulation to anovulation which then eventually leads to permanent loss of ovarian function [22]. Irregular shedding of the endometrium is apparently due to slow degeneration of the corpus luteum with prolonged exposure of the menstruating endometrium to the waning progesterone. In the present study a total of 15(2.3%) cases with irregular shedding of endometrium were found which was less than 6% cases reported by Baral et al [20]. However all cases in the present as well as the quoted study were equally distributed in different age groups.

Exogenous hormone (pill effect) changes in the endometrium were seen in 11 cases (1.7%) Out of which 54.5% were seen in the perimenopausal women. Muzzafar et.al have reported 2.3% cases pill pattern in the endometrium similar to our observation, however majority of their cases were in the 31-40 year age group while in our study cases were in the 41-50 year age group. Atrophic endometrium was seen predominantly in the peri and postmenopausal women and accounted for 1.1% of the total cases. Other authors in discordance with our study reported 2.4% [7] and 7% [24]. The exact cause of bleeding in atrophic endometrium is not known it is thought to be due to anatomic vascular variation or defective local haemostatic mechanism [7]. Specimens inadequate for reporting were 18, accounting for 2.8% of the total cases. Those labelled unsatisfactory for reporting showed scant glands and stroma, fragmented tissue and large areas of haemorrhage. Limited literature is available on the criteria for adequate and inadequate endometrial specimen.

## Conclusion

To conclude, a significant number of endometrial samples on histopathology revealed changes, rendering endometrial curetting and biopsy an important diagnostic procedure in evaluation of AUB. Endometrial causes of AUB are age related, therefore it is specially recommended in women of the perimenopausal age presenting with AUB, to rule out preneoplasia and malignancy. Accurate analysis of endometrial samplings is the key to effective therapy and optimal outcome.

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