

# Morphological spectrum of endometrial pathology in middle-aged women with atypical uterine bleeding: A study of 219 cases

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## ABSTRACT

**Background:** Perimenopause, also called the menopausal transition, is the interval in which a woman's body makes a natural shift from more-or-less regular cycles of ovulation and menstruation toward permanent infertility, or menopause.

**Materials and Methods:** A retrospective age specific comparative analysis of 219 perimenopausal women presenting with abnormal uterine bleeding was done who underwent endometrial sampling during a 4-year period from January 2008 to April 2012 at the Hakeem Abdul Hameed Centenary Hospital. Endometrial tissue collected by sampling procedures such as dilatation and curettage (D and C), endometrial biopsy and fractional curettage had been sent to the pathology laboratory for evaluation.

**Results:** The most common clinical presentation was represented by menorrhagia (46.4%) followed by metrorrhagia (20%), menometrorrhagia, polymenorrhea, polymenorrhagia among others. Evaluation of the endometrium revealed various patterns on histopathology, functional causes accounted for majority of the diagnosis. Secretory endometrium seen in 71 cases (32.4%) was the most common. While proliferative endometrium on histopathology was the second most common diagnosis; seen in 67 patients (30.5%). Endometrial hyperplasia was seen in 24 (10.9%) cases out of which simple hyperplasia without atypia was seen in 19, complex hyperplasia without atypia was seen in 4 and complex hyperplasia with atypia was seen in 1 case. The other diagnoses, which accounted for the rest of the functional causes of atypical uterine bleeding, were disordered proliferative endometrium 15 cases (6.8%), luteal phase defects 3 cases (1.3%).

**Conclusion:** Atypical uterine bleeding in perimenopausal women is most commonly dysfunctional in origin. In addition, a significant number show underlying organic pathologies thereby highlighting the importance of endometrial curetting and biopsy as a diagnostic procedure in the evaluation.

**Key Words:** Atypical, bleeding, endometrium, hyperplasia

## INTRODUCTION

Perimenopause, also called the menopausal transition, is the interval in which a woman's body makes a natural shift from more-or-less regular cycles of ovulation and menstruation toward permanent infertility, or menopause. This phase generally occurs at around 40-50 years of age. Abnormal uterine bleeding is a commonly encountered gynecological problem in this age group. Abnormal uterine bleeding 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.<sup>[1]</sup> It includes both dysfunctional uterine bleeding (DUB) and bleeding from structural causes like fibroids, polyps, endometrial carcinoma, and pregnancy complications. A demonstrable organic cause is not seen in DUB and endometrial curettage plays an important role in excluding organic uterine disorders.<sup>[2,3]</sup> This procedure allows an extensive sampling of the uterine cavity and has a higher sensitivity

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than endometrial biopsy especially with smaller *in situ* lesions. Menopause is an important event occurring during middle age in women and represents the end of a woman's reproductive life. The age at which natural menopause occurs is between the age of 45 and 55 years worldwide and a study from north India concluded that the mean age at menopause was 44.54 years<sup>[4]</sup> We undertook a study to determine the types and frequencies of endometrial pathologies in perimenopausal women presenting with abnormal uterine bleeding at our hospital who underwent endometrial sampling.

## MATERIALS AND METHODS

This was a retrospective age-specific comparative analysis of 219 perimenopausal women presenting with abnormal uterine bleeding, who underwent endometrial sampling during a 4-year period from January 2008 to April 2012 at the Hakeem Abdul Hameed Centenary Hospital. This hospital caters to the populace who live in the nearby slums and the adjoining areas located around this hospital in New Delhi. All the patients in this study were in the 40-50 age group. Data on the age and presenting clinical features were retrieved from the accompanying laboratory request forms or patients records wherever available. All endometrial biopsies and curettages of women with abnormal uterine bleeding were retrieved and reviewed, the pattern of uterine histopathological changes were identified and classified.

Endometrial tissue collected by premenstrual sampling procedures such as dilatation and curettage (D and C), endometrial biopsy and fractional curettage had been sent to the pathology laboratory for evaluation. The total tissue submitted was processed. Paraffin blocks were prepared and tissue section (4-6 μ) cut. The sections were stained with hematoxylin and eosin stain (H and E) and examined microscopically by the pathologist.

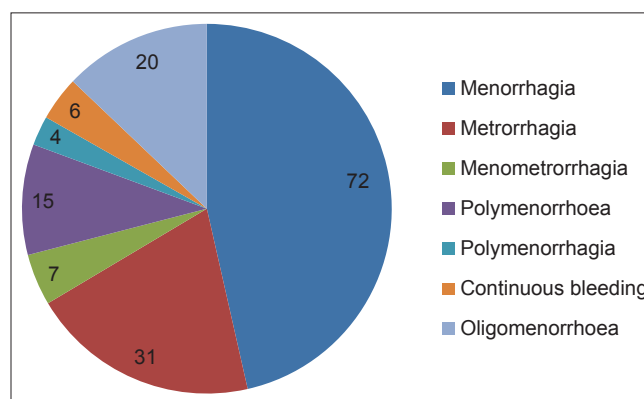
## RESULTS

A total of 219 perimenopausal (40-50 years, mean age of 44.8 years) women in the 40-50 years age group underwent endometrial sampling at the Hakeem Abdul Hameed Centenary Hospital, New Delhi over a 4-year period. The presenting clinical features of these patients are summarized in Figure 1.

Data on the clinical presentation was limited, out of the 219 cases of atypical uterine bleeding, the details of patterns of bleeding were available in only 155 patients. Out of these, the most common clinical presentation was represented by menorrhagia (46.4%) followed by

metrorrhagia (20%), menometrorrhagia, polymenorrhea, polymenorrhagia among others.

Evaluation of the endometrium revealed various patterns on histopathology [Table 1], The PALM-COEIN (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic and not yet classified) classification system for AUB has been recently approved as a FIGO classification system. This classification system was developed with the aim that it could be used by clinicians, investigators, and even patients to facilitate communication, clinical care, and research.<sup>[5]</sup> Functional causes accounted for majority of the diagnosis [Table 1]. Secretory endometrium seen in 71 cases (32.4%) was the most common. Proliferative



**Figure 1:** Pie chart representing clinical presentation of atypical uterine bleeding (N = 155)

**Table 1: Histopathological distribution of cases in patients of AUB according to FIGO classification**

Endometrial histology	FIGO classification (PALM-COEIN) for AUB	No. of patients	Percentage
Proliferative	AUB-E	67	30.6
Secretory	AUB-E	71	32.4
Simple hyperplasia without atypia	AUB-M	19	8.6
Complex hyperplasia without atypia	AUB-M	4	1.8
Complex hyperplasia with atypia	AUB-M	1	0.4
Endometritis	AUB-E	20	9.1
Polyp	AUB-P	6	2.7
Exogenous hormone	AUB-I	6	2.7
Disordered proliferative	AUB-E	15	6.8
Luteal phase defects	AUB-O	3	1.3
Complications of pregnancy	-	3	1.3
Inadequate	-	4	1.8

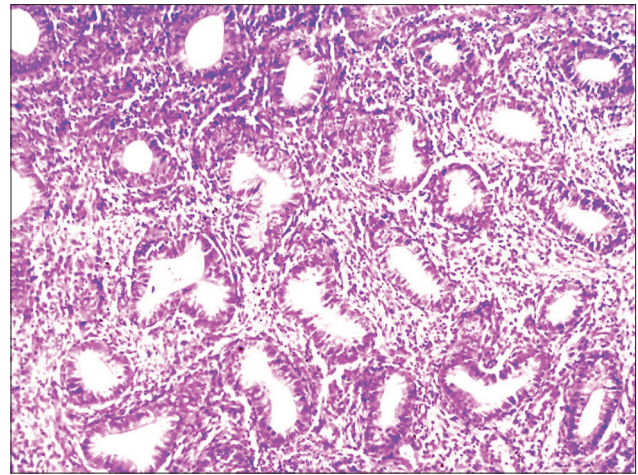
AUB: Atypical uterine bleeding, FIGO: The international federation of gynecology and obstetrics

endometrium on histopathology was the second most common diagnosis seen in 67 patients (30.6%). The other diagnoses, which accounted for the rest of the functional causes of atypical uterine bleeding, were disordered proliferative endometrium 15 cases (6.8%), luteal phase defects 3 cases (1.3%).

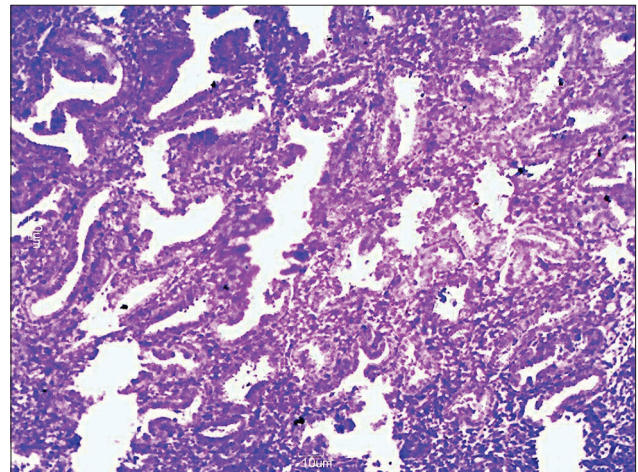
Endometrial hyperplasia was seen in 24 (10.9%) patients who presented with atypical uterine bleeding. On categorizing, the types of endometrial hyperplasia, simple hyperplasia without atypia [Figure 2] was seen in 19 cases, complex hyperplasia without atypia in [Figure 3] 4 cases, and complex hyperplasia with atypia in 1 case. Endometritis was a close second and diagnosed in 20 patients (9.1%) who presented with atypical uterine bleeding. Caseating granulomas and Langhans giant cells, hallmarks of tubercular etiology were demonstrated in 2 out of these 20 cases [Figure 4] while the remaining 18 cases showed nonspecific chronic endometritis. Endometrial polyps were seen in six (2.7%) cases. Polyps, at times are difficult to recognize in curettage specimens. They were identified as polypoidal fragments with epithelium on three sides. Another identifying feature was the presence of fibrous stroma and thick walled blood vessels that had a contrasting appearance to the other endometrial fragments, thereby suggesting a polyp. Irregularly shaped, crowded hyperplastic glands were seen in four of the cases while two cases showed glands with normal cycling endometrium. Pregnancy-related bleeding was seen in three (1.3%) cases with spontaneous pregnancy loss (miscarriage) being the cause of bleeding in all the three. Six (2.7%) cases showed endometrium with evidence of exogenous hormone therapy, which is a common line of medical management in patients of atypical uterine bleeding and often prescribed empirically. Finally, in four (1.8%) cases, the endometrial curettings were scanty and inadequate for any diagnostic opinion.

## DISCUSSION

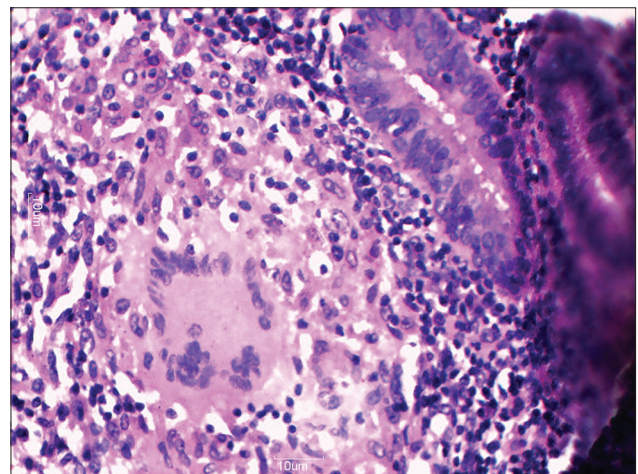
Abnormal uterine bleeding, that is, excessive and irregular continues to be one of the most frequently encountered complaints in gynecologic practice. It accounts for more than 70% of all gynecological consultations in the peri- and postmenopausal years.<sup>[4]</sup> Conventional D and C is commonly used in developing countries with limited resources as a standard and an important method of assessing abnormal uterine bleeding. This study attempts to analyze atypical uterine bleeding among women in the 40-50 age group. Atypical uterine bleeding without structural pathology is seen in women across all age groups but is more common in adolescent and perimenopausal women. The common terminology for these cases is 'dysfunctional uterine bleeding'.



**Figure 2:** Photomicrograph showing dilated glands representing simple hyperplasia without atypia. (H and E, x40)



**Figure 3:** Photomicrograph showing endometrial glands with complex hyperplasia without atypia. (H and E, x40)



**Figure 4:** Photomicrograph showing epithelioid cell granulomas with Langhans giant cell in endometrium (H and E, x40)

DUB is a disorder with a hormonal imbalance as etiopathogenic substrate, without organic cause.<sup>[5]</sup>

Abnormalities along the hypothalamic–pituitary–ovarian axis may result in derangements of follicular maturation, ovulation or corpus luteum formation resulting in changes in the hormonal milieu. These alterations in the normal hormonal patterns may lead to abnormal uterine bleeding. We found that the most common histopathological finding was secretory endometrium in 71 (32.4%) cases. Similar studies in women with atypical uterine bleeding showed incidence of secretory endometrium at 16.1% and 23%, respectively.<sup>[6,7]</sup>

Another entity, luteal phase defect, which is characterized by an insufficient production of progesterone by the corpus luteum and, therefore, an inadequate development of the secretory endometrium, was seen in three (1.3%) cases in this study. Proliferative endometrium was seen in 67 (30.6%) patients, disordered proliferative endometrium was present in 15 (6.8%) cases and endometrial hyperplasia in 24 (10.9%) cases. Hence 106 (48.4%) of the perimenopausal women in the present study were exposed to unopposed estrogen. In the absence of ovulation and the production of progesterone, the endometrium responds to estrogen stimulation by proliferation. This endometrial proliferation with no periodic removal leads to the rupture of the fragile endometrial tissue. The bleeding is characteristically painless and irregular, as was seen in all these cases. In perimenopausal years, anovulatory cycles are most frequent and chronic anovulation is associated with an irregular and unpredictable pattern of bleeding. Several studies from the subcontinent have shown similar findings.<sup>[6-9]</sup> A study of perimenopausal women with atypical uterine bleeding by Bhosle *et al.*,<sup>[10]</sup> from Mumbai showed proliferative endometrium in 66.1% and simple hyperplasia without atypia in 17.8% of cases. Takreem *et al.*,<sup>[11]</sup> in a study carried out in Abbotabad, Pakistan reported 15 cases of endometrial hyperplasia among 100 perimenopausal women. Similarly Khare *et al.*,<sup>[12]</sup> in their study also showed that simple endometrial hyperplasia without atypia and proliferative endometrium were the most common histological findings in perimenopausal women, together accounting for 24 out of 47, that is, 51% of the cases.<sup>[12]</sup>

In addition, our study also detected endometrial polyps in six (2.7%) cases, out of which four were hyperplastic polyps characterized by simple hyperplasia without atypia and two cases were functional polyps with a normal endometrium. Again the common implicating factor here is increased estrogen secretion, which leads to hyperplasia of the basal endometrial layer.

Endometritis was a significant pathological diagnosis in this series and diagnosed in 20 (9.1%) cases. Nonspecific chronic endometritis as an etiology of atypical uterine bleeding in perimenopausal women has also been reported

by Khare *et al.*, and Michail *et al.*, affecting 6.4% and 20.7% of their study groups, respectively.<sup>[12,13]</sup> Additionally, in this study, among the 20 cases of endometritis, 2 cases showed caseating granulomas with epithelioid cells and Langhans giant cells and were diagnosed as ‘granulomatous endometritis’ compatible with tubercular etiology. Reys and Maheshwari in a large study of 500 biopsy proven cases of tuberculosis of the endometrium reported that while sterility was the most common presentation with 190 (38%) cases, bleeding as a presenting symptom was also seen in 111 (22.2%) cases.<sup>[14]</sup> In four (1.8%) cases, the endometrial curettings were scanty and were reported as inadequate for a diagnostic opinion. A study, which evaluated the negative predictive value of endometrial samples that were reported as inadequate in diagnosing endometrial hyperplasia and malignancy, was carried out in 2004 at the School of Medicine, Philadelphia. The findings suggested that an inadequate endometrial sample may be sufficient to rule out endometrial neoplasia because of its high negative predictive value.<sup>[15]</sup>

## CONCLUSION

Atypical uterine bleeding in perimenopausal women is most commonly dysfunctional in origin. In addition, a significant number show underlying organic pathological lesions thereby highlighting the importance of endometrial curetting and biopsy as a diagnostic procedure in the evaluation. Endometrial curettage also plays an important role in perimenopausal women presenting with atypical uterine bleeding in the timely diagnosis of preneoplasia and malignancy. Accurate analysis of endometrial samplings is therefore, the key to effective therapy and optimal outcome.

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