

Histopathological evaluation of endometrial biopsies and curetting's in abnormal uterine bleeding

Vani B. S.¹, Vani R.², Jijiya Bai P.³

¹Dr. B. S. Vani, Assistant Professor, ²Dr. R. Vani, Assistant Professor, ³Dr. Jijiya Bai P., Professor and Head, all authors are affiliated with Department of Pathology; Mallareddy Medical College for Women, Suraram, Hyderabad, Telangana, India.

Corresponding Author: Dr. R. Vani, Assistant Professor, Department of Pathology; Mallareddy Medical College for Women, Suraram, Hyderabad. E-mail: rvanimd@gmail.com

Abstract

Introduction: Abnormal uterine bleeding (AUB) is the most common complaint in the gynecology out-patient department with different presentations and varied causes. Endometrial sampling is needed to investigate the cause of AUB. **Aim:** This study was done to evaluate histopathology of endometrium and observe the incidence of various endometrial pathology patterns in different age groups presenting with abnormal uterine bleeding. **Materials and Methods:** The current study was done at Malla Reddy Medical College for Women, Hyderabad, India, on cases of abnormal uterine bleeding who underwent endometrial sampling. A statistical analysis between age of presentation and specific endometrial causes was done using χ^2 test. **Results:** We studied 231 cases. The most common pattern observed was normal cycling endometrium (56.27%). The other morphological patterns were endometrial hyperplasia (19.48%), disordered proliferative pattern (5.62%), complications of pregnancy (4.76%), benign endometrial polyp (2.6%), chronic endometritis (2.16%) and carcinoma (0.86%). The most common age group presenting with AUB was 40-49 years (47.18%) followed by 30-39 years (33.76%). Endometrial causes of AUB and age distribution was statistically significant with P value < 0.05. **Conclusion:** There is an age specific association of endometrial lesions. Atrophy and carcinoma endometrium are predominant in peri-menopausal and post-menopausal age. Endometrial curettings and biopsy proved to be an important diagnostic procedure for assessment and subsequent management of abnormal uterine bleeding.

Keywords: Abnormal uterine bleeding, Atrophic endometrium, Endometrial carcinoma, Endometrial hyperplasia, Endometritis

Introduction

Abnormal uterine bleeding (AUB) is a menstrual disorder affecting all age groups of women, at times reflecting serious underlying pathology [1]. It is defined as changes in frequency of menstruation, duration of flow, amount of blood loss or intermenstrual bleeding [2]. The cause of AUB varies according to the age, endometrial response to hormones and their variations and other structural lesions.

The FIGO Working Group on Menstrual Disorders has classified the various causes for AUB into structural/organic lesions and non-structural entities [3]. Endometrial sampling and subsequent histopathological study remain the gold standard for diagnosis of causes of AUB [4]. The endometrial histology shows different histopathological patterns in various causes of AUB.

Manuscript received: 14th March 2019

Reviewed: 24th March 2019

Author Corrected: 30th March 2019

Accepted for Publication: 4th April 2019

This study was carried out to evaluate and establish the most common patterns of endometrial histological findings and their incidence in women of different age groups presenting with AUB in MRMCW.

Material and Methods

Place, type and duration of study: This was a retrospective observational study done on cases of abnormal uterine bleeding who underwent endometrial sampling (endometrial curettage and biopsy) from May 2015 to May 2017 in the Department of Pathology, Malla Reddy Medical College for Women in collaboration with the Department of Obstetrics & Gynaecology.

Sampling methods and sample collection: Pertinent data like age, parity, menstrual history and drug history were collected. Patients were selected based on clinical details. The study material included a total of 231

Original Research Article

endometrial samples obtained in the pre-menstrual phase. Endometrial samples were obtained either by endometrial biopsy or dilatation and curettage under sedation as an office procedure. The samples were fixed in 10% formalin and sent to the histopathology laboratory. The gross morphology was recorded with total submission of endometrial samples.

The tissue bits were processed in automatic tissue processor and paraffin blocks were prepared. Tissue sections (4–6 μ) were cut and stained with hematoxylin and eosin stain (H&E). Microscopic examination was done by the pathologists. Hyperplasia was classified as benign (non-atypical) endometrial hyperplasia and atypical endometrial hyperplasia/ endometrioid intra-

epithelial neoplasia (EIN) as recommended by WHO in 2014 based on the architecture and cytologic features

Inclusion Criteria: Patients with isolated endometrial causes of abnormal uterine bleeding

Exclusion Criteria: 1. Patients with leiomyoma, cervical and vaginal pathology and systemic diseases like hypothyroidism and hemostatic disorders. 2. Unsatisfactory samples: Only blood clots and fibrin; no endometrial glands/stroma.

Statistical methods: The data collected for the study was statistically analysed using χ^2 test. P value < 0.05 was considered significant.

Results

Histopathologic examination of the 231 cases showed various patterns in AUB. Normal cyclical pattern showing proliferative and secretory phase in 130 patients (56.12%) was the most common finding. Hyperplasia was observed in 45 patients (19.47%) of which 3 patients presented with atypical endometrial hyperplasia.

Chronic endometritis was seen in 5 patients, including one case of tuberculous endometritis. Complications of pregnancy were seen in 11 (4.76%) cases with abortion being the predominant cause (7 cases); other causes were ectopic gestation, partial mole and complete mole.

A total of 13 /231 cases (5.62%) showed disordered proliferative pattern which were most commonly seen between 41 and 50 years of age. Atrophic endometrium in 13 cases was seen in elderly patients being most common above 40 years age. Carcinoma of the endometrium was seen in 2 cases (0.86%). The spectrum of histopathological diagnoses we encountered in endometrial biopsy is given in Table 1.

The age of the patients ranged from 20-75 years. The age group with the maximum number of patients was 40-49 years (47.18 %), followed by 30-39 years (33.76%). Table 2 depicts the age-wise distribution of endometrial histopathological patterns.

Table-1: Histopathological diagnoses of endometrial biopsy.

| Diagnosis | No of patients | Percentage |
|--------------------------------------|----------------|-------------|
| Proliferative endometrium | 70 | 30.3% |
| Secretory endometrium | 60 | 25.97% |
| Simple hyperplasia without atypia | 42 | 18.18% |
| Simple hyperplasia with atypia | 03 | 01.29% |
| Disordered proliferative endometrium | 13 | 5.62% |
| Atrophic | 13 | 5.62% |
| Pregnancy related complications | 11 | 4.76% |
| Endometrial Polyp | 06 | 2.60% |
| Pill Endometrium | 06 | 2.60% |
| Chronic endometritis | 05 | 2.16% |
| Carcinoma | 02 | 0.86% |
| Total | 231 | 100% |

Table-2: Endometrial histopathological diagnosis according to age group.

| Age group (years) | Endometrial histopathology | | | | | | | | | | |
|-------------------|----------------------------|-----------|--------------------|--------------------------|-----------|-----------|-------------------|------------------|----------------------|-----------|------------|
| | Proliferative | Secretory | Simple Hyperplasia | Disordered Proliferative | Atrophic | Pregnancy | Endometrial Polyp | Pill Endometrium | Chronic Endometritis | Carcinoma | Total |
| 20-29 | 5 | 4 | 1 | 0 | 0 | 10 | 0 | 1 | 1 | 0 | 22 |
| 30-39 | 25 | 21 | 20 | 4 | 1 | 01 | 2 | 3 | 1 | 0 | 78 |
| 40-49 | 39 | 32 | 20 | 7 | 5 | 0 | 2 | 1 | 2 | 1 | 109 |
| 50-59 | 1 | 02 | 0 | 2 | 3 | 0 | 2 | 1 | 1 | 1 | 13 |
| 60-69 | 0 | 1 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 7 |
| >70 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| Total | 70 | 60 | 45 | 13 | 13 | 11 | 06 | 06 | 05 | 02 | 231 |

Discussion

Abnormal Uterine Bleeding is known to arise from varied causes physiological, pathological or pharmacological and leads to considerable social and physical morbidity in all societies thus demanding appropriate evaluation and management. The evaluation of AUB requires adequate history [5] physical examination and laboratory investigations including imaging and endometrial sampling [2]. A plethora of conditions and causes lead to AUB in different age groups most of which can be diagnosed by studying the endometrium. Endometrial sampling is a safe office procedure with a high sensitivity to evaluate the endometrium. However, the procedure may miss focal lesions including polyps and fibroids since it has limited access to tubal cornua of the uterus. Hence a combination of directed endometrial biopsy and saline infusion hystero-graphy/ hysteroscopy is recommended to identify endometrial abnormalities [2].

In our study, the endometrial histopathologic pattern was determined taking into account the age of the patient, the date of onset of the last menstrual period, the length of menstrual cycle and iatrogenic use of hormones [5,6]. The most common endometrial histopathologic pattern observed was normal cycling endometrium. Normal cyclical endometrium including proliferative phase (30.3%) and secretory phase (25.97%) was seen in 56.27% of total cases and comparable to studies conducted by Vaidya et al (40.94%) & Sajitha et al (38.99%). Doraiswamy et al and Sushila Devi et al have also documented normal cyclical endometrium as the commonest observation in their studies [5,6,7,8]. This pattern was high between 30 and 49 years of age.

The bleeding in the proliferative phase may be due to anovulatory cycles and in the secretory phase (Figure 1) due to ovulatory dysfunctional uterine bleeding [8]. Endometrial study thus helps to differentiate ovulatory from anovulatory DUB. Anovulatory DUB is caused by a disturbed function of the hypothalamic-pituitary-ovarian axis most commonly in polycystic ovary syndrome and at the perimenarchal and perimenopausal years. During these stages of life, the cycles may be intermittently ovulatory & anovulatory, leading to great irregularity of menstruation and variability in blood loss [1,9]. It is observed that unopposed estrogen causes increased blood loss by various mechanisms [1]. Without sufficient progesterone to stabilize and differentiate the endometrium, the mucous membrane becomes fragile and sloughs irregularly. In ovulatory dysfunctional uterine bleeding the main defect appears to be in the control of processes regulating the volume of menstrual blood loss, primarily decreased endometrial vasoconstriction and vascular hemostatic plug formation [1] Although most causes of ovulatory dysfunction can be traced to endocrinopathies, the disorder may be iatrogenic caused by gonadal steroids or drugs that impact dopamine metabolism [3].

Disordered proliferative endometrium accounted for 5.62% of our cases with the highest incidence in 40-49 years age group. Disordered proliferative endometrium is common in the perimenopausal years because of anovulatory cycles [5,6]. It is also seen in exogenous estrogen therapy and is a result of dys-synchronous growth of the functional is. Morphologically disordered proliferative endometrium resembles normal proliferative tissue consisting of glands lined by cytologically bland, pseudostratified, proliferative, mitotically active epithelium and having a normal ratio of glands to stroma, but the glands may be cystically dilated or show shallow budding or tubular within abundant stroma. Metaplastic ciliated epithelium and evidence of endometrial breakdown may be seen. It differs from hyperplasia without cytologic

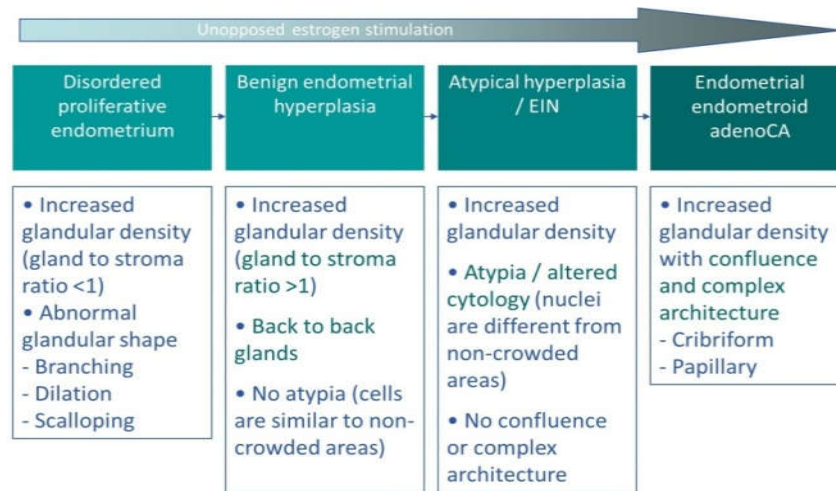
Original Research Article

atypia by virtue of its relatively normal gland: stroma ratio of 1:1 [10]. Endometrial hyperplasia amounts to 19.47% of the cases and most commonly seen in 30-49 years of age. The incidence of hyperplasia in other studies were 10%, 25% and 6% with the most common age group being 41-55yrs [6,7,8]. Endometrial hyperplasia thus is most common in the perimenopausal age group [11]. Unopposed estrogen stimulation in the perimenopausal age causes endometrial proliferation & hyperplasia which in turn leads to fragile mucous membrane and irregular sloughing [2]. There is a risk of endometrial hyperplasia progressing to carcinoma especially in obese women due to the increased availability of peripheral estrogens as a result of aromatization of androgens to estrogens in adipose tissue and lower concentration of sex-hormone-binding globulins. There in lies the importance of endometrial study in identifying endometrial hyperplasia with atypia, which is considered the precancerous condition for endometrial carcinoma.

There are many benign entities that simulate endometrial hyperplasia and need to be excluded before giving the diagnosis. Some such benign entities include cystic atrophy, disordered proliferative endometrium, secretory endometrium or Arias-Stella reaction, endometritis, endometrial polyps and benign papillary proliferations. In endometrial hyperplasia without atypia (Figure 2), there is an exaggerated proliferation of glands of irregular size and shape with increase in gland to stroma ratio compared to proliferative endometrium. In atypical hyperplasia/ EIN, hyperplasia is associated with cytological more specifically nuclear atypia. Criteria to be fulfilled for the diagnosis of EIN are – 1) Area of the glands exceeding that of stroma, 2) cytology differing between architecturally crowded focus and background-that is, cytological demarcation, 3) Maximum linear dimension of the lesion exceeding 1mm, 4) Exclusion of benign mimics, 5) Exclusion of carcinoma [5] The cytology of atypical glands when compared with adjacent normal endometrial glands helps establish nuclear atypia. Nuclear features of atypical hyperplasia include enlargement, pleomorphism, rounding, loss of polarity and nucleoli.

A continuum exists between disordered proliferative endometrium and hyperplasia without atypia, both benign conditions related to prolonged estrogenic stimulation. Continuous unopposed estrogenic stimulation leads to progression of hyperplasia without atypia to atypical hyperplasia/ EIN. Postmenopausal women with high concentrations of estrogen are at a higher risk for developing endometrioid carcinoma. Table 3 [12].

Table-3: Progression of lesions following continual estrogen stimulation.



Atrophic endometrial pattern was seen in 5.62% cases with more than half of them (53.84%) occurring after 50 yrs of age. In atrophic endometrium the epithelium lining the glands are mitotically inactive and bland in terms of cytological appearance. The glandular architecture may be cystic or budded. These glands are embedded in a inactive spindled stroma. Cystic atrophy is the term applied to endometria composed of cystically dilated glands lined by cuboidal to flattened epithelial cells. Various studies on women of all age groups have shown an incidence of atrophic endometrium ranging from 1.1, 4.1 to 5.13% [6,7,11]. Among postmenopausal bleeding cases, atrophy formed the bulk of AUB (50%) in study conducted by Divya et al. Although the exact cause of bleeding in atrophic endometrium is not known, it is postulated to be due to anatomic vascular variations or local abnormal hemostatic mechanisms. Thin walled veins superficial to the expanding cystic glands make the vessels vulnerable to injury [8]. Pregnancy related complications accounted for 4.76% of our cases and the majority of them were in 20 to 29 years age group. It is imperative that they occur in the reproductive period of life. The incidence correlates with other studies [4,8].

Original Research Article

Endometrial carcinoma accounted for 2 out of 231 cases (0.86%), one case from 40-49 yrs and 50-59yrs age group each. Both were the usual type endometrioid adenocarcinoma (Figure 3). Patients with endometrial adenocarcinoma fall into two clinicopathologic clusters. Patients in first group (type-1) tend to be between 40 and 60 years of age. These patients may have a history of chronic anovulation or estrogen hormone replacement therapy, and the carcinomas are usually well differentiated, stage 1 non-myoinvasive tumors with endometrioid histology, mostly associated with endometrial hyperplasia. Most of these tumors are estrogen receptor (ER) positive and progesterone receptor (PR) positive and p53 negative and express low levels of proliferation antigen ki-67, have a very favorable prognosis after hysterectomy. Patients in the second group (type-2) tend to be elderly and typically have no history of hyperestrogenism. In these cases, surrounding nonneoplastic endometrium is almost always atrophic, and there is an insitu component with high-grade cytologic features. The carcinomas that develop in this group of patients are usually of the special variant types like uterine serous and clear cell carcinomas, with poor prognosis. These type-2 tumors tend to be ER/PR negative, strongly express p53, and show high ki-67 labelling these patients are often not cured by hysterectomy. The risk factors for endometrial cancer include anovulatory cycles, obesity, nulliparity, age greater than 35 years, diabetes and tamoxifen therapy. As the risk of endometrial carcinoma increases with age, the American College of Obstetricians and Gynecologists recommends endometrial evaluation in women aged 35 years and older who have abnormal uterine bleeding [2,6]. Endometrial carcinoma thus is commonly seen in the peri- and post menopausal age group [13,14] and post menopausal bleeding in women receiving hormone therapy for more than 12 months definitely needs endometrial study to rule out carcinoma. The incidence of carcinoma is low in our study like Doraiswamy et al and Rupal Shah et al probably because of early detection, but higher in other studies - Divya and Sajita et al.

Endometrial polyp and chronic endometritis made up 2.6% and 2.16% respectively similar to that of Rupal Shah et al(2.6% and 2.6%). Out of the 5 cases of chronic endometritis, one was tuberculous showing wellformed caseating granulomas. Pill endometrium forms 2.6% of the cases.

Endometrial polyps are polypoid structures with a fibrous stroma containing large, thick-walled, coiled vessels showing cystically dilated and occasionally crowded glands lined by inactive, atrophic to weakly proliferative endometrium. Many undergo spontaneous regression. Endometrial tissue from lower uterine segment may be confused with endometrial polyp as the stroma has a fibrous appearance and glands are few in number. The absence of thick-walled stromal blood vessels and the characteristic admixture of mucinous endocervical epithelium suggests an origin from the lower uterine segment [5] Endometrial polyps in postmenopausal women have shown significant increased association with malignancy. Careful microscopic search for malignancy in postmenopausal women with multiple risk factors is advised in daily surgical pathology practice [15].

The presence of more than rare plasma cells is absolutely necessary for a diagnosis of chronic endometritis (Figure4). It is usually associated with lymphocytes, lymphoid follicles, neutrophils and histiocytes. The stroma is spindled or fibroblastic often with stromal breakdown and glandular destruction. Chronic endometritis is usually encountered in the context of pelvic inflammatory disease, in association with the use of intra uterine device or in connection with retained products of conception. Mild non-specific chronic endometritis has been associated with symptomatic bacterial vaginosis, in which potentially pathogenic aerobic and anaerobic organisms replaces the normal flora of genital tract. Granulomatous endometritis is seen in sarcoidosis, tuberculosis and other granulomatous diseases. Tuberculous endometritis is a relatively common cause of infertility. Xanthomatous endometritis seen most often in elderly women is almost exclusively associated with cervical stenosis and pyometra.

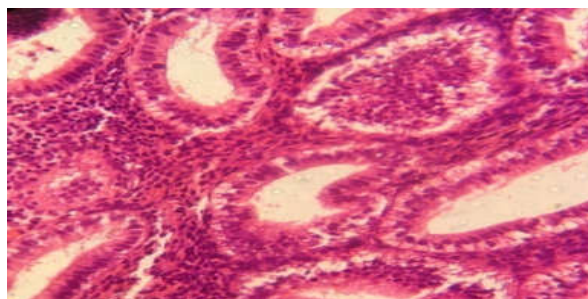


Figure 1

Figure 1: Secretory endometrium. Tortuous glands with prominent subnuclear vacuoles and edematous stroma (H&E, X40)

Original Research Article

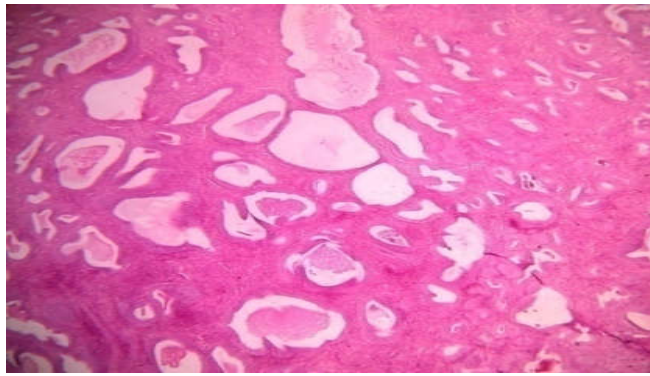
**Figure 2**

Figure 2: Endometrial benign/non-atypical hyperplasia. proliferation of endometrial glands with increase in gland: stroma ratio of $>1:1$ (H&E, X10)

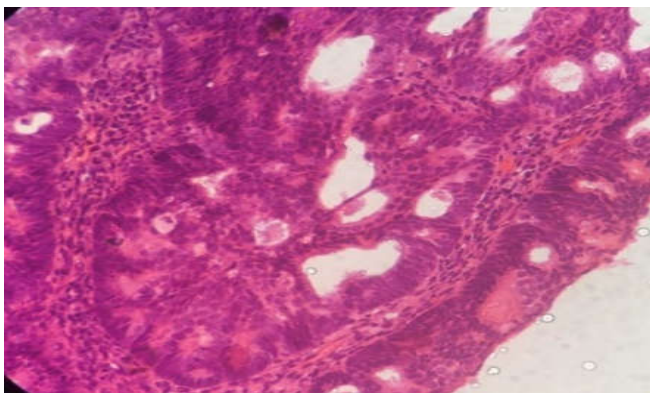
**Figure 3**

Figure 3: Endometrial carcinoma. Endometrial glands are arranged in back to back architecture with lack of intervening stroma and cytological atypia (H&E, X40)

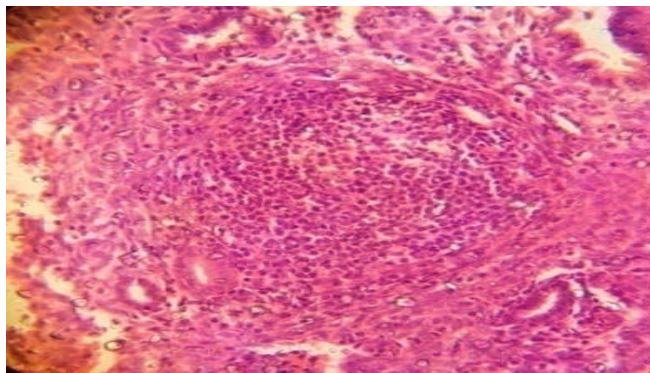
**Figure 4**

Figure 4: Chronic endometritis showing well-formed lymphoid follicle (H&E, X40)

The details of any hormonal therapy should be provided by the clinician to the pathologist since hormones have varying effects on the endometrium and cause abnormal uterine bleeding. The unpredictable bleeding and spotting caused by continuous exposure of endometrium to relatively constant doses of progestogen with simultaneous low levels of estrogen results in a variety of endometrial histological picture showing a weak secretory to complete atrophic pattern [1]. Progestogen-only compounds result in a characteristic atrophic or weak secretory-type gland in an expanded stroma that exhibits varying degrees of pseudo-decidualisation. This pseudo-decidualisation is most prominent just beneath the surface glands and is accompanied by mononuclear inflammatory infiltrate [5].

Conclusion

The study of the endometrium in AUB revealed many structural and functional causes manifest in the form of different endometrial histopathological patterns.

As the endometrial physiology varies with age & reproductive function, the mechanism & presentation of AUB and the resultant endometrial pathology also varies in different age groups.

Thus most causes of AUB have specified age predilection. Endometrial study gives significant etiological information in AUB when interpreted with relevance to age and other clinical data, thus guiding the appropriate management.

Contribution by authors:Dr. Vani BS and Dr.RVani have contributed to conception and design of the study, and compilation and interpretation of data.

Dr Jijiyai Bai has given final approval of the drafted article.

What this study adds to existing knowledge ?

Although endometrial sampling is not mandatory in functional abnormal bleeding which usually occurs in the reproductive age, discretion should be exercised in cases with significant morbidity.

Endometrial study should be considered in perimenopausal age wherein the incidence of atypical endometrial hyperplasia and early stages of carcinoma is more common thus exercising timely management with low morbidity.

Key Messages- Endometrial evaluation

1. Requires adequate clinical data, including details of hormone administration.
2. Helps differentiate ovulatory from anovulatory dysfunctional uterine bleeding, hence directing appropriate treatment.
3. Detects hyperplasia with atypia if present, which are preneoplastic, thus helping in early management and prevention of malignant transformation.
4. Unopposed estrogen stimulation leads to a sequence of events from disordered proliferative endometrium through hyperplasia without atypia and atypical hyperplasia to endometrial carcinoma.

Findings: Nil; **Conflict of Interest:** None initiated

Permission from IRB: Yes

References

1. Livingstone M, Fraser IS. Mechanisms of abnormal uterine bleeding. *Hum Reprod Update*. 2002 Jan-Feb;8(1): 60-7.
2. Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. *Am Fam Physician*. 2004 Apr 15;69(8):1915-26
3. Munro MG, Critchley HOD, Broder MS, Fraser IS. FIGO classification system (PALM-COIEN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynecol Obstet* 2011;113(1):3-13. doi:10.1016/j.ijgo.2010.11.011
4. Khan R, Sherwani RK, Rana S, Hakim S, Jairajpuri ZS. Clinico-Pathological Patterns in Women with Dysfunctional Uterine Bleeding. *Iran J Pathol* 2016; 11(1): 20-26.
5. McCluggage WG. My approach to the interpretation of endometrial biopsies and curettings. *J Clin Pathol*. 2006 Aug;59(8):801-12.
6. Sajitha K, Padma SK, Shetty KJ, Kishan Prasad HL, Permi HS, Hegde P. Study of histopathological patterns of endometrium in abnormal uterine bleeding. *CHRISMED J Health Res* 2014;1(2):76-81. doi:10.4103 / 2348-3334.134265
7. Vaidya S, Lakhey M, Vaidya S, et al. Histopathological pattern of abnormal uterine bleeding in endometrial biopsies. *Nepal Med Coll J*. 2013 Mar; 15(1):74-7.
8. Doraiswami S, Johnson T, Rao S, et al. Study of endometrial pathology in abnormal uterine bleeding. *J Obstet Gynaecol India*. 2011 Aug; 61(4):426-30. doi: 10.1007/s13224-011-0047-2. Epub 2011 Sep 22.
9. Devi LS, Singh MR, Singh LR, Debnath K. The histological and histochemical study of endometrium in dysfunctional uterine bleeding. *J Med Soc* 2012; 26(3):167-70. doi: 10.4103/0972-4958.113240
10. Longacre TA, Atkins KA, Kempson RL, Hendrickson MR. The Uterine Corpus. In: Mills S editor. *Sternberg's Diagnostic Surgical Pathology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
11. Shah RJ, Dayal A, Kothari SL, Patel SM, Dalal B. Histopathological interpretation of endometrium in abnormal uterine bleeding. *Int J Med Sci Public Health* 2014; 3(4):452-456. doi:10.5455/ijmsph.2014.12022

Original Research Article

12. Parra-Herran C. Endometrial hyperplasia – general. Pathology Outlines.com website. <http://www.pathologyoutlines.com/topic/uterusendometrialhyperplasiageneral.html>. Accessed March 27th, 2019.

13. Divya KN, Jayashree K, Bharath C. The Diagnostic Value of Endometrial Biopsy in Postmenopausal Uterine Bleeding. Indian Journal of Pathology: Research and Practice 2017; 6 (1): 45-51. doi:<http://dx.doi.org/10.21088/ijprp.2278.148X.6117.7>

14. Desai K, Patole KP, Kathaley M. Endometrial Evaluation by Histopathology in Abnormal Uterine Bleeding in Perimenopausal and Postmenopausal Patients. MVP Journal of Medical Sciences 2014 Jul;1 (2) : 75-79.

15. Hileto D, Fadare O, Martel M, Zheng W. Age dependent association of endometrial polyps with increased risk of cancer involvement. World J Surg Oncol. 2005; 3:8. doi:[10.1186/1477-7819-3-8](https://doi.org/10.1186/1477-7819-3-8).

.....
How to cite this article?

Vani B. S, Vani R, Jijiya Bai P. Histopathological evaluation of endometrial biopsies and curetting's in abnormal uterine bleeding. Trop J Path Micro 2019;5(4):190-197. doi:[10.17511/jopm.2019.i04.02](https://doi.org/10.17511/jopm.2019.i04.02).
.....