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The Histomorphological Examination of Endometrium in Cases of Abnormal Uterine Bleeding

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Abstract

Background: Abnormal uterine bleeding (AUB) is a frequent gynecological issue and histopathological evaluation of the endometrium is considered the definitive diagnostic method. Endometrial sampling is necessary to determine the underlying cause of abnormal uterine bleeding (AUB). **Aim:** This study was conducted to assess the histopathology of the endometrium and to observe the frequency of different endometrial pathology patterns across various age groups presenting with abnormal uterine bleeding. **Material and Methods:** The current study was done at Department of Pathology in Chamarajanagar Institute of Medical Sciences and Hospital, Chamarajanagar, Karnataka., on cases of abnormal uterine bleeding who underwent endometrial sampling by Dilatation and curettage (D and C), endometrial biopsy and hysterectomy. A statistical analysis between age of presentation and specific endometrial causes was done using $\chi 2$ test. **Results:** We studied 200 cases. The most common pattern observed was normal cycling endometrium (32.5%). The other morphological patterns were endometrial polyp (20%), atrophic phase pattern (19.5%) Endometrial Hyperplasia without Atypia (18%), disordered proliferative pattern and carcinoma (2.5%), Atypical hyperplasia (1.5%) and chronic endometritis (0.5%). The most common age group presenting with AUB was 36-45 years (47.18%) followed by 46-55years (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, endometrial hyperplasia and carcinoma endometrium are predominant in peri-menopausal and post-menopausal age. The study of various endometrial patterns in females with AUB is helpful in achieving accurate diagnosis and guiding appropriate treatment.

Keywords: AUB, Hyperplasia, Atypia, Carcinoma

1 Introduction

Abnormal uterine bleeding (AUB) is a comprehensive term used to define menstrual cycle irregularities, including changes in frequency, regularity, duration, and the volume of flow, occurring outside of pregnancy. A normal menstrual cycle has a frequency of 24 to 38 days and lasts for 2 to 7 days, with 5 to 80 milliliters of blood loss. Variations in any of these 4 parameters constitute abnormal uterine bleeding [1].

The causes of AUB differ based on factors such as age, the endometrium's response to hormonal changes, and other structural abnormalities [2]. The FIGO Working Group on Menstrual Disorders has categorized the causes of AUB into structural or organic lesions and non-structural factors. Endometrial sampling, along with histopathological examination, remains the definitive gold standard for diagnosing the causes of AUB. Endometrial histology reveals various histopathological patterns corresponding to different causes of AUB [3, 4]. Numerous women with abnormal uterine bleeding may undergo unnecessary hysterectomies without receiving a definitive diagnosis [4]. In women aged 40 years and older, and particularly in menopausal patients, it is essential to evaluate and confirm the benign nature of the condition. This ensures that medical treatments or conservative surgical options can be considered, thereby avoiding unnecessary radical surgeries [5]. This study aims to identify the range of endometrial pathologies in patients from various age groups presenting with AUB at our hospital, which primarily serves women from rural areas.

1.1 Objectives

- To study the histopathology of the endometrium in AUB.
- To observe the frequency of different endometrial pathology patterns.
- To study the distribution frequency of various patterns of endometrial pathology in various age groups.

2 Material and Methods

Type of Study: A prospective study was carried out.

Setting: At the Department of Pathology in Chamarajanagar Institute of Medical Sciences and Hospital, Chamarajanagar.

Duration of study: 1 year study from 1st November 2023 to 31st October 2024.

Sample size: Total of 200 endometrial samples were collected from patients presenting with AUB.

Sampling Methods: Endometrial samples received at the Department of Pathology were collected by Dilatation and curettage (D and C), endometrial biopsy and hysterectomy specimen from women presenting with AUB.

Inclusion Criteria: Patients presenting with AUB complaints.

Exclusion criteria:

- Patients with cervical, vaginal and fibroid pathology.
- Patients with systemic diseases like haemostatic disorders.
- Unsatisfactory samples: Only blood clots and fibrin; no endometrial glands/stroma.

Data collection procedure: Data were gathered in the Pathology laboratory over one-year period for evaluation. Additional patient details were obtained from the Medical Records Department, and the histopathological reports for all cases were collected from the Pathology Department.

Data analysis procedure: The collected data were classified based on different endometrial morphologies. The histopathological findings of AUB were divided into functional and organic causes. Functional causes included in this study comprised normal cyclical endometrium (proliferative and secretory phases) as well as abnormal endometrial changes, such as atrophic endometrium, disordered proliferative endometrium, deficient secretory phase, and irregular shedding. Organic intrauterine lesions identified as causes of AUB in this study included chronic endometritis, endometrial hyperplasia, benign endometrial polyps, and endometrial carcinoma.

3 Results

Table 1: Frequency of Different Histopathological Patterns of Endometrial Specimens by D&C or Hysterectomy (n=200)

Histopathological Pattern	No. of Patients	Percentage
Proliferative	50	25
Secretory	15	7.5
Atrophic	39	19.5
Disordered proliferative endometrium	05	2.5
Chronic Endometritis	01	0.5
Endometrial Polyp	40	20
Endometrial Hyperplasia without Atypia	36	18
Atypical hyperplasia	03	1.5
Endometrial Carcinoma	05	2.5
TOTAL	200	100

Table 2: Histopathological Patterns of Endometrium according to Age Group in Years

Histopathological Pattern	25-35 year	36-45 year	46-55 year	56-65 year
Proliferative	23	15	10	02
Secretory	8	7	2	0
Atrophic	0	2	9	30
Disordered proliferative endometrium	1	3	1	0
Chronic Endometritis	0	1	0	0
Endometrial Polyp	10	20	8	2
Simple Hyperplasia without Atypia	2	10	18	6
Atypical hyperplasia	0	1	2	0
Endometrial Carcinoma	0	0	2	3

3 Discussion

AUB can result from a range of causes, including physiological, pathological, or pharmacological factors, and it significantly contributes to social and physical morbidity across all societies, necessitating proper evaluation and management [6]. The assessment of AUB involves a thorough medical history, physical examination, and laboratory investigations, which may include imaging and endometrial sampling. The endometrium reflects the hormonal status in women. Its histological variations depend on the woman's age, the phase of the menstrual cycle, and the presence of any specific pathology [7]. In the present study, AUB was most commonly seen in the age group of 36–45-years.

The most common endometrial histopathological pattern observed was normal cyclical endometrium. Normal cyclical endometrium including proliferative phase (25%). This case (7.5%) was seen in 32.5% of total cases and comparable to studies conducted by Mune, *et al.,* (33.9%), Sajitha, *et al.,* (38.99%) and Vani B. S., *et al.,* (56.27%) [8-10] have also documented normal cyclical endometrium as the commonest observation in their studies. This pattern was high between 25 and 35 years of age. In a normal menstrual cycle, endometrial shedding is followed by proliferation driven by estrogen stimulation. During this phase, the endometrial glands grow and become tortuous (Fig. 1). In the second half of the cycle, secretory activity is marked by endothelial proliferation, wall thickening, and coiling, leading to the formation of spiral arterioles by the ninth post-ovulatory day (Fig. 2). Abnormal Uterine Bleeding (AUB) is one of the most common and complex issues affecting women across all age groups. Bleeding during the proliferative phase may result from anovulatory cycles, while bleeding in the secretory phase is often associated with ovulatory dysfunctional uterine bleeding (DUB). Studying the endometrium aids in distinguishing between ovulatory and anovulatory DUB [11].

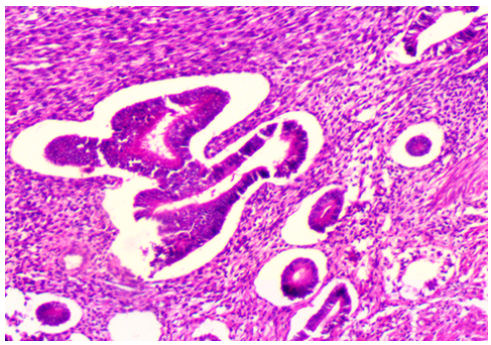

Fig. 1: Endometrium in Proliferative phase (H&E, 40x)

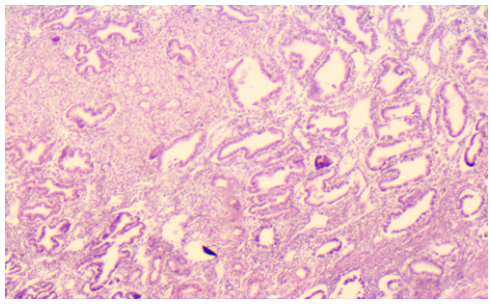

Fig. 2: Endometrium in Secretory phase (H&E, 40x)

Disordered proliferative endometrium accounted for 2.5% of cases in our study, with the highest incidence observed in 36-45years age group. This condition is common during the perimenopausal years due to anovulatory cycles [6, 10]. It can also occur with exogenous estrogen therapy and results from

dysnchronous growth of the functional layer. Morphologically, disordered proliferative endometrium resembles normal proliferative tissue, characterized by glands lined with cytologically bland, pseudostratified, proliferative, mitotically active epithelium and maintaining a normal gland-to-stroma ratio of 1:1 (Fig. 3). However, the glands may exhibit cystic dilation, shallow budding, or tubular shapes within abundant stroma. Features such as metaplastic ciliated epithelium and signs of endometrial breakdown may also be present. Unlike hyperplasia without cytologic atypia, disordered proliferative endometrium retains a relatively normal gland-to-stroma ratio [12].

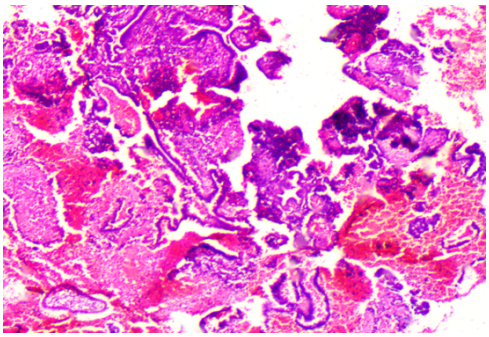

Fig. 3: Disordered proliferative endometrium (H&E, 40x)

Endometrial hyperplasia amounted to 19.5% of the cases and was most commonly seen in 46-55 years of age in the present study. The incidence of hyperplasia in other studies were 22.2%, 39% and 19.47% with the most common age group being 41-55yrs (Table. 2). Endometrial hyperplasia is most commonly observed in the perimenopausal age group [13]. During this phase, unopposed estrogen stimulation results in endometrial proliferation and hyperplasia, leading to a fragile mucous membrane and irregular sloughing [7]. The condition carries a risk of progression to carcinoma, particularly in obese women, due to the increased availability of peripheral estrogens. This occurs through the aromatization of androgens to estrogens in adipose tissue, coupled with lower concentrations of sex-hormone-binding globulins. Therefore, studying the endometrium is crucial for identifying endometrial hyperplasia with atypia, which is recognized as a precancerous condition for endometrial carcinoma [8].

Several benign conditions can mimic endometrial hyperplasia and must be ruled out before establishing a diagnosis. Examples of such conditions include cystic atrophy, disordered proliferative endometrium, secretory endometrium or Arias-Stella reaction, endometritis, endometrial polyps, and benign papillary proliferations. In cases of endometrial hyperplasia without atypia, there is a marked proliferation of glands that vary in size and shape, with an increased gland-to-stroma ratio compared to the proliferative endometrium (Fig. 4). In contrast, atypical hyperplasia, also referred to as EIN (Endometrial Intraepithelial Neoplasia), is characterized by hyperplasia combined with cytological abnormalities, particularly nuclear atypia [6] (Fig. 5).

The diagnostic criteria for EIN include [8]:

- A glandular area exceeding the stromal area.
- Cytological differences between the architecturally crowded focus and the background tissue, referred to as cytological demarcation. A lesion with a maximum linear dimension greater than 1 mm.
- Exclusion of benign mimicking conditions.
- Exclusion of carcinoma.

The presence of nuclear atypia is established by comparing the cytology of atypical glands with adjacent normal endometrial glands. Typical nuclear features of atypical hyperplasia include enlargement, pleomorphism, rounding, loss of polarity and the presence of nucleoli [8].

There is a continuum between disordered proliferative endometrium and hyperplasia without atypia, both of which are benign conditions linked to prolonged estrogenic stimulation. Persistent unopposed estrogen stimulation can result in the progression of hyperplasia without atypia to atypical hyperplasia/EIN. Postmenopausal women with elevated estrogen levels are particularly at risk of developing endometrioid carcinoma [14].

Atrophic endometrial pattern was seen in 19.5% cases with more than half of them occurring after 50 years of age. In atrophic endometrium, the glandular epithelium is mitotically inactive and exhibits a bland cytological appearance. The glandular architecture can appear cystic or budded and these glands are surrounded by an inactive, spindle-shaped stroma. The term "cystic atrophy" refers to endometrium characterized by cystically dilated glands lined with cuboidal to flattened epithelial cells (Fig. 6).

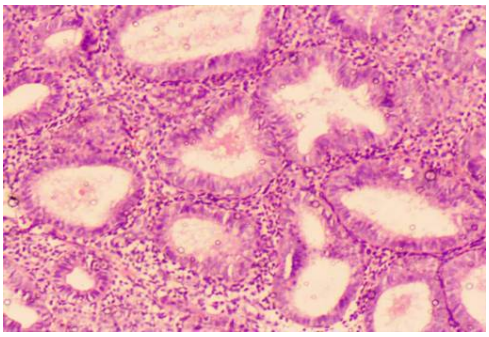

Fig. 4: Endometrium in Simple hyperplasia without atypia (H&E, 40x)

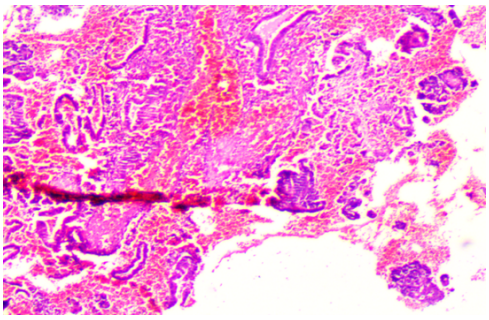

Fig. 5: Endometrium in Atypical hyperplasia / EIN (H&E, 40x)

While the exact mechanism of bleeding in atrophic endometrium remains unclear, it is hypothesized to result from anatomical vascular variations or localized abnormal hemostatic mechanisms. Thin-walled veins located superficially to the expanding cystic glands are particularly susceptible to injury, making them a likely source of bleeding [15].

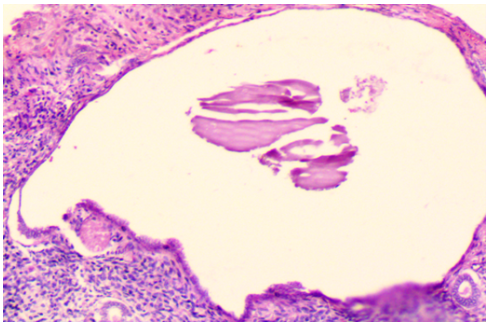

Fig. 6: Endometrium showing Cystic atrophy (H&E,40x)

Endometrial carcinoma was observed in 5 out of 200 cases (2.5%) in this study, with two cases occurring in the 46–55 years age group and three cases in the 56–65 years age group. Four cases were classified as the usual type of endometrioid adenocarcinoma (type-1) and one case classified as endometrioid adenocarcinoma with mucinous differentiation (Fig. 8).

Type-1 tumors are more common in patients aged 40–60 years and are often associated with a history of chronic anovulation or estrogen hormone replacement therapy. These carcinomas are typically well-differentiated, stage 1 tumors with endometrioid histology and minimal or no myometrial invasion (Fig. 7). They are frequently linked to endometrial hyperplasia and are usually estrogen receptor (ER) positive, progesterone receptor (PR) positive, p53 negative and exhibit low levels of the proliferation antigen Ki-67. Type-1 tumors have a very favourable prognosis following hysterectomy [7, 10].

Type-2 tumors, on the other hand, occur in older patients, usually without a history of hyperestrogenism. The surrounding non-neoplastic endometrium in these cases is almost always atrophic, and an in situ component with high-grade cytologic features is typically present. These tumors are often of special variants, such as uterine serous and clear cell carcinomas, which are associated with a poor prognosis. Type-2 tumors are generally ER/PR negative, strongly express p53, and show high Ki-67 labeling. Unlike Type-1, these tumors are often not cured by hysterectomy [7, 10].

Risk factors for endometrial carcinoma include anovulatory cycles, obesity, nulliparity, age over 35 years, diabetes, and tamoxifen therapy. Given the increased risk of endometrial carcinoma with age, the American College of Obstetricians and Gynecologists recommends endometrial evaluation for women aged 35 years or older who present with abnormal uterine bleeding [7, 10].

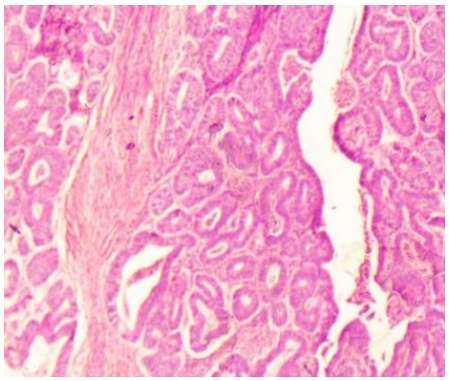

Fig. 7: Well formed glandular architecture in Type-I Endometrioid adenocarcinoma (H&E, 10x)

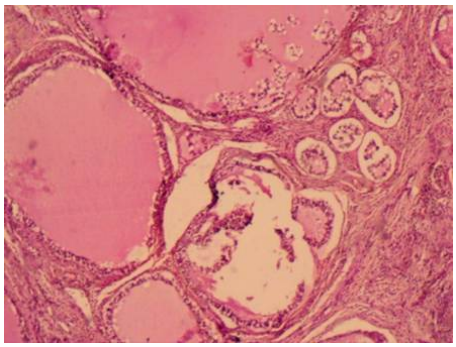

Fig. 8: Type-I Endometrioid adeno-carcinoma with mucinous differentiation (H&E, 10x)

Endometrial carcinoma is most frequently seen in peri and postmenopausal women [16, 17]. Postmenopausal bleeding in women undergoing hormone therapy for more than 12 months warrants an endometrial study to rule out carcinoma [10, 17].

Endometrial polyps are polypoid formations consisting of a fibrous stroma that contains large, thick-walled, coiled vessels. They feature cystically dilated and occasionally crowded glands, which are lined by inactive, atrophic, or weakly proliferative endometrium. In many cases, these polyps undergo spontaneous regression [6]. Endometrial polyps in postmenopausal women have been found to have a significantly increased association with malignancy. Therefore, a thorough microscopic examination for malignancy is recommended in postmenopausal women, particularly those with multiple risk factors, as part of routine surgical pathology practice [18].

For a diagnosis of chronic endometritis, the presence of more than rare plasma cells is essential. It is typically accompanied by lymphocytes, lymphoid follicles, neutrophils, and histiocytes. The stroma often appears spindled or fibroblastic, with evidence of stromal breakdown and glandular destruction. Chronic endometritis is commonly encountered in cases of pelvic inflammatory disease, the use of intrauterine devices or retained products of conception [8].

Mild, nonspecific chronic endometritis has been linked to symptomatic bacterial vaginosis, a condition in which pathogenic aerobic and anaerobic organisms replace the normal genital tract flora. Granulomatous endometritis occurs in conditions like sarcoidosis, tuberculosis, and other granulomatous diseases. Tuberculous endometritis, in particular, is a relatively common cause of infertility. Xanthomatous endometritis, most often seen in elderly women, is almost exclusively associated with cervical stenosis and pyometra [8].

Clinicians should provide detailed information about any hormonal therapy to the pathologist, as hormones can have diverse effects on the endometrium and contribute to abnormal uterine bleeding. Continuous exposure of the endometrium to relatively constant doses of progestogen, along with low estrogen levels, often leads to unpredictable bleeding and spotting. This results in a range of endometrial histological patterns, from weak secretory changes to complete atrophy [19].

Progestogen-only compounds typically produce a characteristic histological appearance, with atrophic or weak secretory-type glands embedded in an expanded stroma. This stroma often exhibits varying degrees of pseudo-decidualization, which is most prominent just beneath the surface glands and is accompanied by mononuclear inflammatory infiltration [6].

Table 3: Comparison of Different studies in percentage relating to Histological pattern

Histological pattern	Present study	Mune *et al.*	Sajitha *et al.*	Vani B. S. *et al.*
Normal cyclical pattern (Proliferative + Secretory)	32.5%	33.9	38.99	56.27
Atrophic	19.5	13.2	8	5.62
Disordered proliferative endometrium	2.5	13.7	12.2	5.62
Chronic Endometritis	0.5	2.4	0.64	2.16
Endometrial Polyp	20	8	5.12	2.60
Endometrial Hyperplasia without Atypia	18			18.18
Atypical hyperplasia	1.5	22.2	39	1.29
Endometrial Carcinoma	2.5	2.3	7	0.86

5 Conclusion

Numerous structural and functional factors that show up as various endometrial histopathology patterns were identified by the endometrium study in AUB. The etiology, presentation and resulting endometrial pathology of AUB vary by age group, much as the endometrial physiology varies with age and reproductive function. As a result, the majority of AUB causes have a specific age preference. When interpreted in light of age and other clinical data, endometrial studies provide important etiological information in AUB, directing the proper course of treatment.

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