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# COMPREHENSIVE IMMUNOHISTOCHEMICAL AND DEMOGRAPHIC ANALYSIS OF ER, PR, AND HER2/NEU IN ENDOMETRIAL BIOPSIES OF PATIENTS WITH ABNORMAL UTERINE BLEEDING: A PROSPECTIVE STUDY

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## Abstract

**Background:** Abnormal Uterine Bleeding (AUB) presents a significant clinical challenge in gynecological practice, encompassing a spectrum of disorders that disrupt the normal menstrual cycle. This study aims to conduct a comprehensive analysis of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression in endometrial biopsies from women diagnosed with abnormal uterine bleeding (AUB), alongside evaluating demographic characteristics, bleeding patterns, and histopathological diagnoses. **Materials and Methods:** The study included 209 women with AUB who underwent diagnostic endometrial biopsies. Patient demographics were categorized by age (reproductive, perimenopausal, postmenopausal) and parity (nulliparous, low parity, multiparous). Bleeding patterns (menorrhagia, polymenorrhoea, metrorrhagia, postmenopausal bleeding, menometrorrhagia) were recorded. Histopathological patterns were analyzed for correlation with age groups and bleeding types. The study also differentiated between non-organic and organic causes of AUB. Immunohistochemistry was used to assess ER, PR, and HER2/neu expression. **Result:** The majority (52.16%) of participants were of reproductive age, with menorrhagia being the most prevalent symptom (45%). Histopathological analysis showed a high incidence of proliferative phase changes (52.63%) and secretory phase changes (14.83%). Non-organic causes of AUB were predominant (80.9%), suggesting potential for non-surgical treatments. A significant proportion of premalignant (60.6%) and malignant (6.06%) lesions were identified, emphasizing the importance of routine histopathological evaluation in AUB. ER and PR expression varied across lesions, but no significant association between receptor expression and atypical presence was found (ER p-value: 0.2, PR p-value: 0.4). **Conclusion:** The study underscores the complexity of AUB, highlighting the importance of personalized diagnostic and treatment approaches. It challenges traditional reliance on surgical interventions, advocating for a nuanced understanding of AUB etiology.

## INTRODUCTION

Abnormal Uterine Bleeding (AUB) presents a significant clinical challenge in gynecological practice, encompassing a spectrum of disorders that disrupt the normal menstrual cycle. AUB can have a profound impact on a woman's physical, emotional, and social well-being.[1] AUB is defined by bleeding that deviates from normal volume, duration, frequency, or regularity and occurs outside of pregnancy. Its prevalence varies, but it is notably more common during the reproductive extremes – the adolescent and perimenopausal years.[2] The etiology of AUB is multifaceted, ranging from benign causes like hormonal imbalances to more serious conditions, including malignancies.[3] The FIGO (International Federation of Gynecology and Obstetrics) classifies AUB into nine categories (PALM-COEIN), focusing


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on structural and non-structural causes, thereby facilitating a systematic diagnostic and therapeutic approach.[4]

Estrogen and progesterone receptors (ER and PR) play crucial roles in endometrial physiology and pathology.[5] Their expression patterns in the endometrium are key factors in the pathogenesis of various menstrual disorders. Altered receptor expression has been associated with conditions such as endometrial hyperplasia and carcinoma. The HER2/neu oncogene, known for its role in breast cancer, has also been studied in the context of endometrial pathology, although its significance remains less clear.[6]

This study is grounded in the hypothesis that immunohistochemical analysis of ER, PR, and HER2/neu in endometrial tissues can provide deeper insights into the pathophysiology of AUB. A thorough understanding of these molecular patterns is crucial for advancing diagnostic precision and tailoring individualized treatment strategies.

The demographic aspect of this study considers age and parity as critical factors. Women's reproductive life is divided into distinct phases - reproductive age, perimenopause, and postmenopause, each with unique hormonal milieu influencing endometrial biology. Parity, the number of times a woman has given birth, also has implications for AUB. Nulliparous women, those without a history of childbirth, might exhibit different patterns and causes of AUB compared to women who have had multiple pregnancies.

Patterns of bleeding, an integral part of AUB diagnosis, vary significantly. Menorrhagia, or heavy menstrual bleeding, is the most common symptom, while other patterns include polymenorrhoea (frequent menstruation), metrorrhagia (irregular, non-cyclical bleeding), and postmenopausal bleeding. Understanding these patterns in conjunction with histopathological findings is vital for accurate diagnosis and effective management.

The histopathological examination in AUB offers valuable insights into the uterine environment. Conditions like proliferative and secretory phase patterns, endometrial hyperplasia, and atrophic changes are observed and analyzed in correlation with demographic and bleeding data. Such an analysis provides a holistic view of AUB, highlighting potential etiologies and guiding therapeutic decisions.

**Aims and Objectives**

This study's primary goal is to thoroughly analyze histopathological patterns in endometrial biopsies from individuals experiencing abnormal uterine bleeding (AUB), with a specific focus on Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2/neu expression in premalignant and malignant cases. Objectives include describing AUB-related histopathological patterns, categorizing AUB causes based on age and bleeding patterns, distinguishing functional and organic causes, and scrutinizing ER, PR, and HER2/neu levels in endometrial hyperplasia and carcinoma. This research aims to predict hyperplasia progression to carcinoma, enabling early non-surgical treatment and assessing endometrial carcinoma prognosis, ultimately benefiting patient care.

## MATERIALS AND METHODS

**Study Design:** A prospective study design was employed in the Department of Pathology at Government Medical College, Srikakulam, spanning a two-year period from October 2020 to September 2022. This design allowed for the collection of data over time, ensuring a comprehensive evaluation of the research objectives.

**Study Subjects:** The study population consisted of patients seeking medical care at the Gynaecology Department of GGH, Srikakulam, encompassing both inpatient and outpatient cases. To provide a thorough assessment of the subjects, a detailed medical history was meticulously obtained, with a specific focus on their menstrual complaints. This comprehensive approach ensured that the study captured a diverse range of patients and menstrual-related issues.

**Inclusion Criteria**

To select eligible participants, the following inclusion criteria were applied:

**Age Groups:** Women from reproductive, perimenopausal, and postmenopausal age groups were included, encompassing a wide spectrum of the female population.

**Menstrual Complaints:** Patients with abnormal uterine bleeding and those presenting with menstrual irregularities were considered. These irregularities included irregular menstrual cycles, excessive and prolonged menstrual bleeding, and postmenopausal bleeding.

**Exclusion Criteria**

**Patients were excluded based on the following criteria:** Medical Conditions: Females diagnosed with acute pelvic inflammatory disease, clotting disorders (coagulopathy), or acute cervical or vaginal infections were excluded, as these conditions could confound the study results.

**Medication Usage:** Women who were currently using hormone replacement therapy, oral contraceptive pills, intrauterine contraceptive devices, or steroidal and non-steroidal anti-inflammatory medications were excluded to avoid interference with the study's objectives.

**Consent and Diagnosis:** Patients who had not provided informed consent for endometrial biopsy and those who were already known cases of endometrial carcinoma were not included in the study, ensuring ethical considerations and avoiding duplicative data collection.

**Data Collection:** Informed consent was diligently obtained from all participants, ensuring ethical and legal compliance. Comprehensive data were collected for each patient, including age, signs and symptoms, duration of complaints, past medical


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history, family history, personal history, and detailed menstrual history. This thorough data collection process allowed for a robust analysis of patient characteristics and history.

**Sample Processing:** Biopsy samples were carefully collected and preserved in 10% formalin to maintain their integrity. Subsequently, they underwent appropriate fixation, processing, and embedding. Sections of 2-4µm thickness were skillfully cut using a microtome and stained with the standard Hematoxylin and Eosin (H&E) stain. For cases of endometrial hyperplasia and endometrial carcinoma, Immunohistochemistry (IHC) was performed using ER, PR, and Her2/neu markers to enhance diagnostic accuracy, ensuring precise characterization of the tissue samples.

The histological analysis of tissue samples involved two distinct staining protocols. Hematoxylin and Eosin Stain (H&E) was employed to visualize cellular structures. This process encompassed deparaffinization, hematoxylin staining for nuclei, bluing, acid alcohol differentiation, eosin Y staining for color contrast, and dehydration before mounting.

Immunohistochemistry (IHC) staining focused on specific protein markers: ER, PR, and HER2/neu. It included steps like tissue section preparation, epitope retrieval, blocking endogenous peroxidase, applying primary antibodies, link antibodies, and enzyme conjugates. ER and PR were evaluated semi-quantitatively based on nuclear staining intensity and proportion, leading to categorization into three groups. HER2/neu staining adhered to ASCO/CAP guidelines, categorizing samples into four groups (0+, 1+, 2+, and 3+) to determine HER2/neu status. These protocols provided essential insights for diagnostic and research purposes.

**Statistical Analysis:** Data analysis was conducted using IBM SPSS Software Version 21, a widely recognized and established statistical analysis tool. This software facilitated the organization, evaluation, and interpretation of the collected data, enabling meaningful statistical insights. Chi-Squared Test: Employed to assess the association between receptor expression (Estrogen Receptor - ER and Progesterone Receptor - PR) and the presence of atypia in endometrial lesions.

**Ethical Considerations:** This study was approval by the Institutional Ethics Committee of Government Medical College, Srikakulam, Andhra Pradesh. All patients provided informed consent for the collection and future utilization of their biopsy specimens for research purposes.

## RESULTS

### Patient Demographics and Characteristics

**Total Patients:** The study encompassed 209 women, each diagnosed with Abnormal Uterine Bleeding (AUB) and undergoing diagnostic endometrial biopsy, providing a substantial sample size for robust analysis [Table 1].

**Age Distribution:** Reproductive Age (18-40 years): Comprising over half (52.16%) of the study population, this age group forms the backbone of the study, reflecting the prevalence of AUB in the reproductive years.

Perimenopausal (41-50 years): A significant portion (40.66%) of the participants, highlighting the transitional phase's importance in AUB research.

Postmenopausal (>50 years): Though the smallest group (7.18%), their inclusion is vital for a comprehensive understanding of AUB across different life stages.

**Parity Distribution:**

**Nulliparous:** Representing 2%, this demographic is crucial for understanding AUB in women without prior childbirth experience.

**Low Parity (P1-P2):** Dominating the study with 57%, this group provides insights into AUB's impact on women with fewer childbirths.

**Multiparous (P3-P6):** Making up 41%, this segment allows for the examination of AUB in women with a higher number of childbirths, which may influence the condition's presentation and severity.

**Patterns of Bleeding**

**Menorrhagia:** Being the most prevalent symptom in 45% of cases, this finding underscores the importance of focusing on heavy menstrual bleeding in AUB research.

**Polymenorrhoea and Metrorrhagia:** The substantial representation (23.4% and 14.8%, respectively) of these symptoms highlights the diverse nature of bleeding patterns in AUB.

**Postmenopausal Bleeding (PMB) and Menometrorrhagia:** These less common patterns (10.5% and 6.3%, respectively) are crucial for understanding the full spectrum of AUB presentations [Table 2].

**Age-specific Bleeding Patterns**

**Menorrhagia:** Predominantly observed in younger cohorts, this pattern's prevalence suggests hormonal factors could be a significant contributor in these age groups.

**Polymenorrhoea and Metrorrhagia:** Their higher occurrence in younger women might reflect underlying hormonal imbalances or structural uterine changes common in these age groups.

**PMB:** Its dominance in postmenopausal women (80% of PMB cases) points towards the significance of investigating endometrial changes and other postmenopausal conditions [Table 3].

**Histopathological Patterns**

**Proliferative Phase and Secretory Phase:** The high incidence of these phases (52.63% and 14.83%, respectively) in AUB cases suggests a potential link between the menstrual cycle's phases and the development of AUB.

**Endometrial Hyperplasia without Atypia and Atrophic Endometrium:** The presence of these conditions (9.5% and 3.34%, respectively) indicates the diverse etiological spectrum of AUB.

**Other Diagnoses:** The variety of other diagnoses, including atypical hyperplasia and adenocarcinoma,


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underscores the complexity of AUB's histopathological underpinnings [Table 4].

**Histopathological Patterns by Age Group**

**Reproductive Age:** The dominance of the proliferative phase suggests the influence of regular hormonal cycles in AUB pathogenesis in this group.

**Perimenopausal Age:** The mixed histopathological findings highlight the transitional nature of this phase and its impact on uterine biology.

**Postmenopausal Age:** The prevalence of atrophic and hyperplastic changes reflects the altered hormonal milieu post-menopause and its role in AUB [Table 5].

**Non-Organic vs. Organic Causes of AUB**

**Non-Organic Causes:** The predominant occurrence of non-organic causes (80.9%) in AUB implies that many cases could be potentially managed with less invasive, possibly hormonal or medical therapies. This finding challenges the traditional approach that often leans towards surgical interventions and emphasizes the need for a more nuanced understanding of AUB etiology.

**Organic Causes:** The presence of organic causes in 19.09% of the cases is clinically significant. It necessitates comprehensive diagnostic evaluations, including imaging and biopsy, to exclude serious pathologies like malignancies or polyps. This finding underlines the importance of a differential diagnosis in AUB, recognizing that a substantial subset of patients may require more aggressive treatment modalities, including surgical intervention [Table 6].

**Premalignant and Malignant Lesions**

The identification of premalignant lesions in 60.6% and malignant lesions in 6.06% of the cases underscores the critical role of endometrial biopsy in the diagnostic workup of AUB. This high prevalence of potentially serious histopathological changes necessitates a high degree of clinical vigilance.

The findings advocate for routine histopathological evaluation in AUB, especially in high-risk groups, to facilitate early detection and timely management of endometrial pathologies [Table 7].

**Immunohistochemistry Results**

**ER and PR Expression:** The observed variability in ER and PR expression across different histopathological lesions offers a window into the complex hormonal interplay in endometrial pathology. This variability could inform personalized therapeutic strategies, tailoring hormonal treatments based on the specific receptor profile of the lesion.

**HER2/neu:** The absence of HER2/neu overexpression in all premalignant and malignant cases suggests a divergent pathophysiological mechanism in endometrial lesions compared to other cancers, such as breast cancer, where HER2/neu plays a pivotal role. This finding may redirect the focus towards other molecular pathways in the research and treatment of endometrial pathologies [Table 8].

**Correlation of Bleeding Pattern with Histopathological Diagnosis**

The study's results indicate a complex and non-uniform relationship between bleeding patterns and histopathological diagnoses. This complexity necessitates a tailored approach in AUB management, moving away from one-size-fits-all strategies and towards more individualized diagnostic algorithms [Table 9].

**Table 1: Patient Demographics and Characteristics**

| Demographic Category | Description | Percentage (%) |
|---|---|---|
| Reproductive Age (18-40 years) | Major group | 52.16 |
| Perimenopausal (41-50 years) | Significant portion | 40.66 |
| Postmenopausal (>50 years) | Smallest group | 7.18 |
| Nulliparous | Women without childbirth | 2 |
| Low Parity (P1-P2) | Fewer childbirths | 57 |
| Multiparous (P3-P6) | Higher number of childbirths | 41 |

**Table 2: Patterns of Bleeding in AUB**

| Bleeding Pattern | Description | Percentage (%) |
|---|---|---|
| Menorrhagia | Most prevalent symptom | 45 |
| Polymenorrhoea | Second most frequent | 23.4 |
| Metrorrhagia | Occurrence in patients | 14.8 |
| Postmenopausal Bleeding (PMB) | Noted in postmenopausal women | 10.5 |
| Menometrorrhagia | Less common pattern | 6.3 |

**Table 3: Age-specific Bleeding Patterns**

| Age Group | Bleeding Pattern | Dominance (%) |
|---|---|---|
| Reproductive Age | Menorrhagia | High |
| Perimenopausal Age | Menorrhagia, Polymenorrhoea, Metrorrhagia | Moderate |
| Postmenopausal Age | PMB | 80 (of PMB cases) |

**Table 4: Histopathological Patterns in AUB**

| Histopathological Diagnosis | Percentage (%) |
|---|---|
| Proliferative Phase | 52.63 |
| Secretory Phase | 14.83 |
| Endometrial Hyperplasia without Atypia | 9.5 |
| Atrophic Endometrium | 3.34 |


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**Table 5: Histopathological Patterns by Age Group**

| Age Group | Predominant Histopathological Pattern |
|---|---|
| Reproductive Age | Proliferative Phase |
| Perimenopausal Age | Mixed Findings |
| Postmenopausal Age | Atrophic and Hyperplastic Changes |

**Table 6: Non-Organic vs. Organic Causes of AUB**

| Cause Type | Percentage (%) |
|---|---|
| Non-Organic Causes | 80.9 |
| Organic Causes | 19.09 |

**Table 7: Prevalence of Premalignant and Malignant Lesions**

| Lesion Type | Percentage (%) |
|---|---|
| Endometrial Hyperplasia without Atypia | 60.6 |
| Atypical Hyperplasia | 33.33 |
| Endometrial Carcinoma | 6.06 |

**Table 8: Immunohistochemistry Results**

| Marker | Observation |
|---|---|
| ER and PR Expression | Variable across lesions |
| HER2/neu Overexpression | Absent in all cases |

**Table 9: Correlation of Bleeding Pattern with Histopathological Diagnosis**

| Bleeding Pattern | Corresponding Histopathological Findings |
|---|---|
| Menorrhagia | Predominantly Proliferative Phase |
| Metrorrhagia | Mixed Findings |
| Polymenorrhoea | Varied |
| PMB | Atrophic and Hyperplastic Changes |

**Table 10: Statistical Analysis of ER and PR Expression by Chi-Squared Test**

| Lesion Type | ER Expression Negative | ER Expression Positive | PR Expression Negative | PR Expression Positive | Total |
|---|---|---|---|---|---|
| Lesion with Atypia | 7 | 6 | 5 | 8 | 13 |
| Lesion without Atypia | 7 | 13 | 5 | 15 | 20 |
| Total | 14 | 19 | 10 | 23 | 33 |

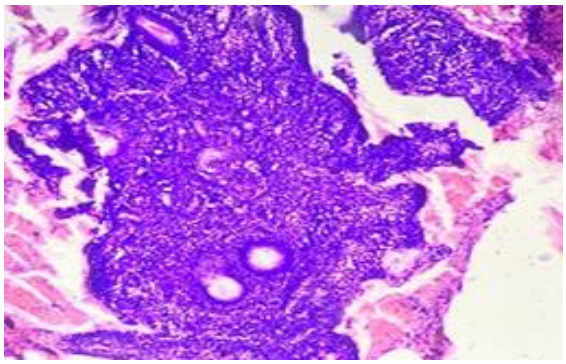

**Figure 1: Proliferative phase endometrium showing tubular glands and compact stroma; Biopsy no: ; H&E Stain, 10x**

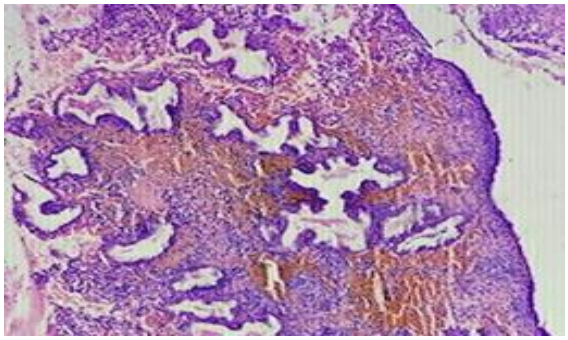

**Figure 2: Secretory phase endometrium showing convoluted glands with edematous stroma and areas of hemorrhages; Biopsy no: H&E Stain, 10x**

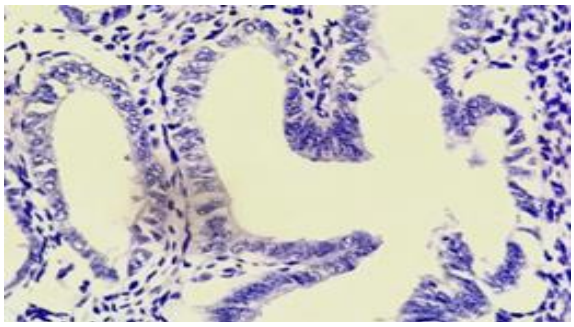

**Figure 3: Endometrial hyperplasia without atypia showing no overexpression with Her2/neu; Biopsy no; IHC, 40x**

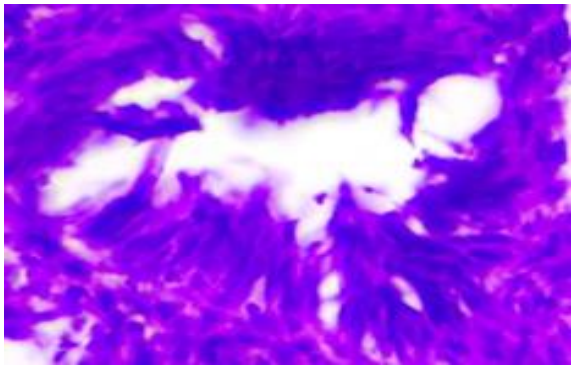

**Figure 4: Atypical hyperplasia showing gland lined by stratified layer of atypical cells; Biopsy no: ; H&E stain, 40x**


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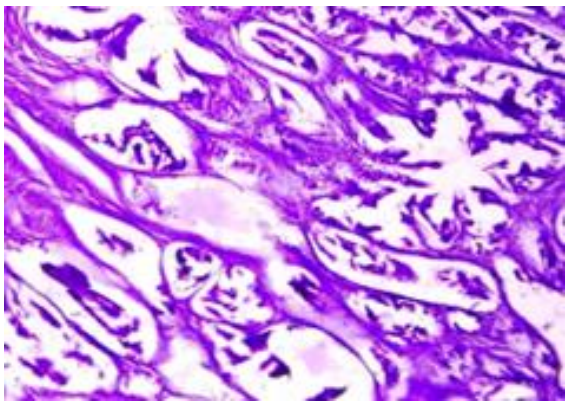

**Figure 5: Endometrial adenocarcinoma showing well-differentiated glandular arrangement of atypical cells; Biopsy no: ; H&E stain, 10x**

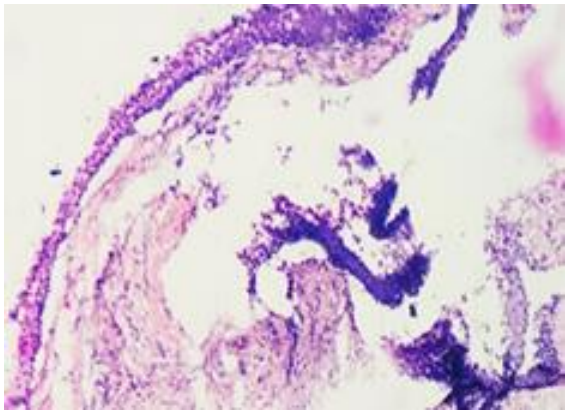

**Figure 6: Biopsy is 'unassessable" showing only few areas of cervical epithelium; Biopsy no: ; H&E Stain, 40x**

### Statistical Analysis

In a study analyzing the expression of Estrogen Receptor (ER) and Progesterone Receptor (PR) in endometrial lesions, Chi-Squared Test results revealed no statistically significant association between receptor expression and the presence of atypia. Specifically, the ER expression showed a p-value of 0.2, while PR expression had a p-value of 0.4. These findings indicate that the differences in ER and PR expression between atypical and non-atypical lesions are not statistically significant, suggesting that hormonal receptor status may not be a reliable indicator of atypia in endometrial lesions. This lack of significant correlation highlights the need for a broader approach in understanding the role of hormonal receptors in endometrial pathology and their implications in clinical management [Table 10].

## DISCUSSION

The age range of the patients in this study was consistent with findings from prior research by various authors. Rupal Shah et al,[7] reported a similar age range (21-70 years) in their study, while Gitika Hyanki et al,[8] observed a broader age range of 17-74 years. Alshdaifat et al,[9] reported an age range of 19-86 years, and IM Asuzu et al. found a range of 22-62 years among their study participants.

The highest incidence of Abnormal Uterine Bleeding (AUB) in our study was observed in the reproductive age group (52.16%), followed by the perimenopausal age group (40.66%). This finding aligns with Alshdaifat et al,[9] where the age group most commonly affected was 18-40 years. Similarly, IM Asuzu et al,[10] also reported that the age group most commonly affected was 18-50 years.[11]

Menorrhagia was the most commonly reported presenting complaint among the patients in this study, accounting for 45% of cases. This finding is consistent with several other studies by Prasannalakshmi S et al, where menorrhagia was also the most common presenting complaint, with varying percentages.[12-15]

Polymenorrhea was the second most common presenting complaint in our study, which differs from Mariam Abid et al's study, where it was the most common complaint.[16]

The histopathological patterns observed in this study were broadly in line with findings from other studies. Proliferative endometrium was the most common histopathological pattern in our study, as well as in studies conducted by Murugan R et al,[11] Prasannalakshmi et al,[12] Prathipaa R et al,[13] Sadbhavana Ranjan et al.[1]4

The least common histopathological diagnosis in our study was products of conception, followed by endometrial carcinoma, which is consistent with the majority of the other studies cited.

Functional causes of AUB were more common than organic causes in all of the studies, including ours. Proliferative and secretory patterns were the most common functional causes in our study, similar to the findings in other research, except for studies by Zeeba S. Jairajpuri et al,[15] Murugan R et al,[11] where disordered proliferative endometrium was more common than atrophic endometrium.

Among the organic causes, endometrial hyperplasia was the most common in our study, consistent with several other studies. Endometrial carcinoma was the least common diagnosis in our study, consistent with most other studies.

The age-wise distribution of various diagnoses in our study differed from some other studies. Proliferative endometrium was mostly reported in the 18-40 age group, similar to Mariam Abid et al., while other studies like Murugan R et al,[11] and Prathipaa R et al,[13] found it more common in perimenopausal women.

Similarly, the distribution of secretory endometrium in our study was observed in reproductive age group women, which is in agreement with Mariam Abid et al,[16] and Prathipaa R et al,[13] but differs from Murugan R et al., where perimenopausal women were more affected.

In our study, endometrial atrophy was more common in postmenopausal women, consistent with Mariam Abid et al,[16] Murugan R et al.[11]

Positive expression of estrogen receptor (ER) and progesterone receptor (PR) in our study showed patterns that were generally consistent with previous


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research. ER and PR expression tended to decrease as the degree of atypia increased, which is a common finding in endometrial hyperplasia and carcinoma.

Her2/neu overexpression was not observed in any hyperplastic or cancerous lesions in our study. However, it's important to note that Her2/neu overexpression can be associated with high-grade endometrial tumors, such as serous and clear cell carcinomas, which were not included in our study. Therefore, the significance of Her2/neu in endometrial tumors cannot be fully assessed based on our findings.

**Limitations:** The study has notable limitations, encompassing a modest sample size, a sole-center approach, potential selection bias, a retrospective design, and constrained long-term tracking. Variability in the interpretation of immunohistochemistry among observers and the incapacity to evaluate supplementary biomarkers or external factors are also constraints. These limitations compromise the study's applicability and its ability to comprehensively evaluate abnormal uterine bleeding. Additionally, the study was impacted by the COVID-19 pandemic, which reduced the sample size and hindered the assessment of ER and PR significance in distinguishing between hyperplasia and carcinoma due to low expression rates.

## CONCLUSION

Our study involving involving 209 women with Abnormal Uterine Bleeding (AUB) highlights the complexity of this condition. The diverse histopathological patterns, varying hormonal receptor expressions, and different bleeding patterns emphasize the multifaceted nature of AUB. The absence of HER2/neu overexpression challenges established norms, and the lack of a statistically significant link between receptor expression and atypia highlights the need for a more individualized clinical approach. Our findings strongly advocate for personalized diagnostic and treatment strategies in addressing AUB, taking into account its diverse etiological factors and clinical presentations.

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