Original Article

Endometrial Hormonal Receptor Expression and Blood Vessel Density in Abnormal Uterine Bleeding: A Cross-sectional Descriptive Study

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Abstract

Introduction: Abnormal uterine bleeding (AUB) is bleeding which is abnormal in amount, duration, frequency, and cyclicity and differs from the normal pattern. The aim of the study is to evaluate the expression of endometrial estrogen (ER) and progesterone receptor (PR) immunohistochemically and blood vessel density in AUB patients. Furthermore, we will correlate hormonal receptor expression and blood vessel density with various endometrial pathologies presenting with AUB. **Materials and Methods:** A cross-sectional study of 60 cases with clinical diagnosis of AUB, (30 cases of cyclical endometrium and 30 cases of hyperplasia/carcinoma) was done. Histological typing of endometrial lesions was done. Microvessel density (MVD) was calculated by counting the average number of blood vessels/10 HPFs. Evaluation of MVD was done on hematoxylin and eosin (H and E) stain and also reticulin stain which highlighted the basement membrane. Immunohistochemistry for steroid hormone receptors, ER and PR was done as per avidin-biotin technique with Diaminobenzidine as the chromogen. Carcangiu scoring system for semiquantitative analysis of ER/PR expression in endometrial samples was adopted. **Results:** There was a significant difference in microvessel density between different histopathology microscopic diagnoses ($P < 0.05$). The mean value of microvessel density on reticulin stain was significantly higher as compared to the mean value of MVD on H and E. A decrease of the hormonal receptor expression, ER and PR was observed in parallel with the decreased histological degree of differentiation, the lowest values occurring in the case of endometrioid Grade 3 carcinomas. **Conclusion:** Angiogenesis is significantly correlated with increasing severity of the lesion. The correlation of immunohistochemical findings with histologic grade can be useful in predicting biological behavior in patients.

Keywords: Abnormal uterine bleeding, hormonal receptor, immunohistochemistry, microvessel density

Introduction

Abnormal uterine bleeding (AUB) refers to a deviation in the frequency, duration, and amount of bleeding compared to normal menstruation or postmenopause. It poses significant challenges to a woman's health, impacting her family, personal, and social life.[1,2] AUB affects approximately 50% of women in perimenopause or menopausal transition and 10%–30% of women in the reproductive age group.[3] It encompasses both dysfunctional uterine bleeding and bleeding attributed to structural issues such as fibroids, polyps, endometrial carcinoma, and complications during pregnancy.[4,5]

Estrogen (ERs) and progesterone receptors (PRs) play crucial roles in regulating uterine endometrium growth and development. In AUB, the primary mechanism involves unbalanced estrogenic stimulation, resulting in excessive endometrial proliferation and hyperplasia.[6,7] Also endometrial angiogenesis is an ongoing process and alteration in blood vessel morphology and density have an important role in the pathogenesis and significant changes are reported in both endometrial hyperplasia and carcinomas in patients presenting with AUB.[8,9]

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Our study aims to assess ER and PR expression in the endometrium and blood vessel density in patients with AUB. It also seeks to correlate receptor expression and vessel density with different endometrial pathologies associated with AUB.

Materials and Methods

Study design and study settings

This cross-sectional study was carried out at the Department of Pathology, Hamdard Institute of Medical Sciences and Research and associated Hospitals from June 2022 to November 2023. Perimenopausal women who reported to the gynecology outpatient department with AUB were the subjects of this study. A detailed menstrual history was taken and recorded in all cases.

Ethical permission and patient consent

Informed consent in the language they understood was obtained from all patients. Consent from the Institutional Review Board of our institution was also obtained which granted the acceptability of our research proposal.

Sample size

This study subjects included 60 perimenopausal women (aged 40–50 years) diagnosed with AUB from the gynecology department who underwent endometrial sampling and hysterectomy. These patients were divided into two groups. Group 1 consists of 30 cases of cyclical endometrium, proliferative, and secretory phases, respectively, and Group 2 consists of 30 cases with endometrial hyperplasia and/or carcinoma.

Method of collection of data

The specimens were received in 10% buffered formalin and hematoxylin and eosin (H and E) stained pathology slides from the specimens were retrieved.

Immunohistochemistry for steroid hormone receptors, ER and PR was done as per avidin-biotin technique with Diaminobenzidine as the chromogen. Carcangiu scoring system for semiquantitative analysis of ER/PR expression in endometrial samples was adopted. Microvessel density (MVD) was calculated by counting the average number of blood vessels/10 HPFs. Evaluation of MVD was done on H and E stain and also reticulin stain which highlighted the basement membrane.

Histological typing of the endometrial lesions, steroid hormone receptor expression, and microvessel density were compared with the clinical profile, and imaging findings and were statistically evaluated.

Statistical analysis

The data were entered in MS Excel sheet and analysis was done using the Statistical Package for the Social Sciences (SPSS) version 21.0 IBM SPSS, (Chicago, State of Illinois, USA). Quantitative variables were compared using an Independent *t*-test between the two groups and Kruskal–Wallis test was used for comparison between more than two groups. Qualitative variables were correlated using the Chi-square test.

Results

Sixty perimenopausal women with AUB were evaluated in whom endometrial biopsy was the most common sample type (50.00%), followed by total hysterectomy (43.33%) and radical hysterectomy (6.67%), as depicted in Figures 1a, b and 2. We noted a higher incidence of AUB in multiparous and grand multiparous women. A detailed personal history regarding the pattern of AUB was taken in all the cases. More than 60% of the patients in our study, both Group 1 and Group 2 had regular cycles associated with a heavy flow of menstrual blood.

Histological typing of the endometrial lesions was done. The distribution of cases according to the histopathological diagnoses in both groups is shown in Figure 3. Endometrioid endometrial carcinoma is the most common form of endometrial cancer and usually develops following a typical sequence of endometrial hyperplasia. In the present study, out of 14 endometrial carcinoma patients, the most common form of endometrial carcinoma was the endometrioid adenocarcinoma villoglandular variant seen in 5 (35.71%) patients [Figure 4]. The distribution of endometrial carcinoma in our study subjects is depicted in Figure 5.

Endometrial thickness (ET) was significantly higher in cases with AUB compared to those without, with mean values of 8.68 ± 3.41 mm in group 1 and 15.84 ± 5.77 mm in group 2 [Table 1]. Different histopathological diagnoses showed significant variations in ET, with endometrial adenocarcinoma having the highest mean ET, while proliferative endometrium had the lowest, as shown in Table 2.

MVD was calculated on H and E stain and also reticulin stain which helped to better delineate the basement membrane. We found that reticulin stain was useful to delineate thin-walled microvasculature in the endometrium which was unidentifiable on routine H and E staining. A significant difference in the mean MVD was observed on H and E and reticulin stain [Figures 6–9] across various histopathological microscopic diagnoses, with a $P < 0.05$ indicating statistical significance. Overall mean MVD in endometrial adenocarcinoma was significantly higher

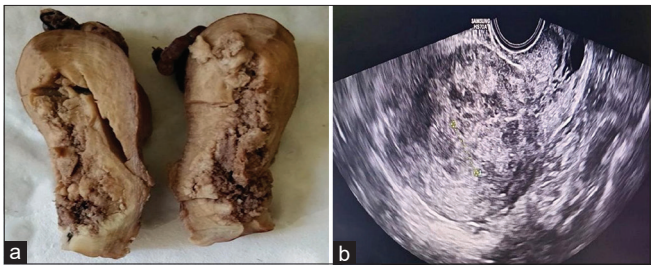

Figure 1: (a) Gross photograph of hysterectomy specimen cut open and showing an exophytic growth extending into the cervical canal, (b) Transvaginal ultrasound photograph showing bulky uterus with heterogenous echotexture and endometrial thickness of 20 mm in a case of endometrial carcinoma

compared to other diagnoses [Figure 10], while the mean density in early proliferative endometrium was significantly lower compared to other diagnoses. The mean MVD observed in reticulin stains was significantly higher compared to the mean density observed in H and E stains [Table 3].

Immunohistochemical evaluation for ER and PR using the Carcangiu scoring system was done. Carcangiu scoring is a semiquantitative analysis of ER/PR expression based on the percentage of stained cells and the intensity of nuclear staining. The sum of both parameters gives the immunohistochemical score. Tumors were divided into three categories depending on the immunohistochemical score. Category I tumors were considered immune-negative, whereas Category II and Category III tumors were considered immune-positive.

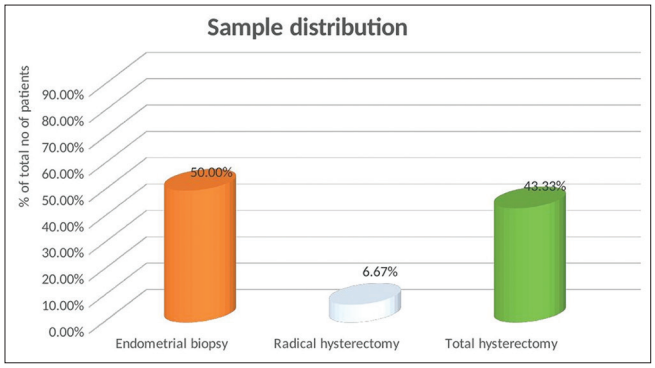

Figure 2: Distribution of sample type among the study subjects

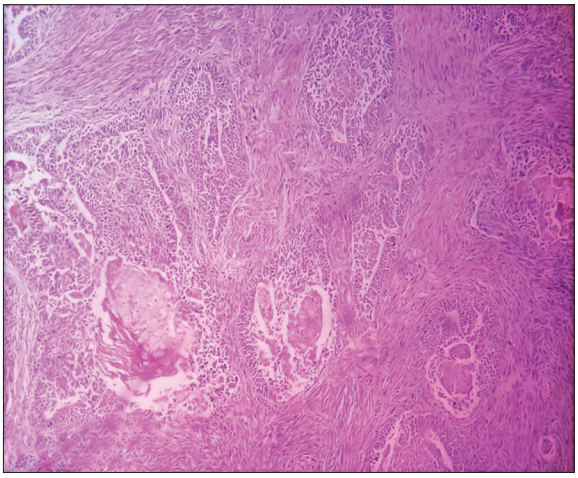

Figure 4: Microphotograph showing endometroid endometrial carcinoma (Grade I) invading myometrium with squamous morules (H and E, ×10)

In Group 1, we found that the immunohistochemical score for ER and PR in the glandular epithelium declined significantly ($P < 0.05$) in the glandular epithelium from the proliferative to early secretory phase, reaching the lowest expression in the late secretory phase ($P < 0.05$). Both simple endometrial hyperplasia and atypical hyperplasia cases showed a strong immunopositivity for ER and PR [Figure 11]. Category III PR positivity was seen in all 16 cases of hyperplasia. Category II ER positivity was seen in 30% and Category III ER positivity was in 70% of endometrial hyperplasias. We found that all 11 cases of endometroid endometrial carcinomas were immunopositive for ER and PR expression. About 27.27% of cases belonged to Category II and 72.73% of cases belonged to Category III for ER expression and 54.54% of cases belonged to Category II and 36.36% of cases belonged to Category III for PR expression. Conversely, the single case of clear cell adenocarcinoma and two cases of serous adenocarcinoma in this group were immunonegative for both ER and PR expression [Figure 12]. The association of immunohistochemical score for both ER and PR with the histopathological diagnosis with the respective *P* values is shown in Table 4.

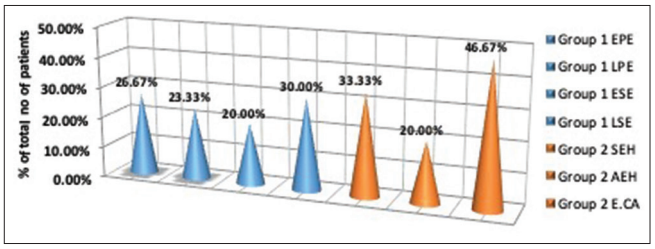

Figure 3: Distribution of cases according to histopathological diagnosis. EPE: Early Proliferative Endometrium; LPE: Late Proliferative; SEH: Simple Endometrial Hyperplasia; AEH: Atypical Endometrial Hyperplasia; E. CA: Endometrial Carcinoma

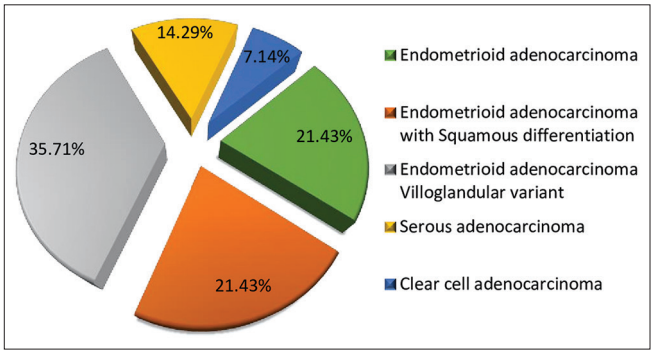

Figure 5: Distribution of type of endometrial carcinoma in study subjects

Table 1: Comparison of endometrial thickness (mm) between Groups 1 and 2

ET (mm)	Group 1 (*n*=30)	Group 2 (*n*=30)	Total	*P*
Mean±SD	8.68±3.41	15.84±5.77	12.26±5.92	<0.0001‡
Median (25th–75th percentile)	8.15 (5.975–10.8)	16.05 (12.5–20)	11.55 (7.075–16.575)	
Range	3.5–18.1	4.7–24	3.5–24	

‡Independent *t*-test. SD: Standard deviation, ET: Endometrial thickness

Table 2: Association of endometrial thickness (mm) with histopathological diagnosis

ET (mm)	Mean±SD	Median (IQR)	*P*
Early proliferative endometrium (*n*=8)	4.96±0.84	4.9 (4.75–5.1)	<0.0001¶
Late proliferative endometrium (*n*=7)	7.34±1.17	7.1 (6.6–8)	
Early secretory endometrium (*n*=6)	9.08±1.15	9.6 (8.275–9.8)	
Late secretory endometrium (*n*=9)	12.74±2.35	12.4 (11.1–13.2)	
Simple endometrial hyperplasia (*n*=10)	13.45±6.58	15.3 (6.75–18.25)	
Atypical endometrial hyperplasia (*n*=6)	11.27±3.87	11.55 (9.9–13.5)	
Endometrial adenocarcinoma (*n*=14)	19.5±3.16	20 (18–22)	

¶ANOVA. SD: Standard deviation, IQR: Interquartile range, ET: Endometrial thickness

Table 3: Comparison of mean values of microvessel density on hematoxylin and eosin staining and reticulin staining

Diagnosis	MVD (H and E stain)		MVD (reticulin stain)		*P*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Early proliferative endometrium (*n*=8)	2.55±0.23	2.55 (2.45–2.65)	2.99±0.24	2.9 (2.8–3.075)	<0.0001§
Late proliferative endometrium (*n*=7)	2.9±0.21	3 (2.75–3)	3.37±0.26	3.3 (3.25–3.5)	<0.0001§
Early secretory endometrium (*n*=6)	3.83±0.98	3.7 (3.3–3.8)	4.25±1.02	4 (3.75–4.25)	0.0001§
Late secretory endometrium (*n*=9)	4.24±0.77	4.2 (3.8–4.4)	4.73±0.84	4.6 (4.4–4.8)	<0.0001§
Simple endometrial hyperplasia (*n*=10)	4.33±1.2	4.5 (3.45–5.05)	4.72±1.16	4.9 (3.925–5.425)	<0.0001§
Atypical endometrial hyperplasia (*n*=6)	5.32±0.45	5.3 (4.975–5.55)	5.72±0.34	5.7 (5.45–5.8)	0.001§
Endometrial adenocarcinoma (*n*=14)	6.39±1.1	6.4 (5.35–7.25)	6.83±1.07	6.8 (5.875–7.75)	<0.0001§

§Paired *t*-test. MVD: Microvessel density, H and E: Hematoxylin and eosin, SD: Standard deviation, IQR: Interquartile range

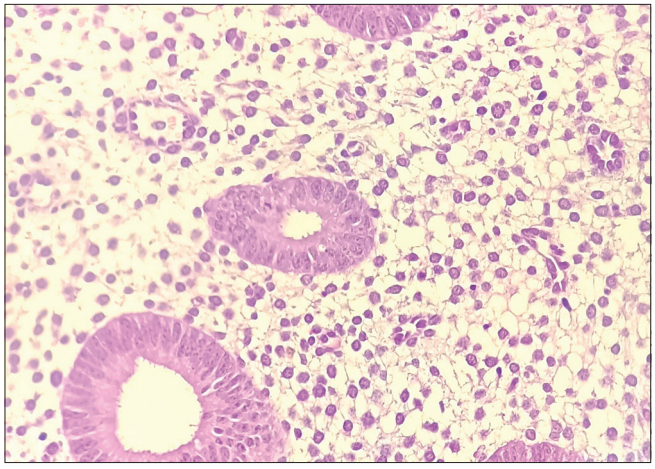

Figure 6: Microphotograph showing microvessels in proliferative endometrium (H and E, ×40, Group 1)

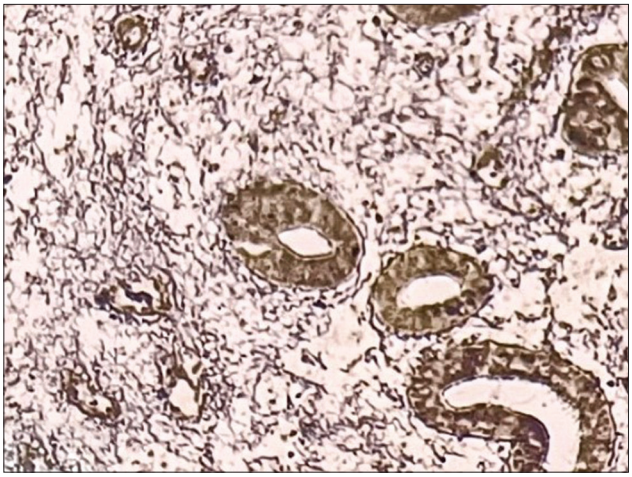

Figure 7: Microphotograph showing microvessels in proliferative endometrium (Reticulin, ×40, Group 1)

Discussion

AUB is one of the most frequently encountered gynecologic complaints among perimenopausal women. It is the most common cause of hysterectomy in this age group comprising over 70% of gynecological consultations among these patients. It has been observed that AUB is linked to nearly every form of endometrial pathology, ranging from atrophy, hyperplasia, irregular ripening, and irregular shedding to endometrial malignancy.

In 2010, the International Federation of Gynecology and Obstetrics introduced a revised classification system for AUB causes, further updated in 2018. This system, utilizing the acronym polyp, adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified, addresses various factors such as polyps, adenomyosis, fibroids, malignancy, and coagulation disorders. It aims to streamline diagnosis and treatment decisions, enhancing the management of AUB.[10,11]

Several studies in perimenopausal women with AUB have shown that heavy and prolonged menstrual bleeding (previously known as menorrhagia) was the most common menstrual pattern which was similar to the findings of our study.[1,3] An important investigation in the workup of AUB cases is the ultrasonographic evaluation of the ET. Sonographic measurement of ET is documented to be a valuable primary

Table 4: Association of immunohistochemical score (estrogen receptor) and immunohistochemical score (progesterone receptor) with histopathological diagnosis

IH score (ER) and IH score (PR)	Early proliferative endometrium (*n*=8)	Late proliferative endometrium (*n*=7)	Early secretory endometrium (*n*=6)	Late secretory endometrium (*n*=9)	Simple endometrial hyperplasia (*n*=10)	Atypical endometrial hyperplasia (*n*=6)	Endometrial adenocarcinoma (*n*=14)	Total	*P*
IH score (ER)									
Mean±SD	5.12±0.35	5.71±0.49	5±0	2.67±1	5.1±0.88	5.5±0.55	4.14±1.17	4.62±1.25	<0.0001¶
Median (25th–75th percentile)	5 (5–5)	6 (5.5–6)	5 (5–5)	2 (2–3)	5 (4.25–6)	5.5 (5–6)	5 (3.25–5)	5 (4–5)	
IH score (PR)									
Mean±SD	5.12±0.35	5.43±0.53	5±0	2.56±1.01	5.4±0.52	5.5±0.55	3.43±1.22	4.45±1.36	<0.0001¶
Median (25th–75th percentile)	5 (5–5)	5 (5–6)	5 (5–5)	2 (2–3)	5 (5–6)	5.5 (5–6)	3 (2.25–4.75)	5 (3–5)	

¶ANOVA. ER: Estrogen receptor, PR: Progesterone receptor, IH: Immunohistochemical, SD: Standard deviation

Figure 8: Microphotograph of endometrial carcinoma showing microvessels at endo-myometrial interface (H and E, ×10, Group 2)

Figure 9: Microphotograph of endometrial carcinoma showing microvessels at endo-myometrial interface (Reticulin, ×10, Group 2)

Figure 10: Microphotograph showing microvessels in serous adenocarcinoma (Reticulin stain ×40, Group 2)

tool in evaluating patients with uterine bleeding. In the present study, the mean value of ET (mm) on ultrasonography (USG)

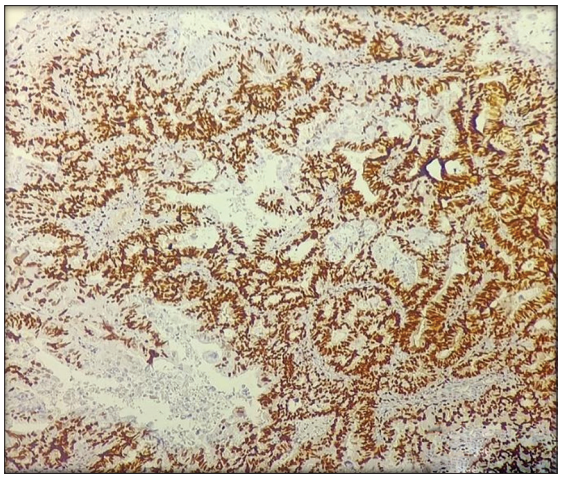

Figure 11: Microphotograph of immunohistochemistry in atypical endometrial hyperplasia showing ER Positivity with an immunohistochemical score of 5 (Immune-positive) (×10)

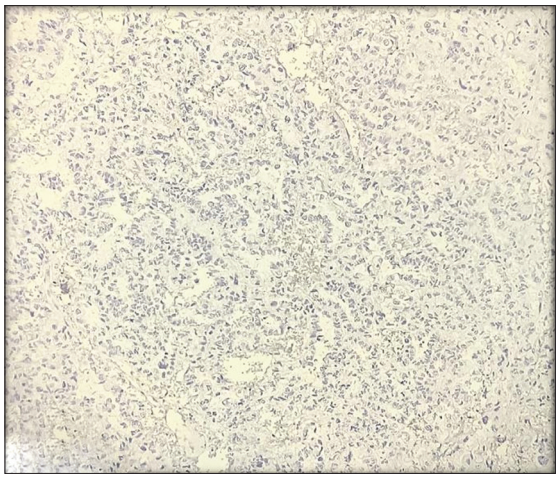

Figure 12: Microphotograph of immunohistochemistry in serous adenocarcinoma showing progesterone receptor negativity with an immunohistochemical score of 2 (Immune-negative) (×10)

in Group 1 was significantly less as compared to that of Group 2 (9.48 ± 4.48 vs. 14.45 ± 5.35 $P < 0.05$). The mean value of ET in proliferative endometrium (significantly lowest) was 8.42 ± 4.61 mm; disordered proliferative endometrium, 10.91 ± 4.33 mm; endometrial polyp, 10 ± 0 mm; hyperplasia without atypia, 13.09 ± 4.93 mm; endometrial intraepithelial neoplasia, 11.38 ± 3.02 mm; and in endometrioid adenocarcinoma (significantly highest) was 16.89 ± 5.63 mm. Similarly, Dreisler *et al*. reported the importance of USG in identifying focal lesions in both premenopausal and postmenopausal women. For premenopausal women, the best negative likelihood ratio (LR- =0.11) was obtained at an ET of 5.2 mm, with a negative predictive value (NPV) of 99% and a positive predictive value (PPV) of 10%. For postmenopausal women, the best LR (0.08) was obtained at an ET of 2.8 mm, with NPV of 99% and a PPV of 26%.[12]

The role of vascular proliferation in AUB, particularly within the normal endometrium and conditions such as endometrial hyperplasia and carcinoma, has been extensively studied and was also investigated in the subjects of this study. Investigators have reported MVD and characteristics of vessels as potential prognostic indicators in patients presenting as AUB, aiding in the selection of patients for antiangiogenic and other therapeutic modalities.[13]

Jain *et al*. found that AUB patients exhibit significantly greater microvascular density during the secretory phase compared to the proliferative phase similar to our study.[14] Kataria *et al*. observed an increase in microvessel count from simple to complex and atypical endometrial hyperplasia, thus indicates a potential link to malignant transformation progression.[13] Similarly, our research observed a higher mean vessel count in endometrial adenocarcinoma compared to both simple and atypical hyperplasia. We found that the range of MVD in our study, both on H and E (2.2–6.1) and reticulin stain (2.8–6.8), was quite similar to the findings of Akhtar *et al*., who reported values ranging from 2.1 to 6.6 on H and E and 2.2–7.2 on reticulin stain. A significant finding was the higher MVD counts observed in atypical endometrial hyperplasia, similar to what was reported by Akhtar *et al*.[8]

On studying the immunohistochemical scores for ER and PR in the glandular epithelium, we found a notable decrease in IH score as progressed from the proliferative to the late secretory phase. Manjani *et al*. observed a gradual reduction in the expression of ER and PRs from the proliferative endometrium to hyperplasia, and ultimately to endometrial carcinoma. They concluded that these receptor levels have prognostic significance.[15] Masjeed *et al*. found higher ER expression in nonatypical endometrial hyperplasia compared to atypical hyperplasia and endometrial carcinoma.[16] Similarly, Gogoi observed elevated levels of both ER and PR in both glandular and stromal cells of the endometrium in cases of AUB without atypical hyperplasia, compared to endometrial carcinoma cases.[17] In our study, we observed decreased expressions of ER and PR with an increase in both grade and stage which is in accordance with the study by Stoian *et al*.[18] Masjeed *et al*. proposed that examining steroid receptor expression in AUB patients with endometrial carcinoma may offer valuable insights into tumor biological behavior, facilitating the development of personalized treatment regimens, thus further underlining the importance of steroid hormone receptor studies in endometrial pathology.[16]

Conclusion

The study highlighted the importance of evaluation of MVD, especially in atypical endometrial hyperplasia which may have a role in predicting the development of endometrial malignancy across various age groups. ER and PR expression is diminished in high-grade endometrial carcinomas compared to low-grade tumors, suggesting a potential correlation between immunohistochemical results and histologic grade for predicting patient outcomes. Thus, it is recommended that clinical examination; routine histopathology and IHC

markers should be judiciously used for an accurate diagnosis in women with AUB.

Ethical approval and patient consent

a. This study has been approved by the institute ethical committee with approval letter number – HIMSR/IEC/007/2022
b. This study has been conducted in accordance with the ethical principles mentioned in the Declaration of Helsinki (2013)
c. Patients have consented to participate in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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