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Expression of VEGF in Endometrial Hyperplasia with and Without Atypia And Endometrioid Endometrial Carcinoma and Its Association With Clinicopathological Parameters.

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KEYWORDS

EH-Endometrial Hyperplasia, EEC-Endometroid Endometrial Carcinoma, VEGF-Vascular Endothelial Growth Factor.

ABSTRACT:

INTRODUCTION:

Endometrial carcinoma accounts for the second most common malignancy in women globally. The main risk factor being unopposed estrogen can cause the progression of endometrial hyperplasia to endometrial carcinoma. One of the important mechanisms behind the progression of cancer is angiogenesis.

Vascular Endothelial Growth Factor (VEGF) is one of major proangiogenic growth factor which is directed to assess the biological behavior of endometrial cancer and thereby using as an excellent targeted antiangiogenic therapy.

AIM:

To study the expression of VEGF in normal endometrium, endometrial hyperplasia (EH) and Endometrioid Endometrial Carcinoma (EEC) by immunohistochemistry and to evaluate its association with clinicopathological parameters.

MATERIALS AND METHODS:

The study was conducted in the Department of Pathology in a tertiary medical college, Kanchipuram, Chennai, India from November 2022- November 2023(13 months) constituting 30 patients who underwent hysterectomy. Histopathological diagnosis was obtained along with the grade and stage of cancer and immunohistochemical evaluation was done on the representative sections using VEGF antibody. Statistical analysis was done using SPSS software version 27.0

RESULTS:

Out of 30 cases, 3 cases were diagnosed as normal proliferative endometrium, 6 cases as EH without atypia, 5 cases as EH with atypia and 16 cases as EEC. Among 16 EEC cases, grade 1, 2 and 3 comprised 5,6 and 5 cases respectively. Strong VEGF positivity was observed in EEC (30%) compared to mild positivity in atypical EH (13.33%) and EH without atypia (10%) and 6% of normal proliferative endometrium showed negative expression thereby showing significant statistical association(p-value<0.002). Also, VEGF expression was significantly increased in grade 3 (31.25%) and grade 2(25%) cases in comparison to mild positivity in grade 1 cases (31.25%) demonstrating significant statistical association between VEGF scoring and grading of EEC.

CONCLUSION:

VEGF expression was significantly increased in high grade of EEC and can be used to differentiate endometrial carcinoma from its precursor lesions.

INTRODUCTION

Endometrial carcinoma (EC) is the most frequent and ranks second in the most common gynecological malignancies all over the world[1,2]. The incidence of endometrial carcinoma in India is 4.3/1,00,000 women[3]. The pathogenesis of EC is multifactorial involving genetic variation of various molecules[4]. Incidence of endometrial cancer is directly related to the increasing age. This is most commonly seen in peri menopausal and postmenopausal women with less than 5% in women

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below 40 years of age[5,6]. EC usually presents with abnormal uterine bleeding, pelvic pain or mass effect, abdominal bloating and can be asymptomatic, the most common clinical presentation being postmenopausal bleeding[7]. Risk factors of EC primarily encompass early menarche, late menopause, increasing age, obesity, diabetes, menstrual disorders, anovulatory cycles, polycystic ovary syndrome, infertility and exogenous and endogenous estrogen[8]. Endometrial hyperplasia (EH) and EC can be diagnosed by several radiographic modalities[9] and it usually presents as thickened endometrium or endometrial polyp[10].

EH divides hyperplastic endometrium into Atypical endometrial Hyperplasia/Endometrial Intraepithelial Neoplasia (AH/EIN) and Endometrial Hyperplasia without atypia based on histopathological features[11]. EH usually occurs due to the unopposed action of estrogen and is the major precursor lesion of endometrial carcinoma[12]. EH primarily constitutes a group of lesions showing increase in gland to stroma ratio compared to the normal proliferative endometrium. Development of EH to endometrial cancer (EC) is associated with the level of architectural complexity, cytological atypia and myometrial invasion[13]. The risk of progression to carcinoma was 23% and 2% in atypical endometrial hyperplasia and endometrial hyperplasia without atypia respectively[14]. EC can be divided into various classes based on their histological features of which adenocarcinomas hold the majority of about 80%. Endometrioid adenocarcinomas constitute 65% and serous and clear cell adenocarcinomas form 20%[15].

Angiogenesis paves an important role in the development and progression of endometrial hyperplasia to endometrial carcinoma. This is explained by the microcirculatory- tissue theory[16,17]. Malignant endometrial cells have the tendency for uncontrolled growth and will be in high demand for oxygen and nutrients. This hypoxia disrupts the energy metabolism, thereby several proangiogenic factors are released from the endometrial cells and as a result a new vasculature will be formed around the tumor causing unlimited proliferation of tumor cells[18]. Several growth factors are released by the endometrium which are involved in angiogenesis such as epidermal growth factor (EGF), transforming growth factor (TGF-β) and Vascular Endothelial Growth Factor (VEGF). High microvessel density (MVD) being an indirect indicator of extreme tumor vascularization contributes to evolution and progression of endometrial cancer. This mechanism is also a major cause for local and distant metastatic spread of tumor[19].

The most common proangiogenic factor is Vascular Endothelial Growth Factor (VEGF). VEGF, also known as Vascular Permeability Factor (VPF) is one of the members of the Platelet Derived Growth Factor family of cystine knot growth factors. It serves as a specific mitogen which helps the endothelial cells for inducing angiogenesis by increasing the capillary proliferation, vascular permeability and protein extravasation[20]. Several studies have proved that VEGF is a major director of tumor angiogenesis in other cancers[21,22]. VEGF can aid in local angiogenesis, proliferation and differentiation of cells along with invasion and metastasis of tumor cells.

Distinguishing between two types of hyperplasia is very important for proper management. But differentiation based on microscopic findings can result in interobserver variation especially in diagnosis of EIN. Also, there is increasing need for grading and staging of endometrial carcinoma thereby determining the prognosis of the disease. This study aims to analyze the expression of VEGF in normal proliferative endometrium, endometrial hyperplasia and Endometrioid Endometrial carcinoma by immunohistochemistry and its association with grades and stages of endometrial carcinoma.

MATERIALS AND METHODS

This retrospective and prospective, cross-sectional study was conducted in the Department of Pathology in Private medical college, Kanchipuram, Chennai, India from November 2022- November 2023(13 months duration). The study included 30 patients who underwent hysterectomy in our institution. This study was conducted after obtaining a full and informed consent from each patient and was approved by the Institutional Ethics Committee (IEC) with reference number MMCH&RI IEC/PG/46/OCT/22.

Inclusion criteria:

1. All cases of hysterectomies diagnosed as endometrial hyperplasia and endometrial carcinoma are included in the study.

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Exclusion criteria:

1. Patients who underwent neo adjuvant therapy are excluded from the study.
2. Endometrial biopsies and samplings are also excluded.
3. Patients who are not willing to participate in the study.

Medical records were obtained from MRD and subsequently all the clinicopathological data such as age, presenting complaints and USG findings were retrieved. Final histopathological diagnosis was made after the complete evaluation of macroscopic **(Figure 1)** and microscopic examination of resected specimens. Histological diagnosis of selected cases was reviewed by two pathologists. Tumor staging was done based on the International Federation of Gynecology and Obstetrics (FIGO)staging system and histological grading according to the World Health Organization (WHO) criteria. Representative section was taken after reviewing all the sections and Immunohistochemistry was done using VEGF antibody. Section from lobular capillary hemangioma was taken as positive control for VEGF. Sections of thickness 4µm were obtained from paraffin blocks for immunohistochemistry and were processed with primary and secondary antibodies.

Scoring of VEGF[23]:

Criteria for VEGF immunopositivity is membranous or/and cytoplasmic positivity. Immunohistochemical evaluation of VEGF was done after assessing the following parameters:

1. Intensity of stain
2. Percentage of Cytoplasmic or membranous positive cells

Color intensity is graded from 0-3 as below:

0- Negative
1- Weak
2- Moderate
3- Strong intensity

Percentage of positive cells are also expressed 0 to 3:

0- Negative
1- < or =25% positive cells
2- 26-50% cells positive
3- > 50% positive cells.

Final Staining Score (FSS)[23] is calculated by totalling the two parameters and the final immunohistochemical interpretation is as follows:

0-2 = Negative reaction
3-4 = Mildly positive reaction
5-6 = Strongly positive immunoreaction.

Statistical Analysis:

The data collected was entered in MS excel software and coding of variables was done. Statistical analysis was done using SPSS software version 27.0 IBM. Descriptive statistics and Chi-square test was used to determine the association between categorical variables. The p value of <0.05 was taken as significant for statistical analysis.

Figure 1: Macroscopic image of endometrial carcinoma

A specimen of Total abdominal hysterectomy with endometrial cavity showing ulceroproliferative lesion.

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RESULTS

The age group of our selected study population is 43-70 years with mean age of 57.17 years and standard deviation of 7.857.

Among 30 hysterectomy cases, 53.33% (16) were diagnosed as endometrioid endometrial carcinoma of which Grade 1, grade 2 and grade 3 forming 31.25% (5), 37.5% (6) and 31.25% (5) respectively followed by 20% (6) as endometrial hyperplasia without atypia,16.66% (5) as endometrial hyperplasia with atypia and 10% (3) as normal proliferative endometrium **(Figure 2).** The microscopic appearance and VEGF Immunohistochemical image of above-mentioned lesions are shown in **Figure 3:**

Figure 2: Frequency of cases taken as specimens

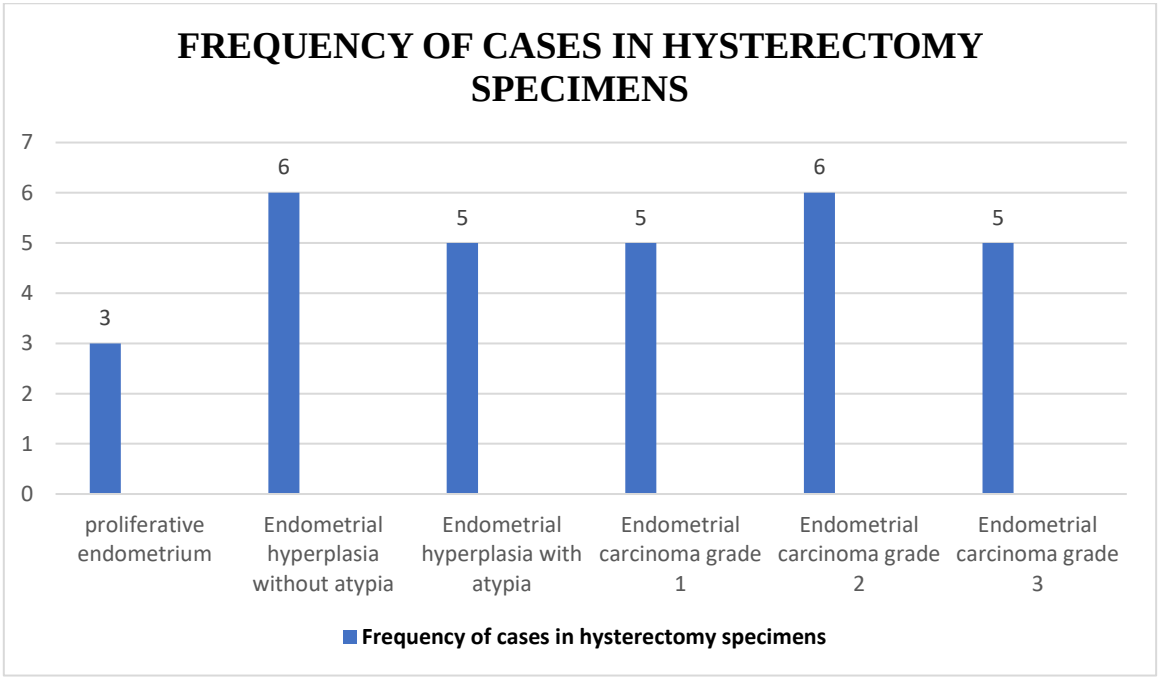
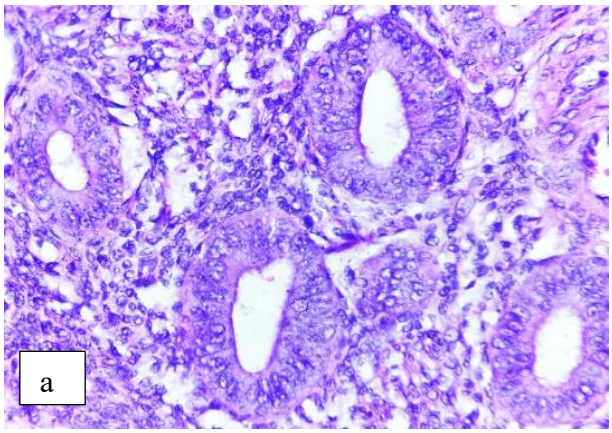
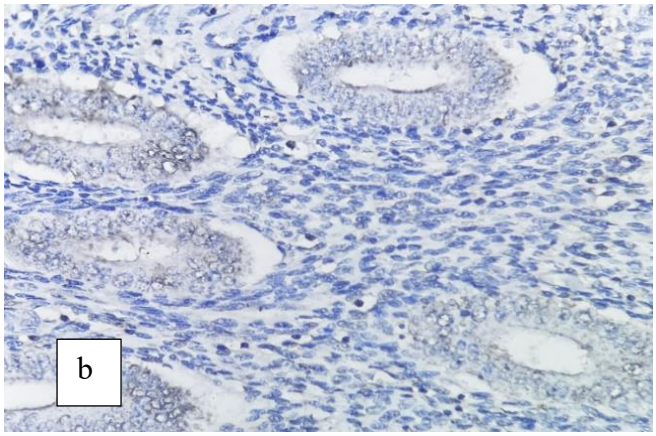


Figure 3: Microscopic appearance and VEGF Immunohistochemical image



a)Proliferative Endometrium- Tubular glands with compact stroma, H&E, magnification 40X



b) Proliferative Endometrium- Negative expression of VEGF Immunohistochemical staining with FSS of 2, magnification 40X

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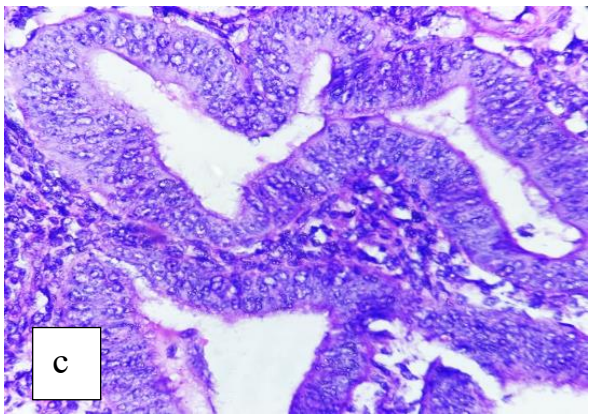
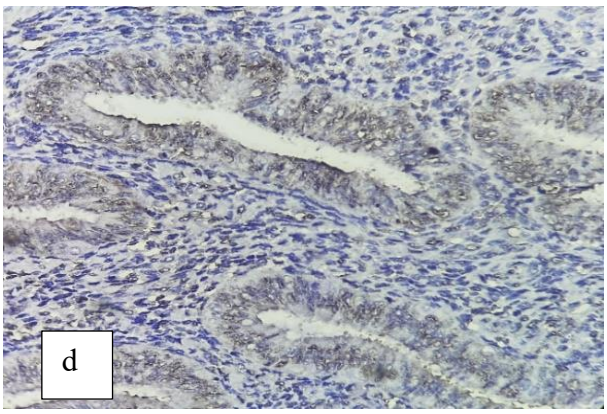
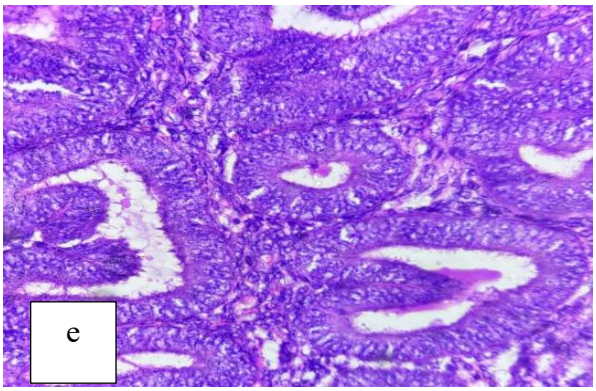


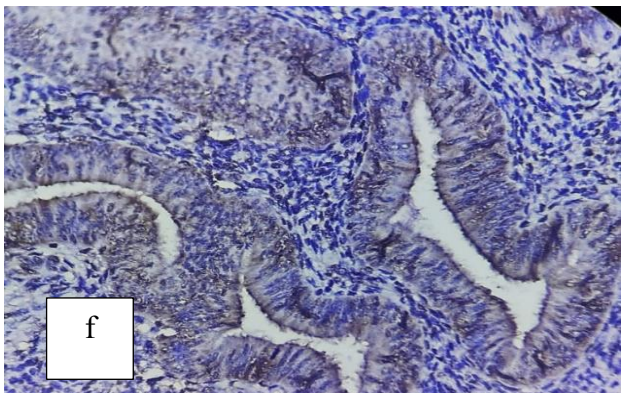
c) EH without atypia- Closely packed endometrial glands without atypia, H&E, magnification 40X



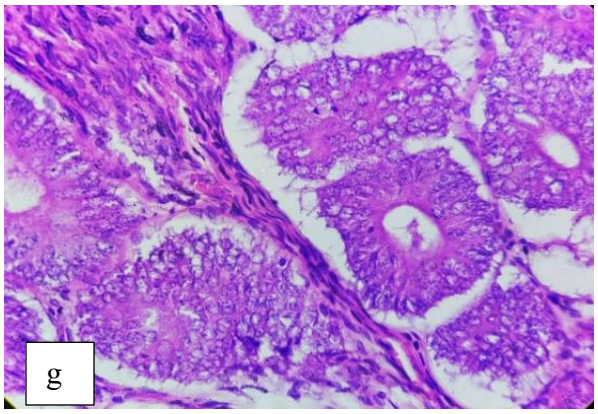
d) EH without atypia- Mild positive expression of VEGF with FSS of 3, magnification 40X



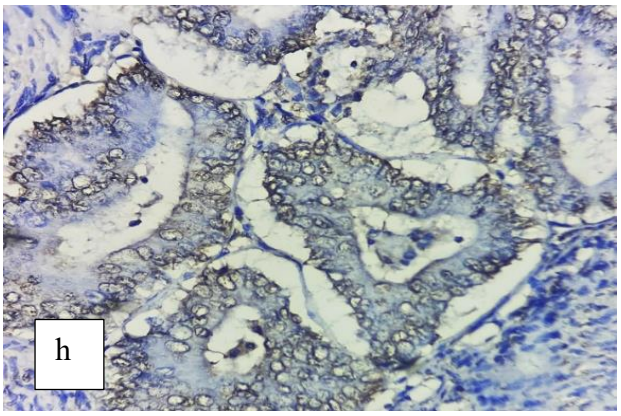
e) EH with atypia- Complex glands with crowding and cellular atypia, H&E, magnification 40X



f) EH with atypia- Mild positive expression of VEGF with FSS of 4, magnification 40X



g) EEC Grade 1- Predominantly confluent glandular architecture, H&E, magnification 40X



h) EEC Grade 1- Mild positive expression of VEGF with FSS of 4, magnification 40X

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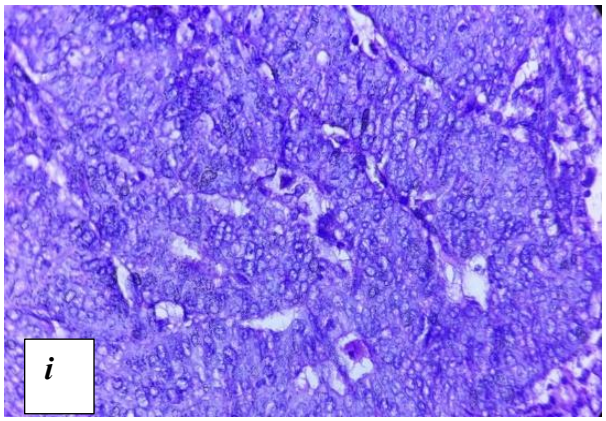
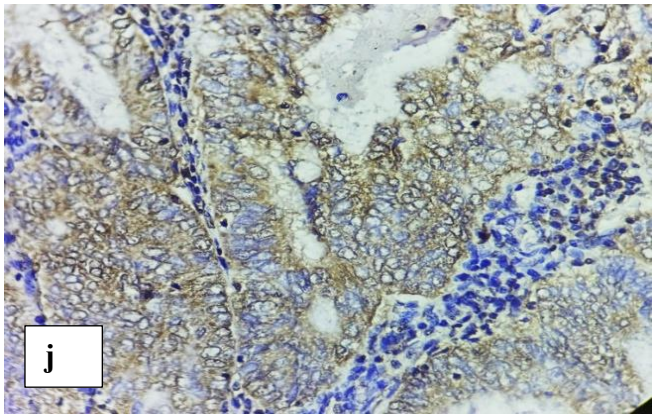
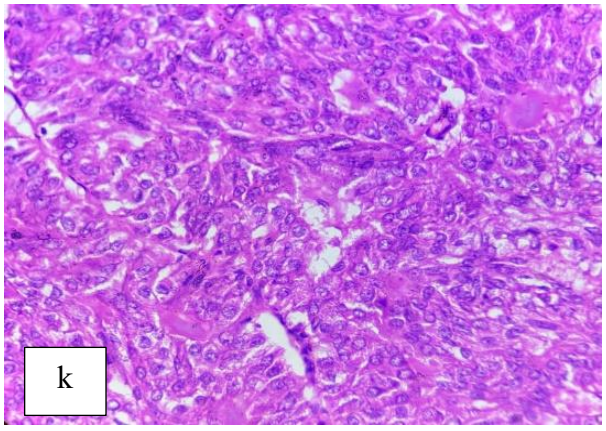


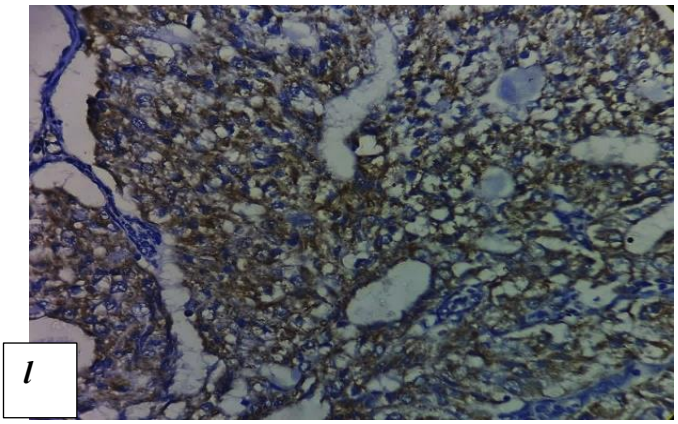
i)EEC Grade 2- Both glandular and solid growth pattern present with cytological atypia, H&E, magnification 40X



j) EEC Grade 2- Strong positive expression of VEGF with FSS of 5, magnification 40X



k) EEC Grade 3- Predominantly solid growth pattern with marked nuclear atypia, H&E, magnification 40X



l) EEC Grade 3- Strong positive expression of VEGF with FSS of 6, magnification 40X

In the present study, 66.6% (4) of the cases of endometrial hyperplasia without atypia were in the 4th decade of life and 33.33% (2) cases in the 5th decade of life. 60% (3) of the cases of atypical endometrial hyperplasia were in the 5th decade of life and 40% (2) in the 4th decade of life. About 75% (12) of the cases of EEC were observed to occur in the 6th decade, and 25% (4) in the 5th decade of life **(Figure 4).** All cases of endometrial hyperplasia without atypia were observed in premenopausal women in comparison to atypical endometrial hyperplasia and EEC among women in postmenopausal age showing significant statistical association (p- value< 0.003) **[Table 1].**

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Figure 4: Age distribution

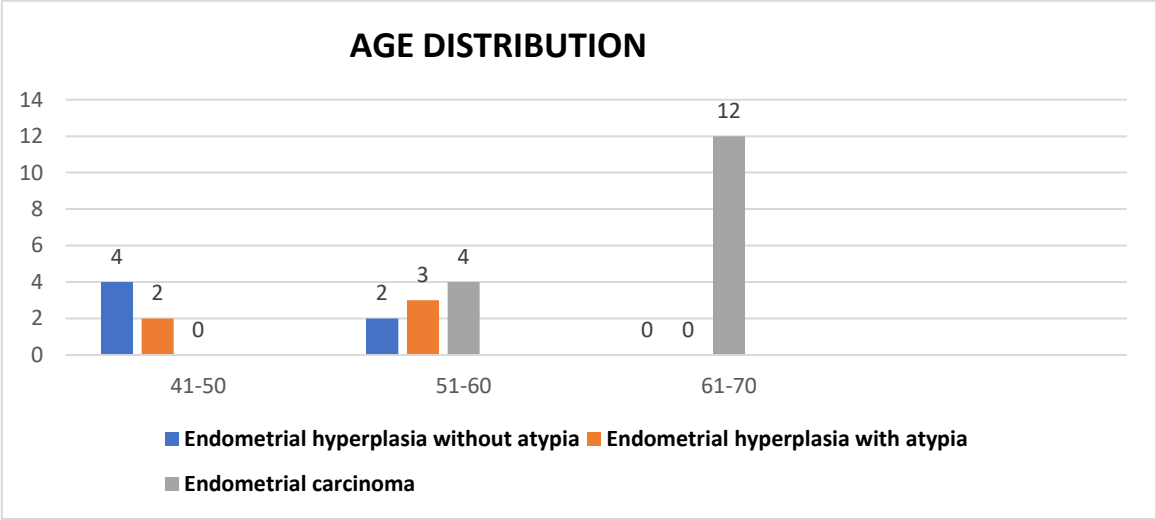

TABLE 1: ASSOCIATION BETWEEN DIAGNOSIS AND AGE:

	Diagnosis					
Age group(years)	**Normal proliferative endometrium**	**Endometrial hyperplasia without atypia**	**Endometrial hyperplasia with atypia**	**Endometrial carcinoma**	**Total**	**p- value**
41-50	**1**	**4**	**2**	**0**	**7**	**0.003***
51-60	**2**	**2**	**3**	**4**	**11**	
61-70	**0**	**0**	**0**	**12**	**12**	
Total	**3**	**6**	**5**	**16**	**30**	

Among 30 cases of endometrial pathology, most of the patients presented with postmenopausal bleeding (56.7%) followed by abnormal uterine bleeding (20%) and abdominal pain (10%) **[Figure 5]**. A 93.75% (15) of EEC cases presented with postmenopausal bleeding per vagina followed by abdominal pain (6.25%) in contrast to 45.45% (5) of EH which primarily presented with abnormal uterine bleeding followed by post-menopausal bleeding (18.18%), abdominal pain (18.18%) and asymptomatic (18.18%). This showed significant association between histopathological diagnosis and clinical presentation(p-value<0.011) **[Table 2].**

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Figure 5: Clinical presentation

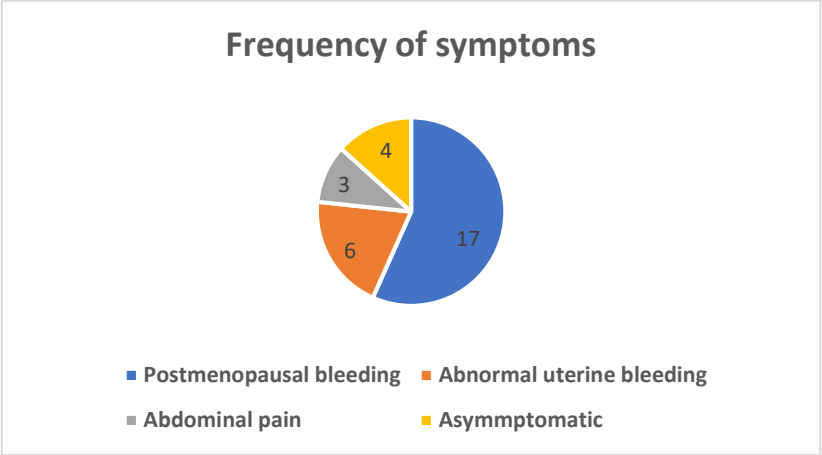

TABLE 2: ASSOCIATION BETWEEN DIAGNOSIS AND CLINICAL PRESENTATION

Diagnosis	Post-menopausal bleeding	Abnormal uterine bleeding	Abdominal pain	Asymptomatic	Total	p-value
Endometrial hyperplasia without atypia	0	3	1	2	6	0.011*
Endometrial hyperplasia with atypia	2	2	1	0	5	
Endometrial carcinoma	15	0	1	0	16	
Proliferative endometrium	0	1	0	2	3	
Total	17	6	3	4	30	

p-value <0.05 is significant

In the study we observed VEGF expression was markedly increasing on comparing from normal proliferative endometrium to endometrial hyperplasia without atypia to atypical endometrial hyperplasia and markedly increased in endometrioid endometrial carcinoma. Expression of VEGF was based on Final Staining Score (FSS) and it showed strong positivity in 9 cases of EEC (30%) in comparison to mild positivity in 4 cases of endometrial hyperplasia with atypia (13.33%) and 3 cases of endometrial hyperplasia without atypia (10%). 6% (2) of normal proliferative endometrium showed negative expression. Corrected Chi-square test showed a significant association between histopathological diagnosis and VEGF scoring(p-value<0.002) **[Table 3].**

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TABLE 3: ASSOCIATION BETWEEN DIAGNOSIS AND VEGF SCORING

DIAGNOSIS	NEGATIVE	MILDLY POSITIVE	STRONGLY POSITIVE	Total	p- value
EH without atypia	3	3	0	6	0.002*
EH with atypia	1	4	0	5	
Endometrial carcinoma	0	7	9	16	
Proliferative endometrium	2	1	0	3	
Total	4	17	9	30	

p-value <0.05 is significant

Out of 16 EEC cases, 31.25% (5) were grade 3 which shows the marked strong positivity in VEGF expression compared to 25% (4) grade 2 cases whereas 31.25% (5) of grade 1 and 12.5% (2) of grade 2 endometrial carcinoma cases showed mild positivity in VEGF expression. Association between VEGF score and grading of EEC is statistically significant (p-value-<0.002). **[Table 4]**

TABLE 4: ASSOCIATION BETWEEN GRADES OF EEC AND VEGF SCORING

	VEGF SCORING				
Diagnosis	Negative	Mildly positive	Strongly positive	Total	p-value
EEC Grade 1	0	5	0	5	0.002*
EEC Grade 2	0	2	4	6	
EEC Grade 3	0	0	5	5	
Total	0	7	9	16	

p-value <0.05 is significant

With respect to myometrial invasion, 81.25% (13) cases showed less than 50% myometrial invasion compared to 18.75% (3) of cases involving more than 50% invasion which shows significant statistical association (p-value 0.008) **[Table 5].**

TABLE 5: ASSOCIATION BETWEEN MYOMETRIAL INVASION AND VEGF SCORING IN ENDOMETRIOID ENDOMETRIAL CARCINOMA

	VEGF SCORING				
Myometrial invasion	Negative	Mildly positive	Strongly positive	Total	p value
Less than 50%	0	6	7	13	0.008*
More than 50%	0	1	2	3	
Total	0	7	9	16	

p-value <0.05 is significant

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Out of 16 EEC cases, 93.75% cases (15) were diagnosed as FIGO stage 1 and 6.25% (1) as stage 3. VEGF showed strong positivity in 8 cases (50%) and mild expression in 7 cases (43.75%) of stage 1 endometrial carcinoma. One case of stage 3(6.25%) carcinoma showed strong expression of VEGF. Corrected Chi-square test revealed insignificant statistical association between VEGF scoring and staging of endometrial carcinoma(p-value<0.09). **[Table 6]**

TABLE 6: ASSOCIATION BETWEEN FIGO STAGING IN ENDOMETRIOID ENDOMETRIAL CARCINOMA AND VEGF SCORING

	ssVEGF SCORING				
FIGO Staging	**Negative**	**Mildly positive**	**Strongly positive**	**Total**	**p-value**
Stage 1	**0**	**7**	**8**	**15**	**0.09**
Stage 3	**0**	**0**	**1**	**1**	
Total	**0**	**7**	**9**	**16**	

p-value <0.05 is significant

DISCUSSION

Angiogenesis is one of the main mechanisms attributing to the progression of endometrial hyperplasia to endometrial carcinoma in view of its rate of invasion and metastatic potential which was described first by Judah Folkman in 1969. This paves a major role in the prognosis of endometrial cancer and its survival[24]. VEGF expressed in normal endometrium was upregulated in endometrial hyperplasia and showed significant increase in endometrial carcinoma. Also, expression of VEGF shows marked increase depending on the progression from grade 1 to grade 3 endometrial carcinoma exhibiting its poor prognostication.

All cases of EH without atypia (20%) and atypical endometrial hyperplasia (16.7%) were most common in the fourth and fifth decades of life whereas 75% (12) of EEC in 6th decade of life and 25% (4) of EEC are more common in fifth decade of life. So, in our study all the cases of EEC were observed in elderly women in postmenopausal age group.

According to Creaseman W et al[25], 75% women with endometrial carcinoma were in postmenopausal age group. Holland CM et al. [26], in their study done on EIN and EC documented the mean age as 57 years and age group of study population was 51-87 years. According to the study by Mayumi Saito et al.[27], the mean age of the patients was 56 years. G. plataniotis and Castiglione et al., in their study reported 90% of women in the study population were more than 50 years and the mean age of the patients was observed as 63 years. SK Samim Rahaman et al[23] documented mean age as 59.08 years and all endometrial carcinoma cases in postmenopausal age. According to study by Chumak Z.V[28], 417 specimens were assessed of which atypical endometrial hyperplasia was seen in the 4th decade of life and endometrial malignancy after 50 years of age.

In the present study, 93.75% (15) of EEC cases clinically presented with postmenopausal bleeding whereas 45.45% (5) of EH patients presented with abnormal uterine bleeding. Majority of the women presented with postmenopausal bleeding which was similar to the study conducted by Gull B et al[29] and SK Samim Rahaman et al[23].

Strong positivity for VEGF were shown by 9 cases of EEC (30%) compared to mild positivity seen in 4 cases of EH with atypia (13.33%) and 3 cases of EH without atypia (10%). There was a significant association between VEGF scoring and histopathological diagnosis (p-value< 0.002). VEGF expression was increased in EEC compared to atypical endometrial hyperplasia consistent with the studies conducted by Mahecha A. M et al[30]and Cai S et al[31]. In the study performed by Guset G et al.[32], and Yokoyama Y et al.[33], reported significant increased VEGF expression with progression from normal proliferative endometrium to EH without atypia to EIN and finally in EC. Study by Chumak Z.V[28] demonstrated expression of VEGF as an important factor for assessing the progression of EH to endometrial adenocarcinoma.

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Studies conducted by Holland C M et al[26], Saito et al[27] and Fine B et al[34], documented increased VEGF expression in EH and EC in comparison to normal endometrium. Studies conducted by Anthony J Guidi et al.[35] and Aparna A Kamat et al[36], reported that there is strong expression of VEGF in EC and demonstrated VEGF as an important angiogenic marker which provided base for anti-angiogenic therapy. According to the study conducted by SK Samim Rahaman et al[23] VEGF expression was significantly increased in EC and atypical endometrial hyperplasia compared to normal proliferative endometrium.

Strong VEGF positivity was seen in all cases of grade 3 EEC (31.25%) compared to 4 cases of grade 2(25%) whereas mild positive expression was observed in 5 cases of grade 1(31.25%) and 2 cases of grade 2(12.5%) EEC which showed significant association between VEGF scoring and EEC grading (p-value< 0.002). Increased expression of VEGF correlates with higher grade of endometrial cancer as documented in study by Sunita B et al[37]. Studies performed by Sanseverino F et al[38] and Hirai M et al[39] observed that VEGF expression rate was increased in high grade EC (grade 2 & 3) compared to grade 1. In the analysis performed by Vincent Castonguay et al.[40] and Aparna A Kamatt et al[36], VEGF overexpression was increasingly demonstrated in high grade EC and was associated with poor prognosis.

In the present study, the majority (81.25%) of the cases of EEC presented with myometrial invasion less than 50% which showed significant association with VEGF scoring (p-value<0.008). An insignificant statistical association (p-value<0.09) was observed between VEGF scoring and FIGO staging which was similar to the study done by SK Samim Rahaman et al[23].

CONCLUSION(S)

Increased expression of VEGF is seen in high grades of Endometrioid Endometrial Carcinoma and is the main factor which determines the prognostication in patients with endometrial cancer. Study of VEGF along with the hormonal receptors could help in assessing the high-risk patients of endometrial cancer. Also, VEGF, being the major proangiogenic growth factor, plays an important role in providing targets for antiangiogenic(anti-VEGF) therapy against endometrial cancer.

LIMITATION(S)

The major limitation of the study is that it constituted only a small study group of 30 patients who underwent surgery in a tertiary hospital and a shorter duration of study (13 months). Therefore, implementing a larger study population in a higher center for longer duration could add new facts and particulars to the present study.

CONFLICTS OF INTEREST

The authors of the study documented that there are no conflicts of interest pertaining to the publication of the paper.

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