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Expression of Vegf and Endoglin in the Spectrum from Endometrial Hyperplasia to Endometrial Carcinoma

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Abstract: ***Endometrial carcinoma develops through a sequence of pathological changes that often begin with endometrial hyperplasia and progress toward malignancy. Angiogenesis is a key biological process in this transformation, with vascular endothelial growth factor (VEGF) and endoglin (CD105) playing important roles in new blood vessel formation. This study evaluated VEGF expression and CD105-positive microvessel density in 100 cases of endometrial hyperplasia without atypia, endometrial hyperplasia with atypia/endometrial intraepithelial neoplasia, and endometrial carcinoma. Immunohistochemical analysis demonstrated a consistent rise in VEGF H-scores and CD105 microvessel density from benign lesions to premalignant conditions and finally to carcinoma. Statistical analysis showed significant differences among all histopathological groups, while receiver operating characteristic analysis confirmed strong diagnostic accuracy for both markers in distinguishing benign lesions from atypical and malignant lesions. Non-endometrioid carcinomas also exhibited higher angiogenic activity than endometrioid carcinomas. The findings highlight the close association between angiogenesis and endometrial lesion progression and support the use of VEGF and CD105 as valuable quantitative.***

Keywords: Endometrial Carcinoma, Endometrial Hyperplasia, VEGF Expression, CD105, Angiogenesis

1. Introduction

Endometrial carcinoma is one of the most common cancers affecting women worldwide and is currently the sixth most common carcinoma. (1, 2) In India, the number of cases appears to be increasing and it contributes to roughly 5% of cancers in women; this rise is often linked to urbanization and lifestyle-related factors, particularly the increasing burden of metabolic syndrome. (3)

In the WHO classification, Endometrial hyperplasia is divided into two main categories: Endometrial hyperplasia without atypia and endometrial hyperplasia with atypia, with endometrial hyperplasia with atypia form being the more important precursor to endometrial carcinoma.(4,5) The likelihood of progression to cancer is generally low for hyperplasia without atypia (about 1–3%), but it is much higher for atypical hyperplasia (around 20–46%).(4,5) Broadly, endometrial cancers are also described as endometrioid carcinomas, which commonly develop through an estrogen-driven pathway, and non-endometrioid carcinomas, which are more often estrogen-independent.(6,7)

Regardless of the specific pathway or subtype, the transition from hyperplasia to invasive carcinoma relies heavily on the induction of a supportive vascular network. Angiogenesis plays a key role in how these lesions progress, because a tumor cannot grow beyond a very small size (around 1–2 mm) unless it develops its own blood supply.(8,9,10,11,12) VEGF is a major driver of this process: it stimulates endothelial cell growth and movement and helps these cells survive, largely through signaling via VEGFR-2.(13,14) VEGF levels rise in response to hypoxia through HIF-1α and are further influenced by pathways such as PI3K/AKT and MAPK, and higher VEGF expression is generally associated with more aggressive disease and poorer outcomes.(15)

Another important marker of tumor-related angiogenesis is Endoglin (CD105), a TGF-β receptor component that is strongly expressed in endothelial cells of actively proliferating tumor vessels.(14,15) Because CD105 is more selective for tumor-associated neovasculature than broad endothelial markers like CD34, it is often considered a better indicator of pathological angiogenesis.(18,27) Endoglin may also promote endothelial–mesenchymal transition, contributing to the formation of abnormal, leaky vessels that can support tumor spread.(18)

Overall, many studies describe a gradual increase in VEGF expression and CD105-associated microvessel density as the histology progresses from hyperplasia without atypia to atypical hyperplasia and then to endometrial carcinoma.(20,21) Typically, hyperplasia without atypia shows low VEGF positivity (often under 10%) and low CD105 microvessel density, atypical hyperplasia shows intermediate VEGF expression (about 13–30%) with a moderate rise in CD105, and carcinoma shows stronger VEGF positivity (around 30–50%) with markedly higher CD105 microvessel density, often most evident at invasive margins.(21,27) Increased VEGF and CD105 are also frequently reported alongside adverse features such as higher FIGO stage, deeper myometrial invasion, lymphovascular invasion, nodal metastasis, and reduced survival (22, 23, 26, 28)

2. Materials and Methods

Study design-
A cross-sectional, analytical study was conducted over an 18-months. The study protocol received approval from the Institutional Ethics Committee and all study related procedures adhered to the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Population and Sample Size-
The study population comprised women diagnosed with endometrial hyperplasia (with or without atypia) or endometrial carcinoma based on histopathological examination of endometrial biopsy or hysterectomy

specimens received during the study period. A total of 100 cases were included, providing adequate statistical power for detection of significant differences in mean VEGF H-scores and microvessel density across histopathological categories (power >80%, alpha=0.05, effect size=0.8).

3. Inclusion and Exclusion Criteria-

Inclusion criteria

- Women of any age with histopathologically confirmed diagnosis of endometrial hyperplasia without atypia, endometrial hyperplasia with atypia (endometrial intraepithelial neoplasia), or endometrial carcinoma.
- Availability of adequate tissue material in formalin-fixed, paraffin-embedded blocks suitable for immunohistochemical analysis,
- Provision of written informed consent for participation in research.

Exclusion criteria

- Insufficient tissue material for immunohistochemical staining,
- Patients who had received chemotherapy, radiotherapy, or hormonal therapy prior to tissue sampling, as such treatments may alter angiogenic marker expression.
- Cases with extensive tissue necrosis or poor fixation precluding accurate immunohistochemical interpretation,
- Patients who declined consent for research participation.

Sample Collection and Histopathological Examination

Endometrial tissue specimens were obtained through biopsy, curettage, or hysterectomy, fixed in 10% neutral buffered formalin for 12-24 hours, processed through graded alcohol dehydration and xylene clearing, and embedded in paraffin blocks. Serial 4-5 µm sections were cut, H&E-stained, and examined microscopically by two independent pathologists. Histopathological classification followed 2020 WHO criteria [4]. Endometrial hyperplasia without atypia showed increased gland-to-stroma ratio without cytological atypia. Endometrial hyperplasia with atypia/EIN demonstrated crowded glands with cytological atypia (enlarged nuclei, irregular contours, loss of polarity) [4,5]. Carcinomas were classified by histological subtype (endometrioid and non-endometrioid) [9]. The final distribution comprised 32 endometrial hyperplasia without atypia, 38 endometrial hyperplasia with atypia/EIN, and 30 endometrial carcinoma cases.

Immunohistochemical Staining:

Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using the manual streptavidin-biotin peroxidase method.

Representative tumor blocks were selected. Formalin-fixed paraffin-embedded sections were mounted on poly-L-Lysine coated slides and heat conditiones at 60 °C for 60 minutes to enhance tissue adherence. Sections were deparaffinized using xylene and rehydrated sequentially through graded alcohol to water.

Heat-induced epitope retireval was performed in Tris-EDTA buffer (pH 9.0) after 20 minutes, slides were cooled at room temperature and rinsed in phosphate buffered saline. Then endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 10 minutes, followed by PBS washes.

The primary antibodies used include

- VEGF, clone VG1, Type- Mouse monoclonal antibody, located in cytoplasm and incubation period was 60 minutes at room temperature.
- Endoglin (CD 105), clone EP274, type- Rabbit monoclonal antibody, located in endothelial cell membrane and cytoplasm of endothelial cells and incubation was done 60 minutes at room temperature.

After antigen retrieval, the slides were washed in PBS and incubated with HRP-conjugated secondary antibody. The chromogen to aid visibility used here was 3,3-diaminobenzidine (DAB) chromogen.

Slides were then counterstained with hematoxylin, dehydrated, cleared and mounted with DPX.

VEGF H-Score and CD105 MVD Assessment

VEGF immunoreactivity was semi-quantitatively scored using the H-score method. (22) For each case, five representative HPFs (400×) were evaluated. The proportion of glandular epithelial cells showing cytoplasmic staining was estimated separately for weak (1+), moderate (2+), and strong (3+) intensity categories (0 indicating no staining). The H-score was computed as: 1 × (% of 1+ cells) + 2 × (% of 2+ cells) + 3 × (% of 3+ cells), producing a total score from 0 to 300. (22) The final score per case was taken as the mean of the five fields. Scoring was performed independently by two blinded pathologists, with high interobserver agreement (ICC >0.85).

CD105 microvessel density was assessed using the Weidner hot-spot approach. (16) Sections were first screened at low magnification (40×/100×) to locate 3–5 areas with the greatest concentration of CD105-positive vessels (hot spots), typically near the tumor–stroma interface or invasive edge. Microvessels were then counted at 200× within each selected hot spot. Any clearly separated CD105-positive endothelial cell or endothelial cell cluster- whether or not a lumen was evident—was counted as a single microvessel. (16, 20) Vessels with an obvious muscular wall, and vessels within necrotic or hemorrhagic areas, were excluded. The MVD for each case was recorded as the mean vessel count per HPF across the assessed hot spots. Two blinded observers performed counts independently (ICC >0.85).

Statistical Analysis

Statistical analysis used SPSS version 27.0. Normality was assessed using Shapiro-Wilk test. Normally distributed variables were summarized as mean ± SD; non-normal variables as median (IQR). One-way ANOVA with post-hoc Tukey's HSD compared VEGF H-scores and CD105 MVD across three histopathological categories. Independent t-test or Mann-Whitney U test compared endometrioid versus non-endometrioid carcinomas. Pearson or Spearman correlation assessed VEGF-CD105 relationships. ROC curve analysis determined optimal diagnostic thresholds using Youden's index. $P<0.05$ was considered significant.

All participants provided written informed consent. The study received Institutional Ethics Committee approval and followed Declaration of Helsinki principles.

4. Results

Demographic Characteristics

The study cohort comprised 100 women with mean age 47.88 ± 9.03 years (range: 28-68 years) and median age 47 years (IQR: 41-55 years). Age distribution demonstrated approximate normality (Shapiro-Wilk test, P=0.312), with the majority of participants concentrated in the 40-55 year age bracket, consistent with the typical age distribution for endometrial pathology in perimenopausal and early postmenopausal women.

The histopathological distribution included 32 cases (32.0%) of endometrial hyperplasia without atypia, 38 cases (38.0%) of endometrial hyperplasia with atypia/endometrial intraepithelial neoplasia (EIN), and 30 cases (30.0%) of endometrial carcinoma. Among the 30 carcinoma cases, histological subtype classification revealed 24 endometrioid carcinomas (80.0% of carcinomas) and 6 non-endometrioid carcinomas (20.0%), including 3 serous carcinomas, 2 clear cell carcinomas, and 1 mixed carcinoma.

VEGF Expression Across Histopathological Categories

VEGF immunohistochemical staining demonstrated predominantly cytoplasmic localization within endometrial glandular epithelial cells, with variable intensity ranging from absent to strong (3+) staining. Stromal cells occasionally displayed weak cytoplasmic positivity but were not included in H-score assessment.

VEGF H-scores demonstrated progressive elevation across the histopathological spectrum; Endometrial hyperplasia without atypia exhibited the lowest mean H-score (71 ± 13, median 73, IQR 64-83, range 41-96), reflecting minimal angiogenic activity in benign proliferative lesions. Endometrial hyperplasia with atypia/EIN demonstrated intermediate H-scores (mean 170 ± 18, median 169, IQR 163-179, range 125-210), representing a 2.4-fold increase compared to hyperplasia without atypia. Endometrial carcinoma showed the highest H-scores (mean 245 ± 43, median 255, IQR 231-276, range 130-294), representing a 3.5-fold increase compared to benign hyperplasia and a 1.4-fold increase compared to atypical hyperplasia.

One-way ANOVA revealed highly significant differences in mean VEGF H-scores among the three histopathological categories (F=522.7, P<0.001). Post-hoc pairwise comparisons using Tukey's HSD test demonstrated statistically significant differences between all group pairs : hyperplasia without atypia vs. hyperplasia with atypia (mean difference=99, 95% CI: 91.2-106.8, P<0.001); hyperplasia without atypia vs. carcinoma (mean difference=174, 95% CI: 165.3-182.7, P<0.001); and hyperplasia with atypia vs. carcinoma (mean difference=75, 95% CI: 67.1-82.9, P<0.001).

Receiver operating characteristic (ROC) curve analysis demonstrated excellent diagnostic accuracy of the H-score in differentiating hyperplasia without atypia from atypia/carcinoma. The area under the curve (AUC) was 0.922 (95% CI: 0.855–0.988; p < 0.001), indicating strong discriminatory ability. A cut-off value of ≥110.5 provided optimal diagnostic performance, yielding a sensitivity of 94.1% and specificity of 87.5%. The Youden index was 0.816, confirming the robust classification capacity of the H-score in identifying premalignant and malignant lesions.

The progressive gradient in VEGF expression across the lesion spectrum supports the hypothesis that increasing angiogenic drive accompanies histopathological progression from benign hyperplasia through premalignant change to invasive carcinoma.

CD105-Positive Microvessel Density Across Histopathological Categories

CD105 immunohistochemistry demonstrated selective staining of vascular endothelial cells, with strongest reactivity in small capillaries and proliferating vessels at the tumor-stromal interface. Mature vessels with thick muscular walls showed minimal or absent CD105 staining, confirming the specificity of CD105 for activated, proliferating endothelium.

Microvessel density demonstrated a stepwise increase paralleling histopathological progression (Endometrial hyperplasia without atypia showed the lowest MVD (mean 8 ± 2 vessels/HPF, median 8, IQR 7-10, range 5-12), reflecting baseline vascular density in benign proliferative endometrium. Endometrial hyperplasia with atypia/EIN exhibited intermediate MVD (mean 17 ± 2 vessels/HPF, median 17, IQR 15-18, range 13-20), representing a 2.1-fold increase compared to hyperplasia without atypia. Endometrial carcinoma demonstrated the highest MVD (mean 25 ± 4 vessels/HPF, median 25, IQR 23-27, range 17-32), representing a 3.1-fold increase compared to benign hyperplasia and a 1.5-fold increase compared to atypical hyperplasia.

One-way ANOVA revealed highly significant differences in mean CD105 MVD among the three histopathological categories (F=438.6, P<0.001). Post-hoc pairwise comparisons using Tukey's HSD test demonstrated statistically significant differences between all group pairs (Table 10): hyperplasia without atypia vs. hyperplasia with atypia (mean difference=9, 95% CI: 7.9-10.1, P<0.001); hyperplasia without atypia vs. carcinoma (mean difference=17, 95% CI: 15.7-18.3, P<0.001); and hyperplasia with atypia vs. carcinoma (mean difference=8, 95% CI: 6.9-9.1, P<0.001).

Comparison Between Endometrioid and Non-Endometrioid Carcinomas

Within the endometrial carcinoma cohort (n=30), separate analysis of endometrioid (n=24) and non-endometrioid (n=6) subtypes revealed significant differences in angiogenic marker expression.

Non-endometrioid carcinomas demonstrated significantly higher mean VEGF H-scores (263 ± 22) compared to endometrioid carcinomas (237 ± 45), with independent samples t-test revealing statistical significance (t=1.89, df=28, P=0.032). This 11% elevation in VEGF expression in non-endometrioid subtypes likely reflects their more

aggressive biological behavior, higher proliferative rates, and greater metastatic potential.

Similarly, non-endometrioid carcinomas exhibited significantly higher mean CD105 MVD (28 ± 3 vessels/HPF) compared to endometrioid carcinomas (24 ± 4 vessels/HPF), with independent samples t-test confirming statistical significance (t=2.18, df=28, P=0.021). This 17% elevation in microvessel density in non-endometrioid subtypes parallels their elevated VEGF expression and supports the concept that high-grade, aggressive endometrial carcinomas demonstrate intensified angiogenic phenotypes.

5. Discussion

This cross-sectional study systematically quantified VEGF expression and CD105-positive microvessel density across the full histopathological spectrum of endometrial lesions, from endometrial hyperplasia without atypia through with atypia to endometrial carcinoma. The findings demonstrate progressive, stepwise elevation of both angiogenic markers paralleling histopathological progression, with excellent diagnostic performance in distinguishing benign from atypical/malignant lesions. These results provide quantitative benchmarks for angiogenic marker expression in endometrial pathology and support their integration into routine diagnostic and prognostic assessment.

The findings of the present study demonstrate concordance with multiple prior investigations while providing enhanced quantitative resolution through H-score methodology and systematic assessment across the complete lesion spectrum.

Table 8: Comparison of present study with similar published studies

Study	N	Key Findings
Present study (2025)	100	VEGF H-score: 71 (benign) → 170 (EIN) → 245 (carcinoma); CD105 MVD: 8 → 17 → 25 vessels/HPF; AUC 0.97-0.98
Bai et al. (2025) [24]	38	VEGF: 78.95% carcinoma vs 25% normal (P<0.001); MVD: 15.66±1.23 carcinoma vs 5.60±0.35 normal (P<0.001)
Gopinath et al. (2024) [25]	30	30% strong VEGF in carcinoma; correlation with grade (P<0.002) and invasion (P<0.008)
Qiang et al. (2024) [26]	1251	Meta-analysis: High VEGF predicts worse OS (P=0.02), DSS (P=0.008); correlates with stage, grade, LN mets
Erdem et al. (2007) [27]	66	CD105 superior to CD34/VEGF for distinguishing carcinoma from hyperplasia (P<0.01)
Yoshida et al. (2010) [28]	82	CD105 MVD: 13.38±7.53 carcinoma vs 5.2±2.1 normal (P<0.001); correlates with stage, LNM, ALI

Table 8 summarizes comparative data from key published studies. The progressive gradient in VEGF and CD105 expression documented in the present study aligns closely with findings from diverse geographical populations and methodological approaches, supporting the biological universality of angiogenic activation as a core component of endometrial carcinogenesis.

Notably, the present study's quantitative H-score methodology provides superior resolution compared to categorical positive/negative classification employed in several prior studies. The H-score range of 41-294 observed across the study cohort demonstrates substantial inter-case heterogeneity that would be obscured by simple categorical classification. This quantitative approach enables establishment of evidence-based diagnostic thresholds (H-score >125, MVD >12 vessels/HPF) with objectively defined sensitivity and specificity, facilitating standardization across laboratories and potential clinical implementation.

6. Study Strengths and Limitations

Methodological strengths include standardized, validated quantitative methodologies (H-score, Weidner hot-spot method) with excellent inter-observer reliability (ICC>0.85), ensuring reproducible quantification. The cohort encompassed complete histopathological spectrum (Enodmetrial hyperplasia without atypia through Endometrial hyperplasia with atypia to Endometrial carcinoma), enabling comprehensive angiogenic marker progression assessment. Systematic histopathological review by experienced pathologists ensured accurate WHO classification. Blinded immunohistochemistry assessment minimized bias. Sample size (n=100) provided adequate statistical power for ROC curve analysis.

Limitations include cross-sectional design minimized the follow up data among individual patients. Lack of molecular subtyping (POLE-ultramutated, MMRd, p53-mutant, NSMP) limited correlation with molecular categories guiding clinical management[8,9,12]. Clinical outcome data (progression-free survival, overall survival) were unavailable, precluding direct prognostic performance assessment. Small non-endometrioid carcinoma numbers (n=6) limit subtype comparison statistical power. Single tertiary referral center in a city potentially limits generalizability.

Moving forward, prospective longitudinal studies are needed to track hyperplasia progression over time in individual patients. It will also be crucial to integrate these angiogenic markers with comprehensive molecular profiling—such as POLE, MMRd, and p53 status- to better understand how angiogenesis interacts with distinct molecular subtypes. Furthermore, exploring multi-marker signatures that incorporate additional angiogenic factors like angiopoietins or Fibroblast Growth Factors could further refine our prognostic models. Ultimately, clinical outcome studies and biomarker-driven trials will be essential to determine if VEGF and CD105 quantification can effectively guide targeted anti-angiogenic therapies.

7. Conclusion

The transition from endometrial hyperplasia without atypia to Endometrial carcinoma is driven by a significant, measurable increase in angiogenesis. Both VEGF expression and CD105-assessed Microvessel density demonstrated a clear, stepwise

elevation that closely mirrored histopathological progression. Because these quantitative markers effectively differentiate between benign tissue and atypical or malignant lesions, integrating them into routine histopathological evaluations could offer valuable diagnostic clarity. Ultimately, establishing these objective benchmarks provides a stronger foundation for risk stratification and could help guide personalized patient management in endometrial pathology.

On behalf of all authors, corresponding author states that there is no conflict of interest.

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