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*Original Article*

# Expression of vascular endothelial growth factor and insulin-like growth factor-1 in endometrial polyps and their clinical significance

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**Abstract:** Objective: This study aimed to evaluate the role of insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) in endometrial polyps (EP). Methods: EP patients (n=40) and controls (n=40) aged ≤40 years were recruited, and hysteroscopy was performed in the mid-secretory phase. Polyp tissues (n=40), adjacent normal endometrium (n=34) and normal endometrium (n=40) were collected for immunohistochemistry. HSCORE was employed to evaluate the expression of IGF-1 and VEGF in the gland and stroma, followed by comparison among groups. Results: The expression of IGF-1 and VEGF in the gland and stroma of adjacent normal endometrium was significantly lower than in polyp tissues and normal endometrium ($P$<0.05). However, there was no significant difference between polyp tissues and normal endometrium ($P$>0.05). There was a positive correlation between IGF-1 expression and VEGF expression in the gland of tissues from EP patients and normal endometrium ($r$=0.345 and 0.087, respectively, $P$<0.05), but correlation was not observed in the stroma of tissues from EP patients and normal endometrium ($P$>0.05). Conclusion: The expression of IGF-1 and VEGF in the gland and stroma of adjacent normal tissues was at a low level on EP patients of mid-secretory phase. Down-regulated IGF-1 expression may reduce VEGF expression in the gland of endometrium to inhibit the angiogenesis of endometrium before embryo implantation and reduce the endometrial receptivity, leading to infertility of EP patients.

**Keywords:** Vascular endothelial growth factor, insulin-like growth factor-1, endometrial polyp, mid-secretory phase, endometrial receptivity

## Introduction

Endometrial polyps (EPs) refer to the limited, benign masses with an elongated pedicle in the inner lining of the uterus. They are mainly composed of stroma formed by some fibrous connective tissues, vessels with thick wall and endometrial glands. Women with EPs are usually asymptomatic, and some may present menstrual abnormalities. EP may cause infertility and is easy to re-occur after treatment. To date, EP has been a common gynecological disease. In our previous study, the clinical characteristics of 400 EP women who had failure in assisted reproduction or other causes of infertility were reviewed, and results showed polypectomy was able to improve the clinical pregnancy rate. This suggests that EP may be an independent factor affecting the embryo implantation during the assisted reproduction and a potential cause of infertility [1]. It is reported that 15-25% of infertility women are diagnosed with EP [2]. For women with unexplained infertility, polypectomy may be beneficial for the improvement of pregnancy outcomes and able to elevate the success rate of assisted reproduction [3]. However, the mechanism underlying the EP induced infertility (embryo implantation and pregnancy outcome) is still unclear.

In the peri-implantation phase, the endometrial vascular remodeling is essential for the embryo implantation and provides vascular receptivity for embryo implantation [4]. Only sufficient blood flow can assure the increased metabolic

requirements of embryos as well as the successful embryo implantation [5]. Some growth factors are involved in the angiogenesis, of which vascular endothelial growth factor (VEGF) is an important one. VEGF is a critical regulator of angiogenesis and the biomarker of endometrial receptivity [6]. Study [7] has confirmed that the VEGF expression in the endometrium of EP patients in mid-secretory phase is lower than in healthy controls. Thus, low VEGF expression may affect the endometrial blood supply and intrauterine environment to disturb the embryo implantation. In addition, there is complete insulin-like growth factor system (IGFs) in the uterus, which is closely related to the endometrial periodic change, endometrial receptivity, embryo implantation and embryo development. IGF-1 is a member of IGF family and is an alkaline peptide with 70 amino acids. IGF-1 is involved in the endometrial decidualization as well as the proliferation and differentiation of trophoblasts and may directly affect the pregnancy outcome [8, 9]. Studies have revealed that IGF-1 is not only related to the endometrial receptivity, and but also involved in the angiogenesis [10]. There is evidence showing that IGF-1 may up-regulate VEGF expression via the proteins and transcription factors related to the activation of estrogen and progesterone receptors, both of which are critical factors involved in embryo implantation and angiogenesis. However, no study has been conducted to detect the expression of both VEGF and IGF-1 in the endometrium of EP patients in mid-secretory phase and evaluate their correlation. In the present study, the expression of VEGF and IGF-1 in the endometrium of EP patients in mid-secretory phase and their role in the endometrial receptivity and embryo implantation was explored, which may provide evidence for the mechanism underlying the EP related infertility in women.

## Materials and methods

### *Clinical characteristics*

A total of 40 patients who received endometrial polypectomy by hysteroscopy and 40 controls with male factor infertility or infertility of unknown causes were recruited into present study between June 2015 and December 2015. Written informed consent was obtained from each patient before surgery. The polyp tissues and adjacent normal endometrium were collected from EP patients, and normal endometrium from controls. The adjacent normal tissues were collected from the normal endometrium around the polyps, and the normal endometrium was taken from women with normal uterine cavity. The clinical characteristics were also recorded.

Inclusion criteria: 1) the menstrual cycle was normal (28-35 days) and surgery was done at day 19-24 of menstrual cycle; (2) patients were aged 20-40 years; (3) patients did not receive steroid treatment within prior 3 months; 4) the results of hysteroscopy showed EP in patients and normal uterus in control group which were confirmed by pathological examination. Exclusion criteria: 1) patients had concomitant uterine lesions (such as cesarean scar diverticulum, intrauterine adhesion, submucosal uterine fibroid, uterine malformations [including uterine septum]); 2) patients had concomitant polycystic ovary syndrome, uterine fibroid, endometriosis or ovarian tumors; 3) patients had abnormal sexual hormones; 4) patients had chromosomal abnormalities; 5) patients had concomitant other diseases such as hyperthyroidism, hypothyroidism, diabetes and hypertension.

### *Sample collection, immunohistochemical detection and scoring with HCORE system*

Polyp tissues and adjacent normal tissues were collected from EP patients, and normal endometrium was from controls. Tissues were fixed in formaldehyde, embedded in paraffin and subjected to immunohistochemistry with 2-step method. Antibodies were anti-IGF-1 polyclonal antibody and anti-VEGF polyclonal antibody from Wuhan Boster Biotech Co., Ltd. Immunohistochemistry was done according to manufacturer's instructions.

Scoring of VEGF and IGF-1 expression: In negative control group, the antibody was replaced with PBS. For each section, 10 fields were randomly selected at a magnification of 400×, and positive cells had granules in the cytoplasm and on the membrane. HSCORE system was employed for the semi-quantification of protein expression [11] according to the staining intensity and distribution of positive cells in the glands and stroma. HSCORE=ΣPi*(i+1), where i represents staining intensity after considering the background staining (0, negative; 1, weakly positive; 2, positive; 3, strongly positive), Pi rep-

**Table 1.** Clinical characteristics of EP patients and controls

| | EP group (n=40) | Control group (n=40) | *P* |
|---|---|---|---|
| Age (yr)* | 32.58 ± 0.69 | 30.80 ± 0.64 | 0.064 |
| Body mass index (kg/m$^2$)** | 20.91 ± 0.26 | 21.07 ± 0.29 | 0.607 |
| Gravidity** | 1.30 ± 0.19 | 1.18 ± 0.21 | 0.512 |
| Menarche (y)** | 14.02 ± 0.21 | 13.63 ± 0.19 | 0.188 |

Notes: *Independent Samples T Test; **Mann-Whitney Test.

resents the proportion of positive cells (0-100%) and 1 is the correction coefficient. The scoring was done by two experienced pathologists in a blind manner, and 3 scores were obtained independently from the glands and stroma and a mean was calculated for the glands and stroma.

*Statistical analysis*

Statistical analysis was done with SPSS version 13.0. Quantitative data are expressed as means ± standard deviation ($\bar{x}$ ± s) and qualitative data as frequency or rate. Quantitative data with normal distribution or (and) homogeneity of variance were tested with independent samples t test or one way analysis of variance (ANOVA) and those with abnormal distribution or heterogeneity of variance were compared with non-parametric tests. Mann-Whitney U was used for comparisons between two groups and *Kruskal-Wallis H* test for multiple groups followed by paired test. Qualitative data or rates were compared with chi square test. Correlation analysis was done with *Spearman* Rank correlation. A value of $P<0.05$ was considered statistically significant.

## Results

*Clinical characteristics*

The characteristics of EP patients and controls are shown in **Table 1**. Finally, 6 tissues were diagnosed as EP tissues and 34 tissues as endometrial tissues. As shown in **Table 1**, there were no significant differences in the age, BMI, number of pregnancy and menarche ($P>0.05$).

*Expression of IGF-1 and VEGF in EP tissues, adjacent endometrial tissues and normal endometrial tissues*

Immunohistochemistry was done to detect the protein expression of IGF-1 and VEGF in the EP tissues, adjacent endometrial tissues and normal endometrial tissues (**Figure 1**). Expression of IGF-1 and VEGF was detectable in the glands and stroma of 3 groups. As shown in **Table 2**, the scores of expression of IGF-1 and VEGF in both glands and stroma of adjacent normal tissues were significantly lower than those of EP tissues and normal endometrial tissues of three groups ($P<0.05$). Although the scores of IGF-1 expression in EP tissues were lower than those of normal endometrial tissues and the scores of VEGF in EP tissues were higher than those of normal tissues, no significant differences were observed between EP tissues and normal endometrial tissues ($P>0.05$).

*Correlation between IGF expression and VEGF expression*

*Spearman* correlation analysis was employed to further explore the correlation between IGF expression and VEGF expression in both EP patients and controls. As shown in **Table 3**, the VEGF expression was positively related to IGF-1 expression in the glands of tissues from EP patients and normal endometrial tissues ($r=0.345$ and 0.087, respectively; $P<0.05$), but correlation between them was not observed in the stroma ($P>0.05$).

## Discussion

Our previous study showed endometrial polypectomy could improve the pregnancy rate [1]. Other clinical studies also confirm that EP is closely related to infertility in women and endometrial polypectomy may significantly improve the pregnancy outcome. However, the mechanism underlying the effect of EP on the pregnancy outcome is still poorly understood. Some investigators propose that it is related to the EP induced reduction of endometrial receptivity [12]. Endometrial receptivity refers to the capability of the uterus to receive oosperm implantation and subsequent development of oosperm into the embryo in a specific phase. “Implantation window” refers to the specific phase in which the uterus receive oosperm implantation. Generally, the “implantation window” is at day 20-24 of normal menstrual cycle or 7-9 days after ovulation when the uterine endometrium is in the mid-secretory phase and the uterus presents the highest receptivity.

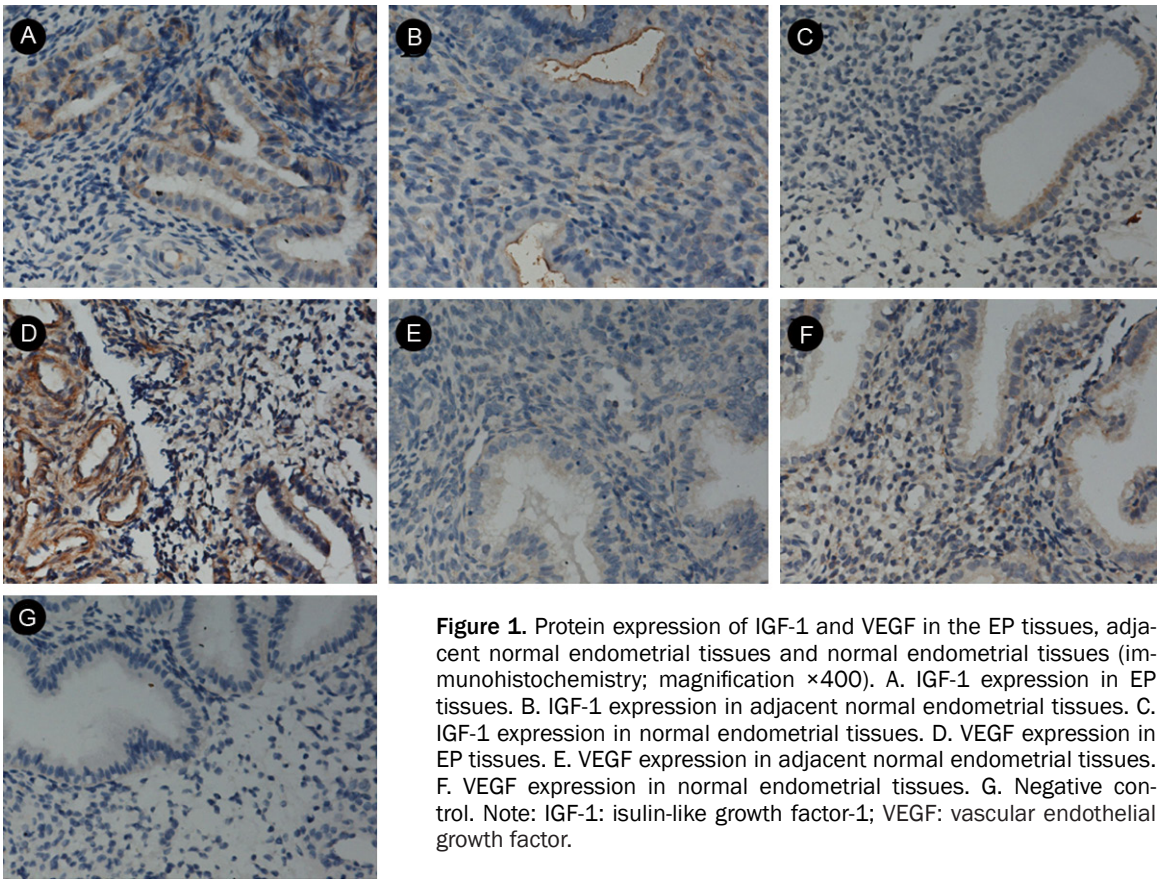


**Figure 1.** Protein expression of IGF-1 and VEGF in the EP tissues, adjacent normal endometrial tissues and normal endometrial tissues (immunohistochemistry; magnification ×400). A. IGF-1 expression in EP tissues. B. IGF-1 expression in adjacent normal endometrial tissues. C. IGF-1 expression in normal endometrial tissues. D. VEGF expression in EP tissues. E. VEGF expression in adjacent normal endometrial tissues. F. VEGF expression in normal endometrial tissues. G. Negative control. Note: IGF-1: isulin-like growth factor-1; VEGF: vascular endothelial growth factor.

The embryo implantation is a complex physiological process regulated by multiple factors and has involvement of cell proliferation, apoptosis, adhesion and angiogenesis. Of these processes, angiogenesis is a key one. In the mid-secretory phase of menstrual cycle, a series of changes may occur in the endometrium, which allows the interaction between the embryo and the endometrium before implantation by expressing signaling molecules and vascular remodeling at the adhesion site. The angiogenesis provides a material basis for the embryo implantation [13]. The successful embryo implantation, placentation and subsequent maintenance of pregnancy require the angiogenesis and regulation at the maternal-fetal interface. Sufficient blood supply via the blood vessels is required before the embryo implantation in the endometrium, which may assure the development of placental villous vessels in the first trimester of pregnancy and promote the transportation of nutrients and oxygen. Available studies indicate that the increases in the vascular density and vascular permeability of the endometrium in secretory phase of menstrual cycle are beneficial for the embryo implantation. That is, the better the blood supply to the endometrium, the better the endometrial receptivity is.

VEGF is a key cytokine involved in angiogenesis [14]. The microvascular density (MVD) of the endometrium peaks in the mid-secretory phase when the VEGF expression is at a high level, showing the consistence in the peak time between MVD and VEGF expression. This indicates that VEGF may promote the angiogenesis in the endometrium [15]. Gong et al [16] found VEGF was highly expressed in the endometrium where the embryo implants at 3-5 days after fertilization, suggesting an active angiogenesis. The endometrium is enwraping the embryo at 5 days after fertilization when the VEGF expression and MVD show the same tendency to the endometrial expression of osteopontin (OPN), a marker of endometrial receptivity. This indicates that VEGF may promote the formation of capillary network to enhance the endometrial receptivity and improve the embryo implantation. When VEGF expression is at a low level,

**Table 2.** Scores of IGF-1 and VEGF expression in EP tissues, adjacent normal endometrial tissue and normal endometrial tissues

| | Location | EP tissues (n=40) | Adjacent normal endometrial tissues (n=34) | Control endometrium (n=40) | *P* value |
|---|---|---|---|---|---|
| IGF-1 | Gland | 1.19 ± 0.04* | 1.05 ± 0.02* | 1.32 ± 0.10* | 0.001 |
| | Stroma | 1.19 ± 0.05* | 1.07 ± 0.03* | 1.29 ± 0.11b* | 0.001 |
| VEGF | Gland | 2.02 ± 0.11* | 1.51 ± 0.14* | 1.70 ± 0.12* | <0.001 |
| | Stroma | 1.33 ± 0.07* | 1.11 ± 0.05* | 1.20 ± 0.04* | 0.001 |

Notes: Comparisons were done with nonparametric Mann-Whitney U test. *Significant differences at the mid-secretory phase were observed between EP tissues and adjacent normal endometrial tissues and between adjacent normal endometrial tissues and normal endometrial tissues (P<0.05).

**Table 3.** Correlation between VEGF expression and IGF-1 expression in the glands and stroma

| Groups | Location | Correlation | Spearman's correlation coefficient | *P* value |
|---|---|---|---|---|
| EP group | Gland | IGF-1/VEGF | 0.345 | 0.003 |
| | Stroma | IGF-1/VEGF | 0.194 | 0.098 |
| Control group | Gland | IGF-1/VEGF | 0.087 | 0.048 |
| | Stroma | IGF-1/VEGF | -0.314 | 0.593 |

the angiogenesis is compromised at the site of embryo implantation, leading to a poor villous formation and reduced endometrial receptivity. In the present study, results showed the VEGF expression in the adjacent normal endometrial tissues of EP patients was significantly lower than in normal endometrial tissues of mid-secretory phase, indicating that the angiogenesis in the adjacent normal endometrium is compromised, which may reduce the endometrial receptivity and then affect the embryo implantation. Although the VEGF expression was at a high level in the EP tissues, the focally thickened endometrium has no normal functions and is unsuitable for the embryo implantation. In addition, Hornung et al [17] found that VEGF secreted by the endometrial glands could affect the nutrient supply to the blastula and induce the chemotaxis and adhesion of blastula to the site of EP. Thus, they proposed that the secretion of VEGF is a marker of blastula development and implantation. Thus, EP might secret VEGF to induce the chemotaxis of blastula to the site of EP. Thus, this may cause the implantation of blastula in the endometrium with EP that has no functions or the adjacent normal endometrium with poor receptivity.

IGF-1 is a specific growth factor expressed in the maternal-fetal interface in the first trimester of mammalians [18, 19]. The IGF-1 expression is closely related to the pregnancy outcome. Thus, some clinicians propose that the IGF-1 expressed in the embryo and endometrium may serve as a marker of endometrial receptivity [20, 21]. Studies have shown that fibroblasts can stimulate the migration of trophoblast cells in the extracellular matrix in the serum free medium only in the presence of IGF-1 [22]. Charmaine et al confirmed that IGF-1 could increase the adhesion of blastula in vitro to improve the embryo implantation [8]. Green et al investigated the impacts of IGF-1 at different concentrations and specific IGF-1 antibody on the mouse embryo in vitro. They found that IGF-1 at an appropriate concentration was determinant for the development of mouse embryo [23]. Our results showed IGF-1 expression in the endometrium of EP patients in mid-secretory phase was significantly lower than in normal endometrium, indicating that reduced IGF-1 expression in the endometrium of EP might reduce the endometrial receptivity, resulting in infertility.

In recent years, there is evidence [24] showing that IGF-1 is involved in the angiogenesis. IGF-1 may stimulate the differentiation, migration and homing of endothelial progenitor cells and induce the proliferation of corneal cells and retinal endothelial cells as well as promote angiogenesis [25]. Similar findings have also been found in cancer cells. Zhu et al [26] found IGF-1 could induce VEGF expression in breast cancer cells to promote angiogenesis, resulting in cancer progression and metastasis. However, inhibition of IGF-1 may cause damage to angiogenesis. For example, in diabetes mellitus, miR-320 has been found to reduce IGF-1 expression, impairing the angiogenesis [27]. In addition, investigators have conducted therapies of some cancers by using IGF-1 inhibitors in which inhibition of IGF-1 may suppress angiogenesis to block the growth of cancer cells [28].

This suggests that VEGF is positively regulated by IGF-1 and specifically acts on vascular endothelial cells to induce cell division. In the present study, our results showed IGF-1 and VEGF expression showed similar tendency in the EP tissues and adjacent normal endometrial tissues, but there was no significant correlation between IGF-1 expression and VEGF expression respectively. As the EP tissue and adjacent normal endometrial tissue are from the same patient, the EP tissues and adjacent normal endometrial tissues was used as a single group for correlation analysis of the expression of VEGF and IGF-1. Results showed the similar tendency in the IGF-1 and VEGF expression in the endometrial glands of EP patients and controls and significant correlation was also observed between IGF-1 expression and VEGF expression in the endometrial glands. This indicates the synergistic effects of IGF-1 and VEGF. Our results were consistent with those reported by Monika et al [29] who for the first time found IGF-1 could induce VEGF mRNA expression and promote VEGF secretion in the endometrium of female mammalians in the first trimester. This indicates that IGF-1 may be a major regulator of VEGF during the embryo implantation. In the endometrial glands, IGF-1 may reduce VEGF expression to affect the angiogenesis in the endometrium, which compromises the endometrial receptivity of EP patients, affecting the embryo implantation and development and finally the pregnancy outcome. In the present study, results showed the IGF-1 and VEGF expression in the endometrial stroma showed a similar tendency, but it displayed an opposite tendency in the normal endometrium although there was no correlation between IGF-1 expression and VEGF expression. Thus, we can not conclude the correlation between IGF-1 expression and VEGF expression in the endometrial stroma and not exclude the involvement of other pathways in the compromised endometrial receptivity of EP patients.

Taken together, the expression of IGF-1 and VEGF is at a low level in the endometrial tissues of EP patients, and there is a positive correlation between IGF-1 expression and VEGF expression in the gland of endometrial tissues from both EP patients and controls. Down-regulated IGF-1 expression may reduce VEGF expression, leading to compromised angiogenesis in the endometrium, which then reduce the vascular permeability of the endometrium during embryo implantation. This is harmful to the infiltration and implantation of the oosperm and reduces the endometrial receptivity, which may be a cause of EP related infertility in women.

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## Disclosure of conflict of interest

None.

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