

# Diagnostic Value of New Features for Endometritis under Hysteroscopy

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## Abstract

**Objective:** To evaluate the value of neovascularization, endometrial irregular hyperplasia and endometrial polypoid hyperplasia in diagnosis of chronic endometritis. **Design:** retrospective cohort study. **Setting:** University teaching hospital. **Patient(s):** A consecutive series of 222 cases of diagnostic hysteroscopy. **Intervention(s):** Endometrial biopsy specimens were obtained after hysteroscopy for routine histology and immunohistochemistry for plasma cells using a CD138 epitope. **Main Outcome Measure(s):** Neovascularization, endometrial polypoid hyperplasia, endometrial irregular hyperplasia of the hysteroscopic features in the diagnosis of CE. **Result(s):** A total of 670 infertile patients underwent hysteroscopy, and the incidence of microscopic neovascularization was about 22.4%. Among them, 222 patients underwent pathological examination and CD138 immunoassay. 94 patients were diagnosed Chronic endometritis pathologically. Neovascularization was moderately consistent with CE. (Kappa coefficient was 0.46, 95% 0.342-0.578,  $P < 0.05$ ; OR=8.153), there was no strong correlation between endometritis, polypoid hyperplasia and irregular hyperplasia. The sensitivity, specificity, positive predictive value and negative predictive value of neovascularization were 71.27%, 75%, 67.68% and 78.05%, respectively, and the diagnostic accuracy was 73.42%. **Conclusion:** There was a moderate consistency between neovascularization and CE, which could be used as a characteristic index for physicians to judge chronic endometritis and improve the accuracy of CE diagnosis by hysteroscopy. Irregular hyperplasia and polypoid hyperplasia of uterus have no statistical significance for the diagnosis of chronic endometrium, but whether they affect embryo implantation rate should be discussed in the future.

## Keywords

Neovascularization, Endometrial Irregular Hyperplasia, Endometrial polypoid hyperplasia, Chronic Endometritis

Chronic endometritis (CE) is currently considered to be a pathological condition in which the endometrial stroma is infiltrated by inflammatory cells [1]. In previous clinical practice, CE was often ignored due to slight lack of specificity of symptoms, difficult diagnosis and time-consuming diagnosis. In recent years, studies have reported that the incidence of CE in infertility patients is gradually increasing, and CE has become one of the common diseases in the reproductive field [2]. According to relevant studies, the incidence of CE in infertility patients is 0.2%-46%; In 2010, Makrakis et al. found that CE incidence was as high as 42% in women with repeated transplant failures;

Bouet et al. found that the incidence of CE in patients with recurrent abortion in early pregnancy was 27% [3-5].

At present, the diagnosis of CE mainly relies on hysteroscopy, pathological examination, and CD138 immunohistochemical staining, in which the presence of plasma cell infiltration in the endometrial stroma by histological staining is the gold standard for the diagnosis of CE. Hysteroscopy is recommended by scholars for its intuitive and comprehensive observation and evaluation of endometrium. At present, the characteristics of CE under hysteroscopy are microscopic polyps, interstitial edema, and patchy hyperemia [6-9]. However, Dongmei Song, M. Ed [10] found that the accuracy of hysteroscopy in diagnosing CE was only 67%, which could not replace histological examination as a diagnostic tool. The reason is that the endometrium presents diversity under hysteroscopy, such as neovascularization, endometrial polypoid hyperplasia, and endometrial irregular hyperplasia. However, the diagnostic value of these clinical phenotypes for CE is not clear. This paper focuses on the diagnostic value of these characteristics in chronic endometritis under hysteroscopy.

## 1. Data and Methods

### 1.1 Data

**Subjects:** Infertility patients who underwent hysteroscopy in the Reproductive Center of the Sixth Medical Center of the PLA General Hospital from August 2018 to April 2021 were collected. The age range was 28-47 years,  $36.1 \pm 5.55$  years. Inclusion criteria: patient age < 50 years; having a normal sexual life; the couple had no major diseases and active infectious diseases, and their chromosomes were normal. Exclusion criteria: (1) The patient has endocrine diseases and other diseases resulting in infertility; (2) Having history of intrauterine operation in the past two months, b-mode ultrasonography showed no uterine malformation, fibroids, mediastinum, etc. Tubal effusion; (3) Having taken birth control pills or other hormonal drugs in the last 3 months; (4) intrauterine adhesion; (5) the male has serious semen abnormalities resulting in infertility. The study was conducted with the informed consent of the participating patients.

### 1.2 Methods

Hysteroscopy was performed during endometrial proliferation. Xenon cold light source, TV camera and monitoring system from Germany STORZ company are used. Hysteroscopy adopts the hard hysteroscopy of STORZ Company TROPHY and the soft hysteroscopy of OLYMPUS Company HYF-XP fiber. Normal saline was used as the distention medium. The initial distention pressure was set at 60-80 mm Hg under anesthesia, and the pressure was adjusted during operation. All surgical procedures were performed by the same group of physicians, with clear field of vision and close observation of intimal changes. During hysteroscopy, each patient was kept and recorded with video for pathological patients.

### 1.3 Main outcome measures

**Neovascularization** (see Figure 1 and Figure 2): Dilated or ruptured superficial and subepithelial blood vessels on the endometrium.

**Endometrial irregular hyperplasia** (see Figure 3): This is a diffuse polypoid appearance in the uterine cavity, characterized by soft protrusions, uneven thickness, and no apparent polyp.

**Endometrial polypoid hyperplasia** (see Figure 4): elongated conical or fingerlike, with prominent pedicles, glands, and stroma but no evident vascular axis.



Figure 1. Small scattered neovascularization.

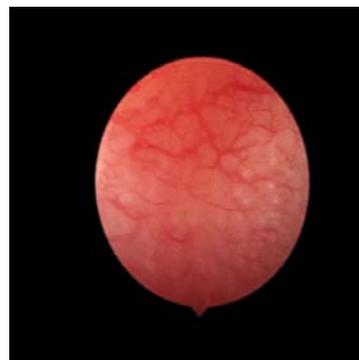
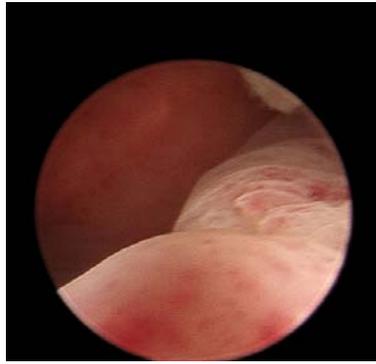


Figure 2. Large hyperplasia of blood vessels.



**Figure 3. Endometrial Irregular hyperplasia.**



**Figure 4. Endometrial Polypoid hyperplasia.**

Chronic endometritis: Plasma cells can be seen under the tissue examination microscope. Chronic endometritis is diagnosed by positive HE staining or CD138 immunohistochemistry.

### 1.4 Statistical methods

SPSS 22.0 software is adopted for statistical analysis. The measurement data of normal distribution were expressed as mean  $\pm$  standard deviation ( $X \pm S$ ), and independent sample T test was used for analysis between groups. The consistency between hysteroscopic neovascularization and pathological diagnosis (Kappa value) was compared. When  $0.4 < \text{Kappa} \leq 0.7$ , the consistency between the two diagnostic methods was considered to be moderate. HE staining and/or CD138 immunohistochemical diagnosis were used as reference.

The Pearson  $X^2$  independence test was used for correlation analysis of categorical variables, and multivariate non-conditional Logistic regression analysis was performed for all variables with  $P < 0.05$  in univariate analysis.  $P < 0.05$  was considered as statistically significant difference.

## 2. Results

A total of 670 infertile patients underwent hysteroscopy, and the incidence of microscopic neovascularization was about 22.4%. In 222 patients, the uterine cavity was scratched with a small scraper and pathological examination was performed. Histopathological examination and immune CD138 detection were performed. Chronic endometritis was diagnosed pathologically in 94 patients (see Table 1). The Kappa coefficient of consistency between CE diagnosis of neovascularization and pathology was 0.46 (95%CI interval 0.342-0.578,  $P < 0.05$ ), indicating moderate consistency between the two (see Table 2). The sensitivity, specificity, positive predictive value and negative predictive value of CE in neovascularization diagnosis were 71.27%, 75%, 67.68% and 78.05%, respectively, and the diagnostic accuracy was 73.42%. Endometrial polypoid hyperplasia, irregular hyperplasia and endometritis are not strongly correlated.

Among 222 patients, 94 cases were pathologically diagnosed as CE, 67 cases of neovascularization (71.27%,  $\text{OR}=8.153$ , 95%CI 4.377-15.186,  $P < 0.05$ ), 24 cases of polypoid hyperplasia (25.53%,  $\text{OR}=1.772$ , 95%CI 0.840-3.739  $P = 0.133$ ) and uneven thickening in 25 cases (26.60%,  $\text{OR}=0.744$  95%CI 0.973-1.096  $P = 0.291$ ).

**Table 1. Consistency analysis of neovascularization, irregular hyperplasia, polypoid hyperplasia and CE**

	The pathologic result		Kappa value	P
	(+)	(-)		
neovascularization			0.46	< 0.001
(+)	67	32		
(-)	27	96		
irregular hyperplasia			-0.024	0.705
(+)	25	37		
(-)	69	91		
polypoid hyperplasia			0.056	0.358
(+)	24	26		
(-)	70	102		

**Table 2. The possibility of CE in neovascularization, endometrial irregular hyperplasia and endometrial polypoid hyperplasia**

	B	p-value	OR	95%CI
neovascularization	2.098	0.000	8.153	4.377-15.186
polypoid hyperplasia	0.572	0.133	1.772	0.840-3.739
irregular hyperplasia	-0.296	0.404	0.744	0.371-1.490
Age, yr	0.032	0.291	1.033	0.973-1.096
constant	-2.521	0.030	.080	

### 3. Discussion

Normal endometrium carries physiological events such as menstruation, ovulation, implantation and pregnancy, and periodic injury and healing occur every month, all of which are characteristics of self-limiting inflammation [11-12]. Leukocytes, neutrophils, eosinophils, macrophages, NK cells and other inflammatory cells normally exist in the endometrium, and their proportion gradually increases from the proliferative stage to the secretory stage, helping implantation and pregnancy. However, there are no plasma cells in normal intima. Therefore, the presence of plasma cells is the gold standard for diagnosing CE. The diagnostic accuracy of CE under hysteroscopy at proliferation stage was better than that at secretion stage. At present, the main cause of CE disease is bacterial or other microbial infection. Antibiotics are the main treatment method, and the effective rate is about 80%-90%. At present, the universally accepted criteria for the diagnosis of endometritis under hysteroscopy are: endometrial congestion: (1) Strawberry sign: large endometrial congestion, with large and white punctured openings in the middle gland. (2) Focal congestion: small area of endometrial congestion. (3) Hemorrhagic spot: dark/brownish red hemorrhagic spot with sharp and irregular boundary, which may be connected with capillaries. (4) Microscopic polyps: diameter less than 1mm; Vascular axles of connective tissue are attached or run along the entire endometrial surface. (5) Interstitial edema: the endometrium is thick and edema at the follicular stage.

Dongmei Song, M. Ed [10]. A study of 1189 patients undergoing hysteroscopy and pathological diagnosis of CE in 2019 found that CD138 (+) was detected in 322 cases (27.1%) of 1189 patients. The characteristics of hysteroscopy were as follows: endometrial congestion: 169 of 322 cases (52.5%); Endometrial interstitial edema :27 cases (8.4%); Micropolyps: 11 of 322 (3.4%). The sensitivity, specificity, positive and negative predictive value and diagnostic accuracy of hysteroscopy were 59.3%, 69.7%, 42.1%, 82.8% and 66.9%, respectively. Conclusions: The detection of endometrial congestion, microscopic polyps or endometrial interstitial edema during hysteroscopy should be cautious of CE, but the overall accuracy of hysteroscopy in diagnosing CE is only 67%, so it should not replace the choice of histological examination as a diagnostic tool.

Normal intimal vessels are known as spiral arterioles perpendicular to the intimal epithelium. Hysteroscopic large neovascularization is parallel to the epithelium. Previous studies have shown that the quantity and quality of leukocyte recruitment, related cytokines and blood vessels varies over time throughout the menstrual cycle and pregnancy [11-21]. Vascular changes are mainly composed of vasoconstriction, vasodilation, increased capillary permeability and angiogenesis. Interleukin 1, interleukin 6, interleukin 8 and peptide growth factor play key roles in reproductive physiology and pathology, mainly through prostaglandin synthesis pathway. Bacterial infection can cause changes in cytokines, leading to vascular dilation and abnormal proliferation. Due to the angiogenesis of adenomyosis, neovascularization is characteristic of adenomyosis under endoscopy. Akie Takebayashi [22] found that endometritis in adenomyosis patients was three times as high as that in non-adenomyosis patients, and neovascularization disappeared in adenomyosis patients under hysteroscopy after 3 doses of Duffelin. It can greatly improve the success rate of transplantation.

In this study, the incidence of neovascularization in infertility patients under hysteroscopy is 22.4%, which is a significant feature of endometrial changes under hysteroscopy. Hysteroscopic neovascularization had moderate consistency with CE (Kappa value 0.46). Logsit regression analysis showed that the detection rate of neovascularization endometritis was up to 8 times higher than that of patients without neovascularization, which can be used as a characteristic index for physician to judge CE and improve the accuracy of CE diagnosis by hysteroscopy. Irregular hyperplasia and polypoid hyperplasia have little correlation with CE, but whether they affect embryo implantation and related mechanisms need to be further studied. In clinical work, endometrial polyps and endometrioid hyperplasia are often confused. The obvious difference is that endometrial polyps not only have different numbers of glands, stroma and blood vessels, but also need distinct pedicles and vascular axes. The microscopic appearance

of endometrial polyp is that normal stroma and plasma cells can be seen around blood vessels.

In conclusion, the detection of endometrial congestion, microscopic polyps, or endometrial interstitial edema during hysteroscopy should be cautious of CE, but the overall accuracy of hysteroscopy in diagnosing CE is only 67%, so it should not replace the choice of histological examination as a diagnostic tool. There was a moderate consistency between neovascularization and CE, and the detection rate of neovascularization endometritis was 8 times higher than that of patients without neovascularization, which could be used as a characteristic indicator for physician to judge chronic endometritis under microscope and improve the accuracy of CE diagnosis by hysteroscopy. Although uneven hyperplasia of uterus and polypoid hyperplasia have no statistical significance for the diagnosis of chronic endometrium, their influence on embryo implantation rate should be further studied.

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