PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 2 Number 4 December 2023

Advances in the Study of Pathological Histology and Pathogenesis of Endometrial Polyps

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doi:10.56397/CRMS.2023.12.06

Abstract

Endometrial polyps (EPs) are common gynecological diseases among women of childbearing age. They are formed by the proliferation of blood vessels and connective tissue in a portion of the endometrium, resulting in the formation of a polyp-like mass that protrudes into the uterine cavity and varies in size and number. Typically, the body of the uterus is the site of implantation of these polyp-like growths, which are attached to the medial wall of the uterine cavity by a long, thin tip. Irregular vaginal bleeding is the first clinical manifestation of endometrial polyps, and it can often lead to infertility. Studies have shown that the prevalence of endometrial polyps in the female population is approximately 25.0%. With the widespread use of hysteroscopic techniques in clinical practice, knowledge and diagnosis of endometrial polyps have significantly improved. However, pathological examination remains the "gold standard" for final diagnosis in clinical practice. This article aims to review the epidemiology, pathological histology, and pathogenesis of endometrial polyps to reveal their mechanisms and characteristics more accurately and guide further clinical research and treatment. The relevant progress in recent years in this field, both domestically and internationally, is reviewed below.

Keywords: endometrial polyps, epidemiology, pathological histology, pathogenesis, research progress

1. Introduction

Endometrial polyps are benign nodules composed of endometrial glands and fibrotic endometrial mesenchyme containing thick-walled blood vessels that protrude from the endometrial surface (Huang LH & Xiang ME, 2014). The main clinical manifestations of EP are prolonged menstruation, increased menstrual flow, irregular vaginal bleeding, and even infertility, but some patients have no obvious clinical symptoms, and the polyps can only be detected during ultrasound or hysteroscopy (Xia

M Q, Gui T, Huang M H, et al., 2019). In recent years, with the continuous improvement of these examination methods, the incidence of EP has been increasing annually, and most patients with EP have the possibility of developing cancer (Guo W K & Zhang S N., 2020). At present, EP is mainly treated surgically, including curettage, hysteroscopic EP removal, and hysteroscopic Endometrial Polyps electrodesis. However, EP is prone to recurrence, and to reduce the recurrence rate of EP, patients are often advised to take drospirenone ethinyl estradiol tablets or have a mannitol ring placed after surgery. Clinical studies have shown that both the long-term use of drospirenone ethinyl estradiol tablets and the placement of a mannitol ring have varying degrees of side effects and still have a certain recurrence rate (Chen Y., 2022). It has been suggested that the development of EP is closely related to the pathogenesis of EP, and adhering to the principle of "prevention is better than cure", research on the pathogenesis of EP can open up new ideas for the treatment of EP. However, the specific pathogenesis of EP is still unclear, and this paper will review the latest research progress on the epidemiology, pathological histology, and pathogenesis of EP.

2. Epidemiology of Endometrial Polyps

Endometrial polyps are commonly observed in women over the age of 35, and their incidence increases with age. According to foreign studies, the prevalence of endometrial polyps is approximately 3% in women under the age of 35, 23% in women over the age of 35, and the highest prevalence is about 31% in postmenopausal women, with a peak incidence at 50 years of age and rarely occurring after 70 years of age. The prevalence of endometrial polyps is significantly higher in infertile patients, and its exact incidence is difficult to determine and varies with the diagnostic method used, ranging from 2.8% to 34.9%. Currently, the prevalence of endometrial polyps in Chinese women is increasing and is approximately 24% to 25% (Zhao LILI & Wang YX., 2022).

3. Pathological Histological Features of Endometrial Polyps

Endometrial polyps are characterized as limited hyperplasia of the basal layer of the endometrium, consisting of endometrial glands with irregular distribution and thick-walled blood vessels, as well as a small amount of dense fibrous connective tissue that protrudes with a tip into the uterine cavity. These polyps may exhibit simple or complex hyperplasia, with or without endometrial hyperplasia throughout the uterus. Endometrial polyps can be located anywhere in the cervix and uterine cavity. Solitary polyps are commonly found at the base of the uterus, followed by the horn of the uterus, while multiple polyps grow diffusely and are located in multiple parts of the uterine cavity. Endometrial polyps can be divided into the following four categories based on their origin and characteristics: 1) functional polyps that originate from the mature endometrium and change cyclically with menstruation, and can be partially or completely shed without special intervention; 2) non-functional polyps that originate from the immature endometrium, only a few of which maintain the basal endometrial morphology and can continue to proliferate thanks to estrogen, forming simple or complex hyperplasia; 3) adenomyoma-like polyps that are a special and rare type of polyps with the same morphology as ordinary endometrial polyps, but with a large number of endometrial glands and mixed with smooth muscle components and thick-walled blood vessels; and 4) postmenopausal polyps, also known as atrophic polyps, which exhibit atrophic changes in both the endometrial glands and interstitium.

4. Study on the Pathogenesis of EP

4.1 Genetic Factors

The occurrence of EP has certain genetic features, mainly chromosomal abnormalities in EP tissue cells (Tallini G, Vanni R, Manfioletti G, et al., 2000). Dal et al. (1995) studied simple benign EP by cytogenetic methods and found rearrangements of chromosomes 6p21-p22, 12q13-15, and 7q22 in EP tissue cells. Vanni et al (1995) also found the presence of (6; Vanni et al (1995) also found (6; 20), (p21; q13) translocations (i.e., translocation of band 1 of region 2 of chromosome 6 to band 3 of region 1 of chromosome 20) in EP tissue cells, while Fletcher et al (1992) suggested that rearrangement of chromosome 6p21 in EP interstitium is a characteristic cytogenetic abnormality, and Vanni et al (1993) experimentally confirmed the presence of rearrangement of 6p21 in polyp tissue cells of EP patients.

4.2 Immunological Factors

Zhu et al (2018) reported that the development

of endometrial polyps (EP) is associated with CD4+ T cells, with interferon γ and interleukin 17 secretion significantly increased in these cells, while transforming growth factor (TGF)-β secretion was relatively low. Bozkurt et al (2015) found that the expression of nuclear factor KB (NF-KB)1 in the endometrium of EP patients was significantly decreased after hysteroscopic treatment. A study by Chao Tian (2016) showed that Toll-like receptor4(TLR4), myeloid differentiation factor 88 (MyD88) and NF-κB were most strongly expressed in EP and weakest in normal endometrium. TLR4 was positively expressed with MyD88 and NF-KB, and NF-KB positive expression was positively correlated with MyD88 and NF-KB positive expression. MyD88 was also positively correlated with NF-KB positive expression, suggesting that TLR4/MyD88/NF-KB activation may be involved in the development of EP. Another study found that the expression of TGF-β1 in EP glandular cells during the proliferative phase was significantly higher than that in the adjacent endometrium, while the expression of TGF-β1 in EP interstitial cells during the proliferative and secretory phases was significantly higher than that in the adjacent endometrium (Xuebing P, Tinchiu L, Enlan X, et al., 2011). These findings suggest that local immune inflammation of the endometrium may be related to the occurrence and development of EP.

Cyclooxygenase 2 is a rate-limiting enzyme that catalyzes the conversion of arachidonic acid into prostaglandins. Cyclooxygenase 2 is an inducible rate-limiting enzyme that can be activated by certain cytokines, inflammatory mediators, oncogenic agents, and certain oncogene products inside and outside the cell, and is involved in various pathophysiological reactions of the body, such as fever, certain inflammatory reactions and promotion of tumor proliferation. Some studies (ZHANG Jia-Nan, TANG Xiao-Han, LU Mei-Song, et al., 2015; Maia H Jr, Pimentel K, Silva TM, et al., 2006) have found that the expression of cyclooxygenase 2 was significantly higher in secretory EP tissues than in normal endometrium, but in both EP and endometrial tissues cyclooxygenase 2 expression peaked in the proliferative phase and decreased in the late secretory phase. However, Kasap et al (2016) showed that the expression of cyclooxygenase 2 in EP tissues was not significantly different from that in normal endometrial tissues in either the proliferative or secretory phase. Pereira et al (2015) also analyzed articles on the expression of cyclooxygenase 2 in EP tissues from 2001 to 2014 and found that a portion of the literature showed that the expression of cyclooxygenase 2 in EP tissues was significantly different from that in normal endometrial tissues. However, some of them showed no difference in the expression of cyclooxygenase 2 between EP tissues and normal endothelial tissues. Therefore, it is not clear whether the abnormal expression of cyclooxygenase 2 is related to the pathogenesis of EP.

4.3 Cell Proliferation/Apoptosis Imbalance Factors

B-cell lymphoma 2 (Bcl-2) is a proto-oncogene that inhibits apoptosis. Ki-67 is a nuclear antigen that is associated with mitosis and cell proliferation, with increased expression indicating active proliferation (Qin X & Xu W S., 2015). Studies have found that Ki-67 expression is low in patients with endometrial polyps (EP), while Bcl-2 is highly expressed in both glandular epithelium and mesenchyme (Risberg B, Karlsson K, Abeler V, et al., 2002; Banas T, Pitynski K, Mikos M, et al., 2018). This suggests that the development of EP is not due to excessive proliferation, but rather impaired apoptotic processes. Additionally, p63 is a protein that regulates epithelial cell proliferation and differentiation and is a marker of basal and reserve cells in the female germinal tract. Expression of p63 has been found to be significantly stronger in EP tissues compared to surrounding endothelium and normal endothelium (Su T T & Sui L., 2014; Nogueira AA, Sant' Ana de Almeida EC, Poli Neto OB, et al., 2006). Furthermore, the expression of p63 has been found to be significantly stronger in postmenopausal EP compared to surrounding endothelium, indicating a potential role of p63 in the pathogenesis of EP. However, further investigation is needed to determine if there are differences in p63 expression levels in EP before and after menopause.

4.4 Endocrine Factors

Numerous studies have implicated an imbalance of estrogen receptor (ER) and progesterone receptor (PR) expression in the endometrium in the pathogenesis of EP (Qiu HJ, Liang DX, Sun Y, et al., 2017; Liang Doxian, Qiu Huajuan, & Ji Yanqin, 2017). Tian Chao et al (2016) found no difference in ER expression between EP, para polypoid endometrium, and normal

endometrium; however, PR expression was weakest in EP and strongest in normal endometrium. Conversely, Peres et al (2018) demonstrated significantly higher expression of ER and PR in EP tissues than in normal endometrial tissues. Peng et al (2009) found that ER expression was higher in EP than in para polypoid tissues, while PR expression was low. These results suggest that EP may form due to an overreaction of local endometrium to estrogen, with reduced PR expression leading to decreased sensitivity to progesterone response or even the absence of response, resulting in local endometrial tissue hyperplasia. Furthermore, de Carvalho et al (2011) investigated differences in ER and PR expression in EP and para polypoid endometrial tissues in postmenopausal women and found higher rates of ER and PR positive cells in both endometrial and EP glands than in the stroma. The rate of ER and PR positive cells was significantly higher in both gland and stroma of EP than in the endometrium. Thus, the occurrence of EP is closely related to an imbalance in ER and PR expression, which appears to differ before and after menopause and between proliferative and secretory phases, although the precise mechanism requires further investigation.

Elbehery et al (2011) compared levels of insulin-like growth factor binding protein 1 (IGFBP-1) in hysteroscopic preoperative and postoperative uterine douche fluid in EP patients and found a significant increase in IGFBP-1 levels in postoperative uterine douche fluid. As a result, they suggested that low levels of IGFBP-1 might be associated with the occurrence of EP. In addition, Wang Yunli' study (2010) observed significantly lower expression of insulin-like growth factor 1 (IGF-1), insulin-like growth factor 1 receptor (IGF-1R), and insulin in the proliferative phase of EP and endometrium around polyps compared to normal uterine tissues. Furthermore, the expressions of IGF-1 and insulin in EP and peri-polyps endometrial tissues were significantly lower than those in normal endometrial tissues. These findings suggest that the reduced expression of IGF-1, IGF-1R, and insulin in EP and peri-polyps endometrial tissues may be related to the development of EP.

Aromatase cytochrome P450 (P450arom) is a key enzyme for estrogen synthesis, catalyzing the conversion of C19 androgens to estrogens. Maia et al (2006) found that the expression of P450arom in EP was significantly higher than that in normal endometrium, although there was no difference in expression during the proliferative and secretory phases. Su Tingting et al (2014) also found that the expression of SF-1 and P450arom in EP was significantly stronger than that in the endometrium surrounding EP and normal endometrium. These findings suggest that P450arom and SF-1 may play a role in the development of EP.

4.5 Angiogenic Factors

The current study indicates that matrix metalloproteinases (MMPs) are closely related to angiogenesis, and among the MMP family, MMP-2 and MMP-9 are most associated with EP (Andreuzzi E, Colladel R, Pellicani R, et al., 2017). Dreisler et al (2009) found that MMP-2 expression exhibited tumor characteristics in EP patients, and the combined expression of MMP-2 and MMP-9 was significantly higher in the serum of EP patients than in those with normal endometrium, as demonstrated by Gershtein et al (2018). Peres et al (2018), however, showed that both MMP-2 and MMP-9 were not expressed in EP or normal endometrial tissues. Early studies showed that MMP-2 and MMP-9 expression could be detected in EP and normal endometrial tissues (Inagaki N, Ung L, Otani T, et al., 2003), and many studies have since revealed that hormone levels in patients may have an effect on the expression of MMP-2 and MMP-9, and that their expression differs between EP and normal endometrium (Erdemoglu E, Güney M, Karahan N, et al., 2008; Tokyol C, Aktepe F, Dilek FH, et al., 2009). These studies suggest that MMP-2 and MMP-9 may be involved in the development of EP, but the specific mechanisms require further investigation.

Vascular endothelial growth factor (VEGF) is a highly specific pro-vascular endothelial growth factor that promotes increased vascular permeability, extracellular matrix degeneration, vascular endothelial cell migration, proliferation, and angiogenesis. The results of previous studies have shown that the expression of VEGF is significantly higher in EP glandular cells than in adjacent endometrium during both the proliferative and secretory phases, while during the proliferative phase, the expression of VEGF is significantly higher in EP mesenchymal cells than in adjacent endometrium. These findings suggest that VEGF may play a role in mediating the development of EP.

5. Discussion and Outlook

Endometrial polyps are a common gynecologic disease, and hysteroscopy is an effective treatment for most cases. However, the high recurrence rate after treatment requires urgent attention. Currently, most research on endometrial polyps is based on histopathology, with few studies examining the cellular-molecular level of EP pathogenesis. This highlights the need for further research in this area. This paper reviews the epidemiology, pathological histology, and pathogenesis of endometrial polyps, providing a reference for future research in the development of EP.

Fund Project

This research was supported by National and autonomous region level college student innovation and entrepreneurship training program project fund funding project (No.:202010599030); Autonomous region level college student innovation and entrepreneurship training program project fund funding project (No.:202010599065).

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