

PATHOGENESIS AND THEORIES OF DEVELOPMENT OF EXTERNAL GENITAL ENDOMETRIOSIS

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Abstract

External genital endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterine cavity, primarily affecting the ovaries, fallopian tubes, and the peritoneum. The pathogenesis of external genital endometriosis remains complex and multifactorial, involving hormonal, immunological, genetic, and environmental factors. Various theories have been proposed to explain its development, including retrograde menstruation, coelomic metaplasia, stem cell differentiation, and lymphatic or hematogenous spread. While the theory of retrograde menstruation remains the most widely accepted, it does not fully account for all clinical cases, suggesting that a combination of mechanisms may be at play. This review explores the current understanding of the pathogenesis and major theories of development of external genital endometriosis, highlighting the need for further research to clarify the underlying biological mechanisms and improve diagnostic and therapeutic strategies.

Keywords: External genital endometriosis, Pathogenesis, Retrograde menstruation, Coelomic metaplasia, Stem cell theory, Hormonal factors, Immune dysfunction, Endometrial implants, Gynecological disorders, Infertility

Introduction

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Endometriosis is a chronic, estrogen-dependent gynecological disorder characterized by the presence of endometrial-like glands and stroma outside the uterine cavity. Among its various forms, **external genital endometriosis** refers specifically to the localization of endometrial tissue on pelvic organs such as the ovaries, fallopian tubes, uterosacral ligaments, and the peritoneum. This condition affects approximately 10% of women of reproductive age and is a leading cause of pelvic pain, dysmenorrhea, dyspareunia, and infertility. Despite its high prevalence

and significant impact on women's health, the exact etiology and pathogenesis of endometriosis remain elusive, which complicates its diagnosis, treatment, and prevention.

Understanding the pathogenesis of external genital endometriosis is critical for the development of effective clinical management strategies. The pathogenesis refers to the biological mechanisms and sequence of events that lead to the development and progression of ectopic endometrial lesions. Multiple theories have been proposed over the past century, each aiming to explain how and why endometrial tissue is found in ectopic locations. Although no single theory can fully account for all manifestations of the disease, a combination of hypotheses is generally accepted in contemporary medical thought.

The most widely accepted theory is **Sampson's theory of retrograde menstruation**, proposed in the 1920s. According to this theory, during menstruation, some of the endometrial tissue flows backward through the fallopian tubes into the pelvic cavity instead of exiting the body through the cervix and vagina. This displaced tissue can implant onto pelvic structures and continue to grow and respond to hormonal changes. While this theory is supported by the fact that retrograde menstruation occurs in the majority of women, it does not explain why only a subset develop endometriosis, suggesting that other factors such as immune dysfunction or genetic susceptibility may play a role.

Another significant hypothesis is the **coelomic metaplasia theory**, which suggests that peritoneal cells—cells lining the abdominal cavity—have the potential to transform into endometrial-like cells under certain stimuli, such as hormonal or inflammatory signals. This theory explains the occurrence of endometriosis in individuals without a uterus, such as in rare cases among men undergoing estrogen therapy and in women after hysterectomy. It also provides a plausible explanation for endometriotic lesions observed in unusual locations where retrograde menstruation is unlikely.

A more recent addition to the array of theories is the **stem cell theory**, which posits that endometrial progenitor or stem cells from the bone marrow or the basal layer of the endometrium may travel to ectopic sites via lymphatic or vascular routes

and differentiate into functional endometrial tissue. This model is supported by the discovery of bone marrow-derived stem cells in the endometrial lining and in ectopic endometrial implants in animal studies. The stem cell theory may explain the recurrence of endometriosis even after total surgical excision of lesions and the presence of endometriosis in remote anatomical sites.

The **embryonic rest theory** or Müllerian remnants hypothesis suggests that residual embryonic cells from the Müllerian ducts, which give rise to the female reproductive tract, may persist in ectopic locations and later differentiate into endometrial tissue. This theory is particularly useful in explaining cases of endometriosis found in adolescents, premenarchal girls, or even neonates.

In addition to these developmental theories, **immune system dysfunction** has emerged as a key factor in the pathogenesis of endometriosis. Normally, the immune system is responsible for clearing misplaced endometrial cells during retrograde menstruation. However, in women with endometriosis, studies have shown altered immune responses, including decreased activity of natural killer (NK) cells, increased levels of inflammatory cytokines, and the presence of autoantibodies. This impaired immune surveillance allows ectopic endometrial cells to survive, implant, and proliferate.

Genetic and epigenetic factors are also thought to contribute to the pathogenesis of endometriosis. Family studies have shown a higher incidence of endometriosis among first-degree relatives, and genome-wide association studies (GWAS) have identified multiple susceptibility loci related to hormone metabolism, cell adhesion, and immune function. Epigenetic modifications, such as DNA methylation and histone acetylation, may alter gene expression in endometrial and immune cells, promoting a pro-inflammatory and pro-survival phenotype in ectopic tissues.

Hormonal imbalances, particularly those involving **estrogen and progesterone**, further influence the development and maintenance of endometriosis. The ectopic endometrial tissue in women with endometriosis often shows increased local estrogen production and decreased responsiveness to progesterone, a condition referred to as “progesterone resistance.” This hormonal environment supports the

survival and proliferation of ectopic endometrial cells while reducing apoptosis and increasing angiogenesis—the formation of new blood vessels to nourish the lesions. The complexity of external genital endometriosis is further highlighted by its variable clinical presentation. Some women may remain asymptomatic, while others experience debilitating pain and infertility. The severity of symptoms does not always correlate with the extent of lesions, making clinical diagnosis challenging. Laparoscopy remains the gold standard for definitive diagnosis, but there is growing interest in non-invasive biomarkers and imaging techniques to improve early detection.

Despite decades of research, endometriosis remains an enigmatic disease. The interplay between multiple biological systems—including the reproductive, immune, endocrine, and genetic systems—underscores the need for a multidisciplinary approach in its study and management. Recognizing the multifactorial nature of its pathogenesis allows researchers and clinicians to move away from a one-size-fits-all model and toward personalized treatment strategies tailored to the individual patient's pathophysiology.

This paper aims to review and critically analyze the major theories of development of external genital endometriosis with a focus on their strengths, limitations, and supporting evidence. By exploring the mechanisms behind this condition, we can contribute to a better understanding of its etiology and pave the way for improved therapeutic interventions and quality of life for affected individuals.

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